# EFICÁCIA E SEGURANÇA DOS CANABINOIDES NO CONTROLE DA DOR CRÔNICA EM PACIENTES COM CÂNCER AVANÇADO: UMA REVISÃO INTEGRATIVA

# EFFICACY AND SAFETY OF CANNABINOIDS IN THE CONTROL OF CHRONIC PAIN IN PATIENTS WITH ADVANCED CANCER: AN INTEGRATIVE REVIEW

# EFICACIA Y SEGURIDAD DE LOS CANNABINOIDES EN EL CONTROL DEL DOLOR CRÓNICO EN PACIENTES CON CÁNCER AVANZADO: UNA REVISIÓN INTEGRADORA

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**Brenda Dantas de Andrade[1], Joice Rodrigues Rachid Amin[2], Larissa Luppi Monteiro de Barros[3], Guilherme Nogueira Mendes de Oliveira[4]**

## RESUMO

Introdução: Este artigo buscou fazer uma revisão integrativa de estudos clínicos com pacientes com câncer avançado, avaliando a eficácia e a segurança do uso de canabinoides como terapia adjuvante no controle da dor crônica. Métodos: Buscou-se no PubMed, Cochrane e Embase, com os descritores “Cannabinoids”, “Cannabidiol”, “Cannabis” e “Palliative Care”, para avaliar a eficácia e a segurança do uso de canabinoides no tratamento de dor, sendo o principal critério de inclusão ensaios clínicos randomizados. Resultados: 181 artigos foram identificados, triados por título, resumo e leitura completa (n=4), comparando-se, principalmente, intervenção, efeitos colaterais e resultados primários. Discussão: Dos quatro ensaios clínicos analisados, dois deles alcançaram a significância estatística (p=0,014), ao comparar a redução da dor pelo grupo em uso de Nabiximols (THC/CBD) e placebo, enquanto outros dois apresentaram p=0,0854 e p=0,84. Os principais efeitos colaterais citados no estudo foram náuseas e vômitos. Conclusão: Apesar da divergência quanto à significância estatística, todos os estudos sugerem que os Nabiximols apresentam potencial clínico como terapia adjuvante na redução da dor.

**Palavras-chave:** Canabinóides. Dor crônica. Cuidados Paliativos.

[1] Medical from
Federal University of the Jequitinhonha and Mucuri Valleys (UFVJM- JK Campus)
E-mail: brenda.dantas@ufvjm.ed.br
[2] Graduating in Medicine from
Faculty of Mines of Belo Horizonte (FAMINAS-BH)
Email: joicerachid@hotmail.com
[3] Graduating in Medicine from
Federal University of Minas Gerais (UFMG)
E-mail: larissaluppimb@gmail.com
[4] Psychiatrist at
Raul Soares Institute - FHEMIG;
PhD in Neurosciences from UFMG;
Professor at the Faculty of Medicine of UFVJM - JK Campus
E-mail: guilherme.nogueira@ufvjm.edu.br

## ABSTRACT

Introduction: This article aimed to perform an integrative review of clinical studies with patients with advanced cancer, evaluating the efficacy and safety of the use of cannabinoids as adjuvant therapy in the control of chronic pain. Methods: PubMed, Cochrane and Embase were searched, with the descriptors “Cannabinoids”, “Cannabidiol”, “Cannabis” and “Palliative Care”, to evaluate the efficacy and safety of the use of cannabinoids in the treatment of pain, with the main inclusion criterion being randomized clinical trials. Results: 181 articles were identified, screened by title, abstract and full reading (n=4), comparing mainly intervention, side effects and primary results. Discussion: Of the four clinical trials analyzed, two of them reached statistical significance (p=0.014), when comparing the pain reduction by the group using Nabiximols (THC/CBD) and placebo, while the other two presented p=0.0854 and p=0.84. The main side effects cited in the study were nausea and vomiting. Conclusion: Despite the divergence in statistical significance, all studies suggest that Nabiximols have clinical potential as an adjuvant therapy in pain reduction.

