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# Medicinal use of Cannabis in the control of chronic non-cancer pain: a narrative review

## O uso medicinal da *Cannabis* no controle da dor crônica não oncológica: uma revisão narrativa

## *El uso medicinal del Cannabis en el control del dolor crónico no oncológico: una revisión narrativa*

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## Abstract

**Introduction:** The therapeutic use of *Cannabis* has been widely debated worldwide, with growing evidence and regulatory advances. In the context of primary health care (PHC), its use is still underexplored, despite the relevance of chronic pain as a common complaint. **Objectives:** The objective of this study was to analyze the state of the art regarding the medicinal use of *Cannabis* extracts, focusing on their application in chronic pain and the strategic role of the family and community physician in their prescription. **Methods:** This is a narrative literature review based on searches in the PubMed, LILACS, Embase, and SciELO databases. Scientific articles in Portuguese, English, and Spanish were included. **Results:** The studies analyzed show that cannabinoids act on receptors of the endocannabinoid system, modulating pain perception. The most common adverse effects include drowsiness, dry mouth, and mild cognitive changes. There is promising evidence regarding the reduction in the use of opioids and psychotropic drugs in patients who use *Cannabis* therapeutically, although gaps remain regarding its long-term safety and efficacy, especially in the PHC context. **Conclusions:** The literature reviewed suggests that *Cannabis* use may represent a viable therapeutic alternative for managing chronic pain, with the potential to reduce the use of psychotropic drugs. However, specific guidelines, professional training, and further clinical studies in the PHC setting are needed.

**Keywords:** *Cannabis*; Chronic pain; Family practice; Primary health care; Cannabinoids.

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## Resumo

**Introdução:** O uso terapêutico da *Cannabis* tem sido debatido mundialmente, com crescente produção de evidências e avanços regulatórios. No contexto da Atenção Primária à Saúde (APS), seu uso ainda é pouco explorado, apesar da relevância da dor crônica como queixa frequente. **Objetivos:** O objetivo deste estudo foi analisar o estado da arte do uso medicinal de extratos de *Cannabis*, com foco na sua aplicação na dor crônica e no papel estratégico do médico de família e comunidade em sua prescrição. **Métodos:** Trata-se de uma revisão narrativa da literatura, com buscas nas bases United States National Library of Medicine (PubMed), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Embase e Scientific Electronic Library Online (SciELO). Foram incluídos artigos científicos nos idiomas português, inglês e espanhol. **Resultados:** Os estudos analisados mostram que os canabinoides atuam em receptores do sistema endocanabinoide modulando a percepção da dor. Os efeitos adversos mais comuns incluem sonolência, boca seca e alterações cognitivas leves. Há evidências promissoras quanto à redução do uso de opioides e psicofármacos em pacientes que fazem uso terapêutico da *Cannabis*, embora persistam lacunas sobre segurança e eficácia em longo prazo, especialmente no contexto da APS. **Conclusões:** A literatura consultada sugere que o uso da *Cannabis* possa representar uma alternativa terapêutica viável para o manejo da dor crônica, com potencial para reduzir o uso de psicofármacos. Contudo, são necessários diretrizes específicas, capacitação profissional e mais estudos clínicos no âmbito da APS.


