

# Use of Medicinal Cannabis for Palliative Care Patients: A Systematic Review

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**How to cite this paper:** da Costa, V.F.D.D. and de Carvalho, W.S.R. (2022) Use of Medicinal Cannabis for Palliative Care Patients: A Systematic Review. *Journal of Biosciences and Medicines*, 10, 242-252.

<https://doi.org/10.4236/jbm.2022.109017>

**Received:** August 24, 2022

**Accepted:** September 20, 2022

**Published:** September 23, 2022

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## Abstract

**Background:** Medical cannabis is a rapidly growing area of medicine. In this sense, due to the numerous benefits associated with its use, it has been increasingly proposed for patients in palliative care, in which the improvement of debilitating symptoms is directly associated with better quality of life. However, due to the complexity of treatments for these individuals, further studies are needed to determine the best possible prescription for them. **Objective:** Understand the endocannabinoid system and evaluate the feasibility of using medical cannabis in palliative care patients. **Methods:** Systematic literature review, addressing the following topics: “cancer, cannabis, and palliative care”. The search was carried out using the Virtual Health Library: LILACS, SciELO, Medline, PubMed, and Cochrane, with articles between 2013 and 2022. **Results and discussion:** A total of 116 articles were found with the descriptors. After reading the abstracts, 22 showed greater association with the theme and were chosen for the preparation of this review. **Conclusion:** It is concluded that medical cannabis is an excellent treatment option for most of the symptoms present in patients in palliative care. In this way, the adoption of this drug by the public becomes logical. However, it is the physician’s role to seek to understand the particularities of these individuals and this new possibility of treatment, which, it seems, will significantly improve the end of life of these patients—this being the main role of the medical teams.

## Keywords

Cancer, Cannabis, Palliative Care

## 1. Introduction

Nowadays, the use of medical cannabis is already a reality. For some diseases, such as epilepsy and autism, it is considered one of the first-line treatments, be-

ing extremely safe and effective. Based on this scenario, its use for other pathological conditions has been studied [1].

Patients in palliative care are terminally ill, in which the cure can no longer be met. Therefore, the main objective of medical teams should provide the best possible quality of life [2]. They need to deal with an extensive debilitating number of symptoms, such as pain, nausea, vomiting, anorexia, and depression [3].

A portion of these symptoms can be aggravated or worsened by treatments and medicines used such as chemotherapies, prolonged use of high opioids, neuroleptic agents, benzodiazepines, and certain antiemetic substances doses [3] [4], which promote neurotoxicity and bad side effects.

In this scenario, medical cannabis is a possible treatment. It can be used in a complementary way to traditional practices already applied to patients or alternatives, being used only the plant substances [5].

The results for the improvement of symptoms and the quality of life of palliative patients is excellent, with an improvement in adverse effects, anxiolytic, antitumor, antiemetic and analgesic with synergism with opioids, actions, increased appetite, improved sleep, and significant reduction of the drug load of these patients [2] [3] [6] [7] [8] [9].

However, cannabis administration involves numerous variables, such as composition, form, possibility of acquisition, drug interaction management [1] and socioeconomic and political issues surrounding *cannabis spp.* Thus, this review seeks knowledge on the subject and determination as a search for the area.

## 2. Objective

Understand the endocannabinoid system and its influence on different physiological systems. From this, understand the most prevalent complaints of patients in palliative care and, thus, the feasibility and benefits of using medical cannabis for this group.

## 3. Material and Methods

### Data Sources and Search Strategy

This systematic literature review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations and assesses the use of medicinal cannabis for palliative care patients.

A broad electronic search was performed using the Virtual Health Library (VHL), which included Lilacs, SciELO, Medline, PubMed, and Cochrane, using the descriptors: Cancer, Cannabis and Palliative Care. These search terms were used individually and in varying combinations.

To ensure the contemporary relevance of the data, the search was limited to articles written in English and Portuguese, published between the years 2013 and 2022.