**Keywords:** Cannabinoids. Chronic pain. Palliative care.

## RESUMEN

Introducción: Este artículo tuvo como objetivo realizar una revisión integrativa de estudios clínicos con pacientes con cáncer avanzado, evaluando la eficacia y seguridad del uso de cannabinoides como terapia adyuvante en el control del dolor crónico. Métodos: Se realizaron búsquedas en PubMed, Cochrane y Embase, con los descriptores “Cannabinoides”, “Cannabidiol”, “Cannabis” y “Cuidados Paliativos”, para evaluar la eficacia y seguridad del uso de cannabinoides en el tratamiento del dolor, siendo el principal criterio de inclusión los ensayos clínicos aleatorizados. Resultados: Se identificaron 181 artículos, cribado por título, resumen y lectura completa (n=4), comparando principalmente intervención, efectos secundarios y resultados primarios. Discusión: De los cuatro ensayos clínicos analizados, dos de ellos alcanzaron significación estadística (p=0,014), al comparar la reducción del dolor por el grupo que utilizó Nabiximols (THC/CBD) y placebo, mientras que los otros dos presentaron p=0,0854 y p=0,84. Los principales efectos secundarios citados en el estudio fueron náuseas y vómitos. Conclusión: A pesar de la divergencia en la significación estadística, todos los estudios sugieren que Nabiximols tiene potencial clínico como terapia adyuvante para la reducción del dolor.

**Palabras clave:** Cannabinoides. Dolor crónico. Cuidados paliativos.

## INTRODUCTION

Among the various impacts caused by cancer, especially the most advanced, chronic pain is a sad reality and its repercussions go beyond the physical aspect, also compromising the psychological and quality of life of most individuals with the disease. According to Johnson (2013), more than 70% of patients with advanced cancer suffer from significant pain. In this sense, it is worth mentioning that opioid therapy is the main approach in the treatment of pain, but a considerable portion cannot achieve pain control at tolerated doses of this substance and thus requires an alternative therapy. In light of this, cannabinoids are being investigated as potential adjuvant analgesics (Portenoy, 2012).

Many uncertainties still exist about the use of cannabinoids for pain relief. Despite advances in medicine, some patients are refractory to available medication and suffer from a heavy burden of discomfort (Good, 2019). Palliative care aims to improve symptom control and quality of life in end-stage patients and the use of medical cannabis can play an important role in controlling symptoms in these patients (Good, 2019).

In some countries these substances are already legalized for certain health conditions, but there are no concordant recommendations for indications and doses. According to Good (2019), delta-9-tetrahydrocannabinol (THC) is the most promising in pain relief, and also has potential benefits in improving nausea and muscle relaxation. However, one should be aware of possible side effects such as psychosis, sedation and intoxication, with the recommended dose being 2.5 to 40 mg/day. Cannabidiol (CBD) is also a promising active compound in cannabis in palliative care. It has no ability to cause intoxication and in animal models it has shown benefit in controlling anxiety, psychosis, inflammation and epilepsy, in addition to demonstrating neuroprotective effects. In addition, it is able to mediate some adverse psychotropic effects of THC (Good, 2019).

Studies that have analyzed the impact of cannabinoids on the gut microbiota have shown positive effects on the immune system, with decreased inflammation related to these symptoms, through decreased intestinal permeability and control of gut bacteria (Thu, 2024). However, there is little high-quality evidence to guide the use of cannabinoids in clinical practice for specific symptom control in palliative care, and even less evidence to prove a decrease in the total burden of symptoms, which is reported by patients as an improvement in well-being (Gurgenci, 2024).

There are still many uncertainties regarding the ideal product, the dose, the appropriate formulation, the proportions of THC or CBD, the best route of administration, and the clinical areas in which its use is beneficial. Great caution should also be exercised

regarding toxicity and the potential for abuse. However, studies in this area have been advancing and recent reviews have shown significant evidence of the beneficial use of cannabis derivatives for the treatment of some types of chronic pain and spasticity in multiple sclerosis (Good, 2019).

Therefore, this study aims to make an integrative review of clinical studies with patients in palliative care in which the efficacy and safety of the use of cannabinoids in pain control in individuals with advanced cancer were evaluated.

## METHODOLOGY

This integrative review included studies that met the inclusion criteria: (1) randomized controlled trials; (2) use of cannabinoids in pain management in palliative care; (3) efficacy and safety. Secondary endpoints included the evaluation of cannabinoids as adjuvant therapy of patients with advanced cancer. There was no restriction on language or follow-up time. Studies that did not meet the inclusion criteria or did not have relevant outcomes were excluded.