**Palavras-chave:** Cannabis; Dor crônica; Medicina Familiar e Comunitária; Cuidados primários de saúde; Canabinoides.


## Resumen

**Introducción:** El uso terapéutico del *Cannabis* ha sido ampliamente debatido a nivel mundial, con creciente producción de evidencia y avances regulatorios. En el contexto de la Atención Primaria de Salud (APS), su uso sigue siendo poco explorado, a pesar de la relevancia del dolor crónico como queja frecuente. **Objetivos:** El objetivo de este estudio fue analizar el estado del arte sobre el uso medicinal de extractos de *Cannabis*, con énfasis en su aplicación en el dolor crónico y el papel estratégico del médico de familia y comunidad en su prescripción. **Métodos:** Se trata de una revisión narrativa de la literatura, basada en búsquedas en las bases de datos PubMed, Lilacs, Embase y SciELO. Se incluyeron artículos científicos en portugués, inglés y español. **Resultados:** Los estudios analizados señalan que los cannabinoides actúan sobre receptores del sistema endocannabinoide, modulando la percepción del dolor. Los efectos adversos más comunes incluyen somnolencia, sequedad bucal y alteraciones cognitivas leves. Existe evidencia prometedora sobre la reducción del uso de opioides y psicofármacos en pacientes que utilizan *Cannabis* con fines terapéuticos, aunque persisten lagunas sobre su seguridad y eficacia a largo plazo, especialmente en el contexto de la APS. **Conclusiones:** La literatura revisada sugiere que el uso del *Cannabis* puede representar una alternativa terapéutica viable para el manejo del dolor crónico, con potencial para reducir el uso de psicofármacos. No obstante, se requieren directrices específicas, formación profesional y más estudios clínicos en el ámbito de la APS.


**Palabras clave:** Cannabis; Dolor crónico; Medicina Familiar y Comunitaria; Atención primaria de salud; Cannabinoides.

# INTRODUCTION

Chronic pain represents a clinical challenge with high prevalence and functional impact, especially in primary health care (PHC), where most cases are managed. Given the limitations of conventional pharmacological therapies and the growing search for therapeutic alternatives, the medicinal use of *Cannabis* has sparked the interest of professionals and patients, boosting scientific production on its potential effects, risks, and benefits.[1-3]

In 1937, the United States passed the Marihuana Tax Act, initiating a context of restrictions on the medicinal and experimental use of *Cannabis*. From then on, authorities began to classify the plant as a prohibited substance. This measure, as expected, made access to consumption more difficult and also hampered the development of scientific studies on the subject.[1-3]

Scientific interest in the substance was renewed in the early 1990s with the description and cloning of specific receptors for cannabinoids in the nervous system, followed by the isolation of endocannabinoids. This initiated a new cycle of research on *Cannabis* derivatives as a therapeutic resource, which resulted in significant growth in the publication of studies and discoveries over the last two decades.[1,3-5]

Currently, the best quality evidence supports the use of cannabinoids for a few conditions, such as chemotherapy-induced nausea and vomiting, specific types of pain, spasticity syndromes, and some forms of childhood epilepsy.[6,7] In clinical practice, this use requires an individualized approach, with continuous

follow-up over weeks. In this context, primary care physicians are best suited to make therapeutic adjustments and closely monitor patients.[8-11]

Pain, understood as a subjective and complex sensory and emotional experience, is one of the main reasons why patients seek medical attention. Chronic pain, in particular—defined as pain that persists for more than three months, continuously or intermittently—has a high prevalence in Brazilians, exceeding the world average. Rates vary between 29.3 and 73.3%, with a higher occurrence in women and older people, especially in the lumbar region.[4,9,11-16]

Pharmacological management of pathological conditions can provide significant improvements, such as reducing pain intensity and increasing functionality. However, for a large proportion of patients with chronic pain, most pharmacological interventions do not promote substantial improvements in quality of life.[9,11-13,15,17]

Recent data indicate an increase in the number of prescriptions for medicinal *Cannabis* in several countries, even in the context of primary health care (PHC), where its use has been associated with a reduction in the consumption of psychotropic drugs and opioids.[9,11] Studies attest that up to 20% of the population served in PHC has already had contact with the substance, and that, of this total, 7% use the plant for medicinal purposes.[18] These data reinforce the ethical need for prescribing physicians in primary care to know the risks and benefits of *Cannabis* use[8,9,11] and to possess the clinical competence to correctly guide patients, based on quality evidence about this therapy. This recommendation is aligned with the World Health Organization's (WHO) Global Patient Safety Action Plan 2021–2030, which aims to improve patient safety by strengthening the monitoring of pharmacological therapies. The plan highlights the importance of involving patients and families as partners in safe care, promoting collaborative and interprofessional work and reinforcing continuing education strategies.[19]