### Eligibility Criteria

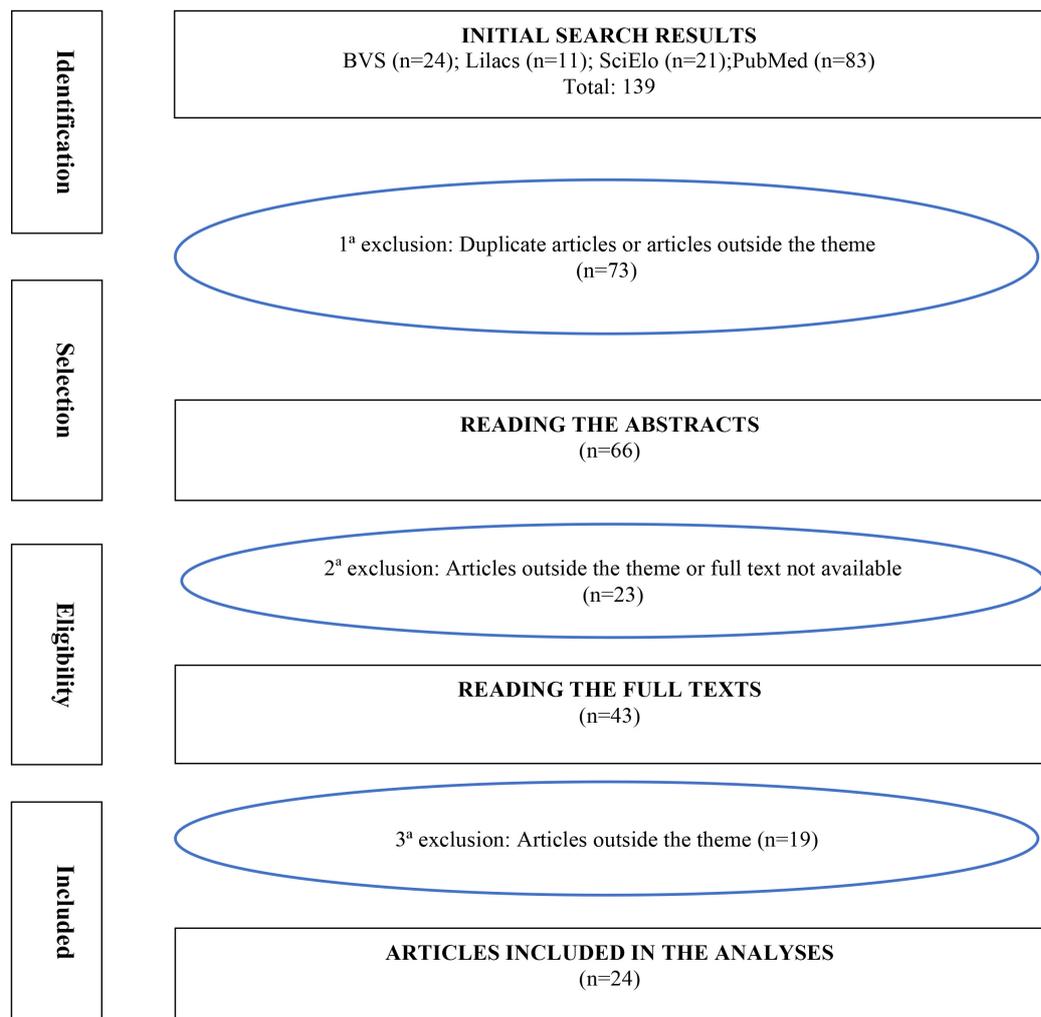
Initially, 139 articles were found, which underwent a relevance test consisting

of the inclusion criteria: 1) Reference to the term medical cannabis; 2) Assessment of palliative patient’s condition and the main factors that worsen their quality of life; 3) Association of cannabis use in this patients profile; 4) publication in selected languages and periods.

After a detailed analysis, 73 articles were excluded due to duplication and failure to present the proposed criteria. After reading the abstracts, 23 articles were excluded for not presenting the full text and the proposed theme; and finally, after reading the articles in full, 19 articles were excluded for not presenting the proposed criteria. Thus, this review is based on the remaining 24 articles that met the pre-established eligibility criteria for the analysis, as shown in (Figure 1).

**Data Extraction and Statistical Analysis**

Studies that met the inclusion criteria were divided among the authors and data were independently extracted into a standardized spreadsheet. The articles were evaluated by the researchers and any discrepancies were resolved by consensus.



**Figure 1.** PRISMA flow diagram: representation of eligibility and inclusion of articles.

In summary, a narrative synthesis was applied to approach the collected data, and a descriptive statistical analysis was performed using the Office 2021 Excel program for Mac.

#### 4. Results

After eliminating duplicates and selecting publications, the articles were read in full, from which the parameters proposed in the analytical matrix of the present study were analysed.

This systematic literature review analysed 24 scientific studies that rigorously met the previously established characteristics in the sample selection. Of this total of articles, 3 were quantitative/qualitative studies, 4 were quantitative study and 17 were qualitative.

The synthesis of these selected scientific articles is presented below, converting the following aspects: author/year of publication, article title, objective, type of study and database (**Table 1**).