An advanced search was performed in the PubMed, Cochrane Database of Systematic Reviews and Embase databases. The search used health descriptors and their available associated terms: "Cannabinoids", "Cannabidiol", "Cannabis" and "Palliative Care" combined with Boolean operators.

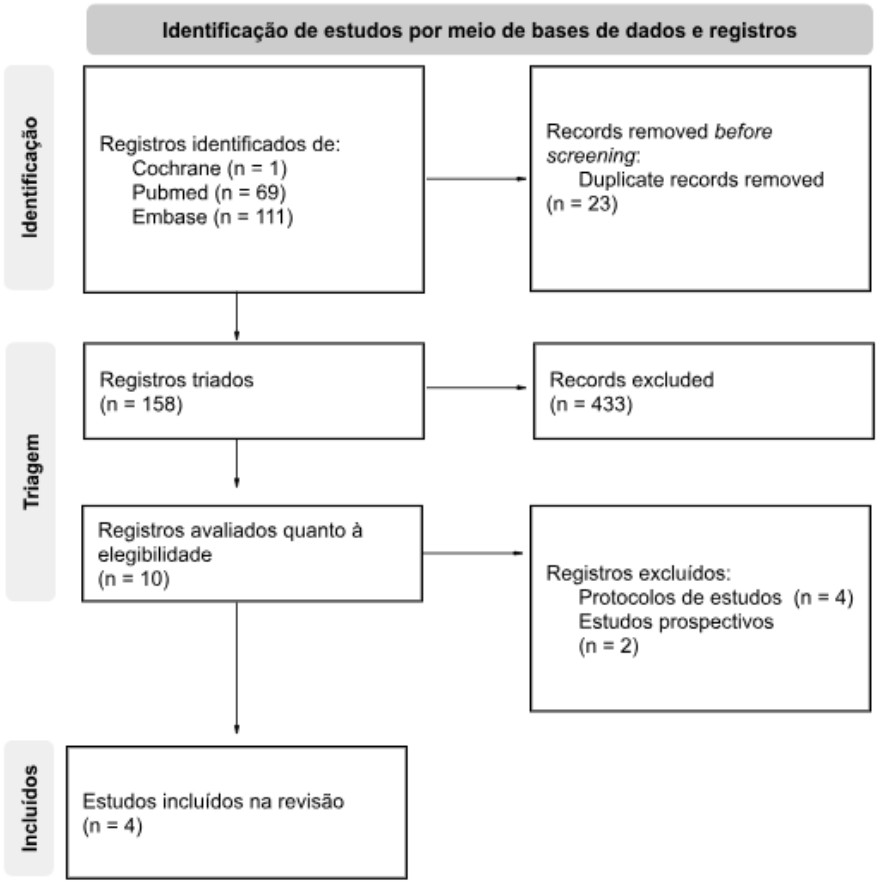
Screening was performed using the inclusion criteria, and studies were selected by title, abstract, and full reading, respectively. The Rayyan website was used for the screening and organization of the studies, ensuring the absence of accounting or selection errors. The process was carried out by two authors, blindly, and discrepancies in any of the selection phases were verified by a third author.

## RESULTS

### SELECTION OF STUDIES

The search resulted in 181 articles, and after the removal of duplicates and the application of the inclusion criteria, 10 articles were selected for full evaluation. We included 4 randomised controlled trials, covering 880 patients with advanced cancer undergoing treatment for chronic pain. The triage flow diagram with more details can be seen in Figure 01.

Figure 1. Triage diagram applying PRISMA 2020 for this review.

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## CHARACTERISTICS OF THE STUDIES

Most of the included studies were in Europe, followed by America and South Africa. The Lichtman study (2018) evaluated 397 patients (45%), which represents most of the patients. Quality of life and pain perception were measured using several questionnaires, but all studies used the Numerical Pain Scale (NRS) in common. In addition, two trials used the Physician's Global Impression of Change (PGIC) in common (Lichtman, 2018; Portenoy, 2012) and two other studies used the Brief Pain Inventory - Reduced Form (BPI-SF) (Johnson, 2013; Portenoy, 2012).