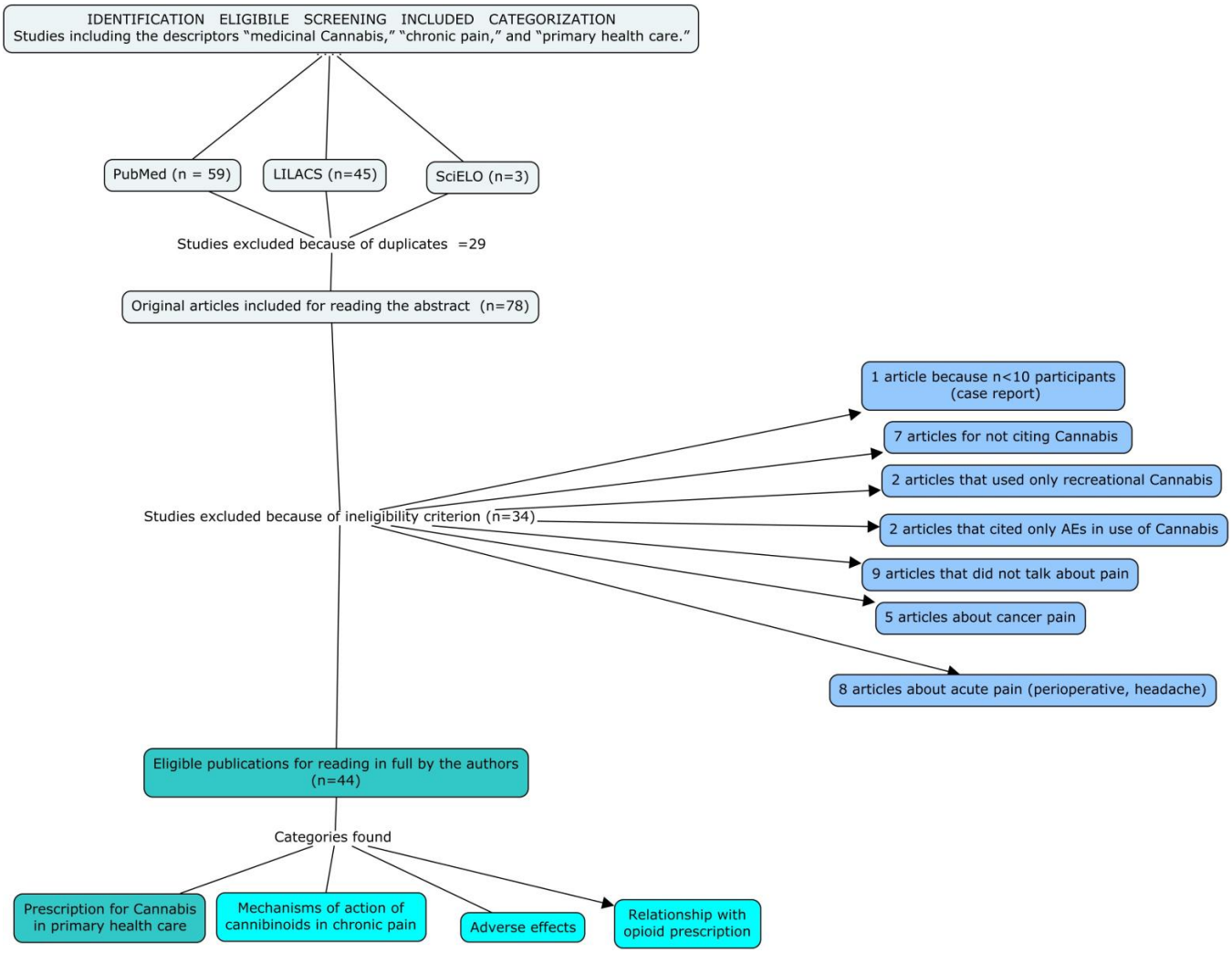
Despite the observed therapeutic potential, controversies still exist regarding the safety of continuous *Cannabis* use, adverse effects (AEs), and methodological limitations of available studies. These gaps reinforce the need to critically investigate the use of *Cannabis* for the management of chronic pain, especially in the clinical practice of family medicine.