**Table 1.** Description of the articles selected for analysis.

Author/Date	Article Title	Study Purpose	Type of Study	Data Base
Divisic, A. <i>et al.</i> , 2021	The use of medical cannabis in pediatric palliative care: a case series	Evidencing the efficacy of cannabis use in chronic pain and epilepsy of children in palliative care	Qualitative	PubMed
Likar, R. <i>et al.</i> , 2017	The use of cannabis in supportive care and treatment of brain tumor	Assessing the use of medical cannabis in critically ill patients with brain cancer	Qualitative	PubMed
Meng, H. <i>et al.</i> , 2020	Cannabis and cannabinoids in cancer pain management	Evidencing the use of medical cannabis in cancer patients	Qualitative	PubMed
Good, P.D. <i>et al.</i> , 2020	An Open-Label Pilot Study Testing the Feasibility of Assessing Total Symptom Burden in Trials of Cannabinoid Medications in Palliative Care	Assess the tolerability of medical cannabis and its effectiveness in palliative care	Quantitative	PubMed
Crocker, J.A. <i>et al.</i> , 2021	Cannabis and End-of-Life Care: A Snapshot of Hospice Planning and Experiences Among Illinois Medical Cannabis Patients with A Terminal Diagnosis	To evaluate the use of medical cannabis in palliative care patients admitted to the hospice	Qualitative	Medline
Christensen, A. <i>et al.</i> , 2019	The Role of Cannabidiol in Palliative Care	To analyze the action of cannabidiols in palliative patients	Qualitative	PubMed
Mechoulam, R. <i>et al.</i> , 2013	The Endocannabinoid System and the Brain	Understand the functioning of the Endocannabinoid System and its effects on the brain	Qualitative	PubMed
Lichtman, A.H., <i>et al.</i> , 2018	Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain	To evaluate the use of Nabiximol for chronic pain in patients with advanced cancer unresponsive to the use of opioids	Quantitative	PubMed
Hightet, B.H. <i>et al.</i> , 2020	Tetrahydrocannabinol and Cannabidiol Use in an Outpatient Palliative Medicine Population	Describe the benefits and side effects of using medical cannabis in palliative care	Qualitative	PubMed

## Continued

Lopes-Júnior, L.C. <i>et al.</i> , 2021	Effectiveness of complementary therapies for the management of symptom clusters in palliative care in pediatric oncology: a systematic review	To evaluate the effectiveness of complementary therapies in the treatment of children and adolescents in palliative care	Qualitative	SciELO
Herbert, A. <i>et al.</i> , 2021	Medicinal cannabis uses in palliative care	Addressing the use of medical cannabis in palliative care for children and adults	Qualitative	Medline
Grof, C.P.L., 2018	Cannabis, from plant to pill	Addressing the diferente ways of handling cannabis	Qualitative	PubMed
Hardy, J. <i>et al.</i> , 2020	Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety of 1:1 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)	Define the role of THC/CBD in improving symptoms of patients with advanced cancer in palliative care	Quantitative	PubMed
Hauser, W. <i>et al.</i> , 2017	Cannabinoids in Pain Management and Palliative Medicine	Address the efficacy and safety of cannabinoid use in palliative patients	Quantitative/ Qualitative	PubMed
Mucke, M. <i>et al.</i> , 2018	Cannabis-based medicines for chronic neuropathic pain in adults	Point out the efficacy, tolerability and safety of using medical cannabis for patients with neuropathic pain	Quantitative	PubMed
Filetti, M. <i>et al.</i> , 2021	Knowledge and attitudes of Italian medical oncologists and palliative care physicians toward medical use of cannabis in cancer care: a national survey	Evidencing the use of medical cannabis by Italian oncologists	Qualitative	Medline
Aman, M.M. <i>et al.</i> , 2021	The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain	Understanding cancer pain and possible therapeutic approaches	Qualitative	PubMed
Oberoi, S. <i>et al.</i> , 2021	Perspectives of pediatric oncologists and palliative care physicians on the therapeutic use of cannabis in children with cancer	To determine the use prospects for the use of medical cannabis in pediatric oncology palliative care	Qualitative	Medline
MacDonad, E. <i>et al.</i> , 2019	Medical Cannabis Use in Palliative Care: Review of Clinical Effectiveness and Guidelines – An Updated	Gather evidence and indications of medical cannabis use in palliative care patients	Qualitative	PubMed
Kleckner, A.S. <i>et al.</i> , 2019	Opportunities for cannabis in supportive care in cancer	Address key uses of medical cannabis for advanced-stage cancer patients	Qualitative	PubMed
Karila, L. <i>et al.</i> , 2014	Acute and Long-Term Effects of Cannabis Use: A Review	Analyzes the consequence of long-term recreational marijuana use	Qualitative	PubMed
Casarett, D.J. <i>et al.</i> , 2019	Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms	To determine the effectiveness of using THC and CBD on the symptoms of palliative patients	Quantitative/ Qualitative	PubMed
Tanco, K. <i>et al.</i> , 2019	Response to Casarett <i>et al.</i> : Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms	Reply to another article pointing out points of view different from the first	Qualitative	PubMed
Crocker, J.A. <i>et al.</i> , 2022	Medical Cannabis and Utilization of Nonhospice Palliative Care Services: Complements and Alternatives at End of Life	Evidencing the use of medical cannabis in palliative patients admitted to the hospice	Quantitative/ Qualitative	Medline