Regarding the intervention, all studies evaluated the effect of Nabiximols, a drug administered through an oral spray at a concentration of 2.7 mg of THC and 2.5 mg of CBD in relation to placebo, while two studies also evaluated the spray of 2.7 mg of THC isolate (Johnson, 2010; Johnson, 2013). Finally, the unanimously reported adverse effects were nausea and vomiting. The main characteristics of the included studies are shown in Table 1.

**Table 1. Studies selected for analysis**

| Author/ year | Type of study | Region and sample | Quality of life and pain questionnaires | Main intervention | Main side effects | Key results |
|---|---|---|---|---|---|---|
| Johnson 2013 | Randomized controlled trial | 21 centres in the UK and one in Belgium; 43 patients | BPI-SF; QLQ-C30; NRS | THC:CBD (2.5mg/2.7mg) (n=13); 2.7 mg THC spray (n=11); or placebo (n=19). | Dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. | The NRS score was statistically significant in favor of THC/CBD spray compared to placebo (p=0.014). There were no significant results in the group treated with THC alone. |
| Johnson 2010 | Randomized controlled trial | 28 European centres; 177 patients | NRS | THC:CBD (2.5mg/2.7mg)(n=60); 2.7 mg THC spray (n=58); or placebo (n=59). | Significant worsening of nausea and vomiting in the THC:CBD group according to QLQ-C30 (p=0.02) | There was a significant difference in the mean NRS score of patients using THC:CBD compared to placebo (p=0.014), but not using THC (p=0.245). |
| Lichtman 2018 | Randomized controlled trial | Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom, and the USA; 397 patients | SGIC; PSQ; PGIC; NRS | Nabiximols (n=199); or placebo (n= 198) | Nausea, dizziness, vomiting, and reduced appetite | There was no significant difference in the mean NRS pain score (p=0.0854), although Nabiximols were superior to placebo on three quality of life instruments. |
| Portenoy 2012 | Randomized controlled trial | North America, Europe, Latin America and South Africa; 263 patients | BPI-SF; EORTC; QLQ-C30; PAC-QoL; MADRS and PGIC; NRS | Nabiximols 4 sprays (n=91); Nabiximols 10 sprays (n=88); Nabiximols 16 sprays (n=90); | Nausea, vomiting, dizziness, and drowsiness | There were no significant differences in pain response between patients receiving nabiximols and placebo (p=0.84), although reported |

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|---|---|---|---|---|---|---|
| | | | | or placebo (n=91). | | analgesia was higher for nabiximols (p=0.035). |

**Legend:** Evaluation of Patient Constipation Quality of Life (PAC-QoL); CBD (cannabidiol); Montgomery-Åsberg Depression Rating Scale (MADRS); Numerical Rating Scale (NRS); Patient Global Impression of Change (PGIC); Global Impression of Change by Subject (SGIC); European Organization for Research and Treatment of Cancer (EORTC); Total Symptom Distress Score (TSDS); Quality of Life Questionnaire (QLQ-C30); Patient Satisfaction Questionnaire (PSQ); THC (delta-9-tetrahydrocannabinol).
**ANDRADE BD et al., 2025**

## DISCUSSION

The studies analyzed reveal valuable information about the efficacy and safety of the use of cannabinoids in the control of chronic pain related to advanced cancer, which did not obtain an important analgesic response upon the administration of opioids in an optimized dose. The main limitations of the studies selected in the present study will also be addressed in this section.

### EFFECTIVENESS

Based on the analysis of the results of the selected clinical trials, the studies by Johnson (2013) and Johnson (2010) demonstrated a significant reduction in pain intensity in patients using THC/CBD (2.5mg/2.7mg), both with a significant difference in the mean NRS score compared to placebo (p=0.014). The same, however, could not be observed in patients who used a spray containing only THC (2.7 mg), compared to the placebo group (p=0.245) (Johnson, 2010).