In this context, we aimed to review the scientific literature on the implications of the use of medicinal *Cannabis* in the context of non-cancer chronic pain, with an emphasis on its applicability in PHC.

## METHODS

Bibliographic searches were conducted in the following electronic databases: (i) Latin American and Caribbean Literature in Health Sciences (LILACS), (ii) United States National Library of Medicine (PubMed), and (iii) Scientific Electronic Library Online (SciELO). The following descriptors/keywords were used: "Primary Health Care", "Medicinal Cannabis", and "Chronic Pain", combined with the Boolean operators "OR" and/or "AND". The time frame adopted was 20 years, considering the growing interest of the scientific community in the topic and the previous classification of the substance as prohibited, as mentioned in the introduction. Articles published in Portuguese, English, or Spanish that used at least one of these keywords or their combinations were included. Studies that only touched upon the topic, addressed other types of pain, or had samples with fewer than ten participants were excluded. In total, 59 articles were identified in PubMed, 45 in LILACS, and 3 in SciELO, totaling 107 publications.

After the initial search, the articles were selected by content, as summarized in the diagram in Figure 1 below, which was later updated with the Embase database:




AEs: adverse effects.

**Figure 1.** Flowchart of the selection process for the articles included in the review.

## RESULTS AND DISCUSSION

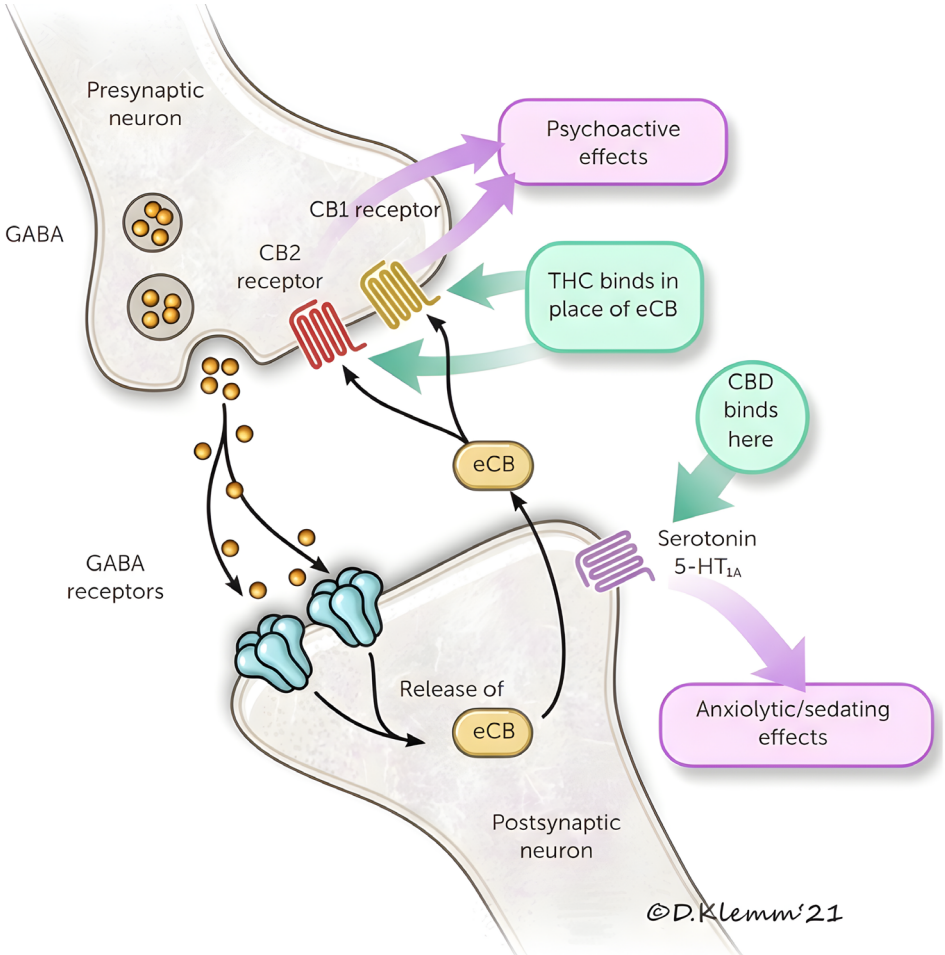
### Mechanisms of action of cannabinoids in chronic pain