Source: Elaborate by the authors.

## 5. Discussion

Patients in palliative care are those with diseases in terminal stages, in which the physician's role is to manage the symptoms in order to promote a more comfortable death with less suffering. In this way, the focus is on the physical, emotional and psychological aspects that most hinder quality of life [2].

Several treatments are proposed and tested for these patients. However, there are many adverse effects, which makes new approaches to be considered. Complementary or alternative treatments can be performed aiming at the best management of these effects, according to the patient's conditions [5] [10].

Pain is an important aspect present in most of these individuals, regardless of the disease they have. In order to improve this situation, many opioids are administered, generating several side effects—nausea, vomiting, anorexia, in which more drugs are needed [3].

In this context, medical cannabis gains space. The endocannabinoid system has aroused increasing interest in research. Currently, its ability to modulate the immune, autonomic nervous, gastrointestinal, endocrine and cardiovascular systems is known [11]. Medicinal substances such as terpenes, flavonoids and cannabinoids, more than 140 different ones, the most studied being 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) found in the flowers and bracts of *cannabis spp* [3] [6] [11] [12].

The endocannabinoid system has CB1 and CB2 as its main receptors and its two most studied neurotransmitters are anandamide (AEA) and 2-arachidonylglycerol (2-AG) [7].

CB1 and CB2 are G protein-coupled receptors that associate with adenylate cyclase and MAPK (mitogen-activated protein kinase). When CB1 activation occurs, some results are observed, such as: decrease in cAMP and, consequently, in PKA; closure of  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  channels; stimulation of MAPK (it has effects on synaptic plasticity and cell migration); and influence on the release of neurotransmitters, such as GABA and glutamate—CB1 agonists decrease the release of glutamate, resulting in an increase in dopamine [7].

CB1 is quite present in the brain, especially in sensory and motor regions, indicating its participation in motivation, cognition and pain modulation [3] [7]. CB2, on the other hand, is usually found in cells and tissues of the immune system, especially in microglia.

As for neurotransmitters, AEA is located in the brain and 2-AG in peripheral tissues. When compared with other neurotransmitters, they have some particularities, such as being produced according to demand, not being stored in vesicles [7]. In addition, they act mainly on the presynaptic membrane (after being synthesized in the postsynaptic membrane, they rapidly target receptors on the presynaptic membrane and inhibit both excitatory and inhibitory stimuli) [3] [7].

In this context, THC and CBD, which are derived from *cannabis sativa*, act on these receptors, triggering the beneficial effects of this process, similar to endo-

cannabinoids. THC is associated with analgesic effects due to its action as an agonist at both CB1 and CB2 receptors [3] [6], and may have different effects depending on the dose [7]. CBD, on the other hand, is more associated with CB2, which explains its atoxicity [13], reduced psychotropic effects of THC [3] [6] and potent anti-inflammatory role [7].

In this scenario, several studies have been carried out to analyze the effects of medical cannabis on the symptoms of palliative patients.

As for pain, the improvement observed in patients is undeniable [1] [2] [3] [6] [8] [9] [11] [14] [15] [16]. Those who have an oncological condition, in which the pain is often mixed, neuropathic and nociceptive, being generated not only by the presence of the tumor, but also by the effects of chemotherapy and radiotherapy [17], an integrative approach becomes essential. According to one study, patients undergoing cancer treatment who used 10 mg of THC experienced pain reduction proportional to 60 mg of codeine and compared to sedation with 120 mg of codeine [3]. This improvement is mostly associated with combating neuropathic pain. In addition, the interaction of cannabinoids with opioids was evaluated, which showed synergistic effects. It has been shown that, with the association, there is a lower risk of tolerance to opioids and, when this already exists, there is the possibility of rekindling previously ineffective opioid analgesia [2].