The primary analysis of data from the research by Lichtman (2018) and Portenoy (2012), who also used Nabiximols (THC/CBD- 2.5mg/2.7mg) as the main intervention, reveals that the difference between the Nabiximols group and the placebo group did not reach statistical significance, with p=0.0854 (Lichtman, 2018) and p=0.84 (Portenoy, 2012). However, the secondary analysis of the results, which mainly take into account the clinical benefits of this complementary therapy, shows that Nabiximols were superior to placebo in three quality of life instruments (Lichtman, 2018) and that reported analgesia was higher for nabiximols (p=0.035), especially when administered at low doses (Portenoy, 2012).

Evidence also suggests the existence of a synergistic effect of THC with opioid receptor agonists in reducing pain (Johnson, 2013; Johnson, 2010), as well as an additional synergy between THC and CBD, in which CBD enhances the analgesic effect of THC and reduces its undesirable side effects, through the antagonism of CB1 receptors (Johnson, 2010).

Thus, this fact indicates that the adjuvant use of Nabiximols in patients with cancer-related pain can provide significant benefits to the treatment of this population (Lichtman, 2018; Johnson, 2013; Portenoy, 2012; Johnson, 2010).

## SECURITY

To evaluate the safety of the use of cannabinoids in the study population, the primary parameter of adverse effects was used, as well as the secondary parameters of tolerability, dropout rates, and deaths during the research.

Common side effects in all four studies were nausea and vomiting. In addition, three of them mentioned dizziness (Lichtman, 2018; Johnson, 2013; Portenoy, 2012) and two pointed to drowsiness as possible consequences (Johnson, 2013; Portenoy, 2012). These events were considered as a probable causal relationship to the medication under study.

Regarding tolerability and dropout rate, in Johnson's 2013 clinical trial, most patients stayed in the study for more than two weeks and only three (7%) dropped out. In the study by Lichtman (2018), dropout rates for reasons other than disease progression were higher in the Nabiximols group, compared to the placebo group (26 versus 22, respectively). In addition, according to Portenoy, 2012, of the patients allocated to the high-dose Naboximol group (16 sprays), 33% were unable to maintain the dose until the end of the study. Thus, in addition to the fact that no significant analgesic effect was observed in this group, this dose was also shown to be poorly tolerated.

Regarding deaths, the following percentages of deaths were recorded, exclusively during the study treatment period: 44.18% (Johnson, 2013), 13% (Johnson, 2010), 13.6% (Lichtman, 2018). However, none of them were attributed to the study medication. Although the study by Portenoy (2012) does not provide numerical data on deaths, he informs that a higher mortality rate was observed in the group of low-dose nabiximols, which is an unexpected finding.

Finally, it is worth noting that, according to Johnson (2010), the combination of THC:CBD showed a more promising efficacy profile than THC alone, supported by evidence of additional synergy between THC and CBD, in which CBD can potentiate the analgesic effect of THC and reduce its undesirable side effects through the antagonism of CB1 receptors, providing a better safety profile for chronic treatment.

## LIMITATIONS

Among the main limitations cited in the research are the possible adjustments in

the dose of opioids performed by patients during the extension of the study, making it difficult to fairly assess the potential opioid-sparing effect after the addition of cannabinoid therapy (Lichtman, 2018; Johnson, 2013; Portenoy, 2012).

The differences in chronic pain treatment approaches between the participating countries (Johnson, 2010) and the difficulty in defining strict eligibility criteria (Lichtman, 2018), important to ensure a good match between patients from different regions, may also have contributed to demographic divergences influencing the results (Lichtman, 2018) and (Johnson, 2010).

In addition, the probable presence of etiological factors associated with advanced malignant disease and the challenges in interpreting the time course and outcomes in a shrinking population may compromise the evaluation of the data (Johnson, 2013).

Finally, possible inaccuracies in the daily information provided by patients (Johnson, 2010) and the limited sensitivity of one or more of the questionnaires used in the surveys (Lichtman, 2018) may have somewhat impaired the interpretation of the results.

## CONCLUSION

Although two of the studies did not reach statistical significance, given the difference between the use of cannabinoids and placebo, all of them reveal that the use of TCH/CBD as an adjuvant therapy in patients with advanced cancer has some clinical efficacy in pain management. Thus, the present review adds to the existing literature by examining the available evidence on the efficacy and safety of the promising use of cannabinoids. However, further studies that mitigate the limitations presented are necessary in order to corroborate the efficacy and safety of the complementary use of this medication.

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