To understand the action of cannabinoids in chronic pain, it is necessary to contextualize that nociception represents only one component of the pain experience. The painful stimulus transmitted to the central pathways is modulated in a complex way by the spinal cord, supramedullary centers, and the brain itself. Thus, the experience of pain is constructed not only by physical stimuli, but also by contexts, memories, and genetic factors, which makes the response to stimuli an individual experience.[13,20]

For this reason, many of the therapeutic approaches recommended for the treatment of peripheral neuropathic pain act by reducing the firing caused by ectopic neural discharges. Initially, nociceptors can be sensitized by inflammatory processes resulting from nerve damage, and as a consequence, peripheral nerve fibers begin to develop patterns of ectopic neuronal discharge.

Studies have investigated whether early initiation of treatment with cannabinoids, immediately after the initial insult, can limit the development of chronic hypersensitivity. The proposal is that this early intervention acts by blocking the propagation of peripheral ectopic impulses to the central nervous system (CNS), thus reducing the risk of pain chronification.[21]

In human physiology, two main endocannabinoids—anandamide and 2-arachidonoylglycerol—bind to receptors of the endocannabinoid system (ECS), as shown in Figure 2. In these neural pathways, gamma-aminobutyric acid (GABA) and glutamate act as inhibitory and excitatory neurotransmitters, respectively.[6,8,12,13] It is observed that tetrahydrocannabinol (THC) stimulates CB1 and CB2 receptors in the central nervous system, as do endocannabinoids. Cannabidiol (CBD), on the other hand, stimulates 5-HT1A serotonin receptors and promotes negative modulation of CB1 receptors.[8,12,13,22]




CB: cannabinoid, CBD: canabidiol, eCB: endocannabinoids, GABA: gamma-aminobutyric acid, THC: tetrahydrocannabinol.
Source: Sazegar.[6]

**Figure 2.** Mechanism of action of cannabinoids on the CB1 receptor. Neurophysiology of CB2 receptor action is not well characterized.

ECS acts in pain control through neurotransmitters that block nociception associated with chronic pain. In addition, it exerts an anti-inflammatory effect through immunomodulation mediated by CB2 receptors.[13,23]

Currently, other central and peripheral pathways involved in pain inhibition are recognized, in addition to the ECS receptors, also stimulated by cannabinoids. These include CGRP receptors, opioid and serotonergic (5-HT) receptors, nuclear receptors, and transient receptor potential (TRP) channels, among others.[24]

Based on this, Vučković et al.,[24] in 2018, stated that “the mechanisms of the analgesic effect of cannabinoids include the inhibition of neurotransmitter and neuropeptide release from presynaptic nerve terminals, modulation of postsynaptic neuron excitability, activation of descending inhibitory pain pathways, and reduction of neurogenic inflammation [...]”.