Another very common symptom in these patients is nausea and vomiting. The positive effect on its improvement has been demonstrated, especially of THC [2] [3] [5] [6] [11] [16] [18]. Cannabinoids have been shown to be more effective than various antiemetics, such as prochlorperazine, metaclopramide, chlorpromazine, thiethylperazine, domperidone, and alizapride [2] [11].

Not restricted to just these occurrences, CBD and THC present good results in cases of anorexia, fatigue and constipation [1] [2] [3] [5] [9] [11] [16] [18] [19], and weight gain was observed in patients who administered 3 mg of THC 1 hour after meals [2] [19]. In addition, its antitumor effect has been verified, mainly for astrocytomas and glioblastomas [2] [6] [16] [18].

However, as already mentioned, the main objective of the physician is to promote the best possible quality of life for these patients. Thus, the psychological aspect cannot be ignored. Given the condition to which they are subjected, in which there are no more technical resources to progress with the treatment, sleep disorders, anxiety and depression are conditions that will be inserted in the context. And cannabis also acts in these aspects [1] [2] [3] [4] [6] [9] [11] [13] [15] [16] [18]. No work was found that elucidated the mechanisms by which cannabinoids improve anxiety and depression, but it is recognized that the endocannabinoid system influences mood regulation, and an improvement in these symptoms is theoretically expected. There is some promising research that demonstrates the positive impact of using CBD on rodents [20]. However, Israeli research has shown that 80% of patients believed that cannabis relieved physical and psychological stresses, improving the way they deal with the situation [18].

From this aspect, it is worth highlighting a point that makes advances involving cannabis very difficult. Marijuana is a drug used for centuries by different peoples, and most of its use is associated with illegality, youth and addiction. However, it is essential to make it clear that plant smoke, often mixed with tobacco and other substances [21], is absolutely different from its medicinal use, in which a strict control of the administered substances is carried out. Thus, there are reliable studies that show the harm associated with the recreational use of cannabis [22], not with its use as a treatment. On the contrary, it is proven that, unlike most drugs, cannabinoids do not have significant side effects, which facilitates adherence and maintenance of treatment [4] [15] [16] [18]. Likewise, much is said about dependence on marijuana smoking, but no study demonstrates that the administration of cannabinoids generates any degree of dependence.

Regarding the supply of cannabis, it can be made in different ways, such as sachets, gels, sprays, oils and tablets [3], presenting different pharmacokinetics depending on the technique applied in the management of the plant [12]. In addition, there can be several combinations, both of THC with CBD, and with conventional treatments. Most of the positive results were due to these associations [9] [13].

In this way, it is remarkable that medical cannabis can bring many beneficial effects to patients in palliative care, greatly improving their quality of life. However, due to the lack of sufficient studies to understand its entire mechanism of action and the effects of the drug interaction with the numerous drugs used by these individuals [16] [23], the administration of cannabis must be done with care. There are studies that argue that its adverse effects are minimal when compared to the improvement of the condition [3] and, especially, of the effects of opioids, and its administration is considered safer [4]. On the other hand, there are studies showing that its use can cause changes in liver function and a possible reduction in the effectiveness of chemotherapy [11], and its use should be restricted to only patients admitted to the hospice [24].

Finally, the lack of regulation of the use of medical cannabis, its substitution of opioids and its use as an alternative treatment rectifies the association of therapy with recreational use, which makes studies difficult and, consequently, the most appropriate prescription [16].

## 6. Conclusions

The use of medical cannabis and its action and efficacy under the endocannabinoid system in palliative patients is undeniable. There is a significant improvement in the main debilitating symptoms of these individuals, such as pain, nausea, vomiting, anxiety and depression. However, there are several challenges involved in prescribing this drug. The formulation and the ideal moment to start the association with conventional treatment, as well as doubts about the mechanism of action and the interaction with the various highly toxic therapies

used by these individuals are some of the difficulties. Associated with them, beliefs and prejudices still plague people when it comes to cannabis. Due to all this, currently, the use of medical cannabis is still chosen, maintaining conventional treatment—whether chemotherapy or any other medication, with the exception of hospice, where there may be a total replacement, depending on the patient's condition [24].

In this sense, more double-blind randomized studies are needed to validate the information that has been seen in medical practice. In this way, it will be possible to fully understand its action, which will make your prescription more assertive, improving the quality of life, comfort and treatment offered to patients. By this means, trust and the demystification of the treatment will be gained.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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