CB1 receptors are present in areas of the brain responsible for regulating appetite, memory, fear, and motor responses. They are also found in peripheral regions, such as the gastrointestinal tract, adipocytes, liver, and skeletal muscle.[8,23] CB2 receptors, on the other hand, are mainly expressed in macrophages and other cells derived from the immune system.[8,13]

In addition to the interaction of cannabinoids with the human endocannabinoid system (ECS), studies have also investigated their potential to reduce emotional stress, fatigue, and other components associated with chronic pain, as well as to modify pain perception.[8] These investigations are aligned with the expansion of the definition of pain, which now includes subjective aspects. This expansion is justified when considering quality of life and the personal experience of pain as therapeutic targets.[11,13,17,20,25]

## Adverse effects of therapy

AEs related to *Cannabis* use can be acute, mainly associated with its psychoactive properties. These include *Cannabis* hyperemesis syndrome, dizziness, anxiety, sedation, disorientation, and confusion.[4,7,8,23] Short-term impairments in memory, judgment, and motor coordination have also been reported.[4,6,9]

In the long term, AEs may include the precipitation of psychiatric disorders, although to a lesser extent than with recreational use. The substance has been associated with triggering episodes of anxiety, depression, and psychosis, as well as exacerbating schizophrenia in people with genetic vulnerability.[6,8]

However, it is difficult to establish a direct causal relationship between cannabis use and the development of these diseases, due to the presence of several confounding factors. For example, individuals who already experience symptoms such as anxiety or stress may be more prone to using the substance.[6,8]

The National Institute for Health and Care Excellence (NICE), the American Psychological Association (APA), the American Medical Association (AMA), and the American Society of Addiction Medicine (ASAM) do not recommend the use of medicinal *Cannabis* for the treatment of chronic pain, considering the AEs of *Cannabis* a significant obstacle to its therapeutic indication.[26,27]

Therefore, some institutions, such as the United States Preventive Services Task Force, recommend risk screening in patients considered for *Cannabis* therapy, taking into account factors such as the risk of abuse of other drugs, the presence of previous clinical or psychiatric illnesses, the possibility of non-adherence to treatment, and legal risks.[27,28] However, the American Academy of Family Physicians does not support this recommendation, claiming a lack of evidence of benefit, except for cases of opioid use disorder.[22]

## Main evidence

Overall, the findings of the 44 studies analyzed show limitations regarding the level of recommendation, due to the methodological weaknesses of the studies, which is related to the previously mentioned history of prohibition.[4,8]

Nevertheless, based on the available evidence, treatment with *Cannabis* can be considered an adjunctive therapy in selected cases, but not as a first-line treatment for any chronic pain condition.[26,28,29]

Among the 44 studies, 15 presented negative recommendations in their conclusions, 20 showed positive recommendations, and nine did not declare a favorable or unfavorable position regarding the use of *Cannabis*.

During the review of the articles, the following categories were identified: *Cannabis* prescription in primary care, mechanisms of action of cannabinoids in chronic pain, AEs of the therapy, and the relationship between *Cannabis* use and the prescription of analgesic psychotropic drugs, especially opioids.

Chart 1 summarizes the main studies that presented evidence on the alteration of pain perception and/or on the most frequently identified AEs. Studies that only addressed the historical context of the drug, the pathophysiology of pain and its broader context, or the relevance of the topic for PHC were excluded.

## Relationship between *cannabis* and the prescription of analgesic psychotropic drugs (mainly opioids)

One benefit highlighted in 14 articles is the possible reduction in the use of other chemical substances for pain control when *Cannabis* is prescribed, especially due to a decrease in opioid prescriptions.[8,25,38] It is believed that *Cannabis* may represent an alternative to opioids,[8,27] considering the differences in the potential for overdose between the two,[39] as well as the lower rate of addiction and dependence associated with cannabinoids—a factor that varies according to the patient's age. It is estimated that the potential for dependence on cannabinoids is comparable to that of caffeine and lower than that of alcohol.[28]

Generally, studies that reveal some benefit from the use of medicinal *Cannabis* for chronic non-cancer neuropathic pain demonstrate that cannabinoids increase the chances of a 30% or greater reduction in pain scores compared to placebo. This effect is dose-dependent in relation to THC and varies according to the route of administration, with inhalation (vaporized) being the most potent.[8,26]

However, it is important to consider the existence of various AEs, both immediate and long-term, in addition to the scarcity of robust studies that reliably support the efficacy of this therapy.

## Prescribing *Cannabis* in primary care

Given the uncertainties regarding the real benefit of cannabis in the treatment of chronic pain, eight studies suggested that its prescription should only be carried out by pain specialists with experience in the therapeutic use of the substance.[12,29] However, recent research conducted in Canada revealed that 62.7% of patients who use medicinal *Cannabis* obtain it through primary care physicians, and that 71.2% of secondary care professionals who prescribe *Cannabis* are not involved in the patients' other medical care.[38]

These data underscore the need to expand the training of PHC professionals on this topic. Among the desired competencies, the ability to monitor the health consequences of medical *Cannabis* use is highlighted, considering its pharmacological properties and potential drug interactions.[6,8,34]

Furthermore, it is known that most patients with chronic pain are treated in PHC. However, many professionals in this area receive insufficient training in pain management and feel unprepared to deal with the complexities involved in the care of these patients.[35] It is important to highlight that, with the advancement of training for PHC professionals and the expansion of interdisciplinary care, family and

**Chart 1.** Table of evidence.

| Study ID | Substance used | Follow-up time | Main findings | Adverse effects (AEs) |
|---|---|---|---|---|
| Casarett DJ et al.[30] | THC>50% vaporized | <1 day | Increasing the proportion of THC increased the pain response from 19.3 to 51.3%. | Increased anxiety and euphoria can generate a placebo effect on pain. |
| Fanelli G et al.[31] | Oil extract with 22% THC | 1 year | 64.7% reported improvement associated with the therapy. | No serious side effects were observed (however, 14.7% discontinued therapy because of AEs). |
| McDonagh MS et al.[32] | Synthetic products with >98% THC | 1 to 12 months | Moderate improvement in pain intensity on a scale of 0 to 10. | Increased risk of sedation, dizziness, and moderate risk of nausea. |
| Reynolds IR et al.[33] | Edible and smoked *Cannabis* (in older adults, >65 years) | 3 years | 83% reported that *Cannabis* helped reduce their pain. | 16% experienced AEs (loss of balance, blurred vision, dry mouth, anxiety, and racing thoughts). |
| Notcutt WG et al.[7] | Oral spray with 2.7 mg THC and 2.5 mg CBD | 30 months | Improved pain management, reduced need for medical care, increased quality of life, and improved sleep. | No significant AEs were reported. |
| STE-MARIE PA et al.[34] | Nabilone and Dronabinol | 5 years | The study did not find any correlation with effects on the pain scale. | There was no statistically significant difference in suicide attempts and suicidal ideation between the placebo and control groups in patients with fibromyalgia. |
| Aviram J et al.[3] | Variable | Variable | n=1,334 patients. There was a 30-50% reduction in pain and a 2-point reduction on the visual analog scale. | Related to the nervous, central and gastrointestinal systems. |
| Becker WC et al.[35] | Oral spray with 2.7 mg THC and 2.5 mg CBD and *Cannabis* smoked | Up to 15 weeks | There was a modest efficacy of medicinal cannabinoids on chronic neuropathic pain. | Mild AEs were common. |
| Peterson AM et al.[17] | Products with a variable percentage of THC | 8 weeks | Significant improvement in pain scores and quality of life. | Not related. |
| Haroutounian S et al.[15] | A THC/CBD mixture was Smoked or taken orally. | 6 months | Improvement in pain symptom score, severity score, most social and emotional disability scores, as well as a decrease in opioid consumption. | Two cases (<1%) of serious AEs were reported (elevated transaminases and an older patient with decreased level of consciousness), and 9 mild AEs, leading to discontinuation of treatment. |
| Nugent SM et al.[36] | Preparations based on the plant or extracts of whole plants, such as nabiximols. | Review conducted at variable times. | There is weak evidence that *Cannabis* relieves neuropathic pain, but insufficient evidence in other pain populations. | Limited evidence suggests that *Cannabis* is associated with an increased risk of adverse mental health effects, as well as an increased risk of motor vehicle accidents and short-term cognitive impairment. Pulmonary effects have not been observed in younger populations. |
| Gulbransen G et al.[37] | CBD at a daily dose ranging from 40 to 300 mg/day. | 3 weeks | There may be analgesic and anxiolytic benefits of CBD in patients with non-cancer chronic pain. | There were no significant AEs. |

community physicians (FCPs) occupy a strategic position to offer biopsychosocial and institutional support to people with chronic pain, aligned with the principles of PHC.[35] In this context, family and community medicine, because of its principles and integration to PHC, plays a strategic role in democratizing access to medicinal *Cannabis* and overcoming historical prejudices related to the plant.[40]

### Perspectives, recommendations, and limitations of the study

It is recommended to individualize the patient's assessment before considering the prescription of medicinal *Cannabis*. In particular, a personal or family history of psychotic disorders should be considered, as there is an increased risk of precipitating psychotic episodes with the use of the substance.[6,8,34]

Prescription should also be avoided in pregnant and breastfeeding women, given the lack of studies that rule out possible risks to pregnancy or the baby's health.[22]

Physicians should remain attentive to negative psychosocial associations, especially given the increase in recreational use of the substance. It is necessary to consider the possibility that some patients may present diagnoses dishonestly to justify the use of medicinal *Cannabis*.[35]

Some authors suggest that cannabinoids should only be considered as a third-line option in the treatment of neuropathic pain, and only when the potential benefits outweigh the risks.[8,22]

Another limitation of studies on the effects of *Cannabis*-based medications stems from global anti-smoking and anti-drug strategies. This issue is particularly relevant considering the drug development process, which typically progresses in phases: phase I (tolerability and safety in healthy/stable volunteers); phase II (pharmacokinetics and initial efficacy in the target population); and phase III (large-scale randomized, multicenter studies to confirm efficacy and safety before approval). However, until these issues are resolved, large-scale phase III studies with *Cannabis*-based medications are unfeasible. This has led to, in some cases, a jump from phase II trials directly to phase IV trials, which already evaluate new indications, pharmacovigilance, and real-world studies.[4] A lack of follow-up of patients regarding the implications of therapy over years of use has also been observed, which could be the subject of future studies, along with research on the integral use of the plant in chronic pain (entourage effect) — in which the synergistic interaction between the various compounds of *Cannabis* (cannabinoids, terpenes, flavonoids, etc.) potentiates the therapeutic effects and modulates the secondary effects.

It is important to acknowledge the limitations of this study, especially the non-inclusion of databases such as Web of Science, Scopus, and Science Direct in the bibliographic search, which may have restricted the scope of the reviewed literature.

Finally, it should be emphasized that, to date, there are no well-established clinical guidelines that address the use of *Cannabis*-based medications and discuss, in depth, the risks and benefits of their use in the treatment of non-cancer chronic pain.[9,37]

## CONCLUSION

The evidence supporting the prescription of medicinal *Cannabis* is still of low quality, lacking new studies with longer follow-up periods, especially in vulnerable populations, which remain underrepresented.

Despite this, cannabis has shown usefulness in reducing self-reported chronic non-cancer pain in many patients, which justifies its use as an adjuvant therapy in selected cases.

AEs related to cannabis should be carefully considered and properly communicated to patients by health care professionals at the time of prescription.

It is essential to expand the training of primary care professionals on the therapeutic use of *Cannabis*, especially given the high prevalence of chronic pain and the increasing demand for this therapy in PHC services.

To increase the safety of prescriptions—not only of *Cannabis*-based medications, but of all therapeutic classes used in primary care—it is recommended, in line with the WHO Global Patient Safety Action Plan 2021–2030, to strengthen the training of family physicians. This training should include aspects such as monitoring the therapeutic response, preventing the misuse of medications, monitoring for possible drug interactions, and promoting the safe and rational use of drugs.

## CONFLICT OF INTERESTS

Nothing to declare.

## AUTHORS' CONTRIBUTIONS

RERA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. MGMS: Investigation, Methodology, Supervision, Visualization, Writing – review & editing. VRB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft.

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