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# Cannabis and Cannabinoids

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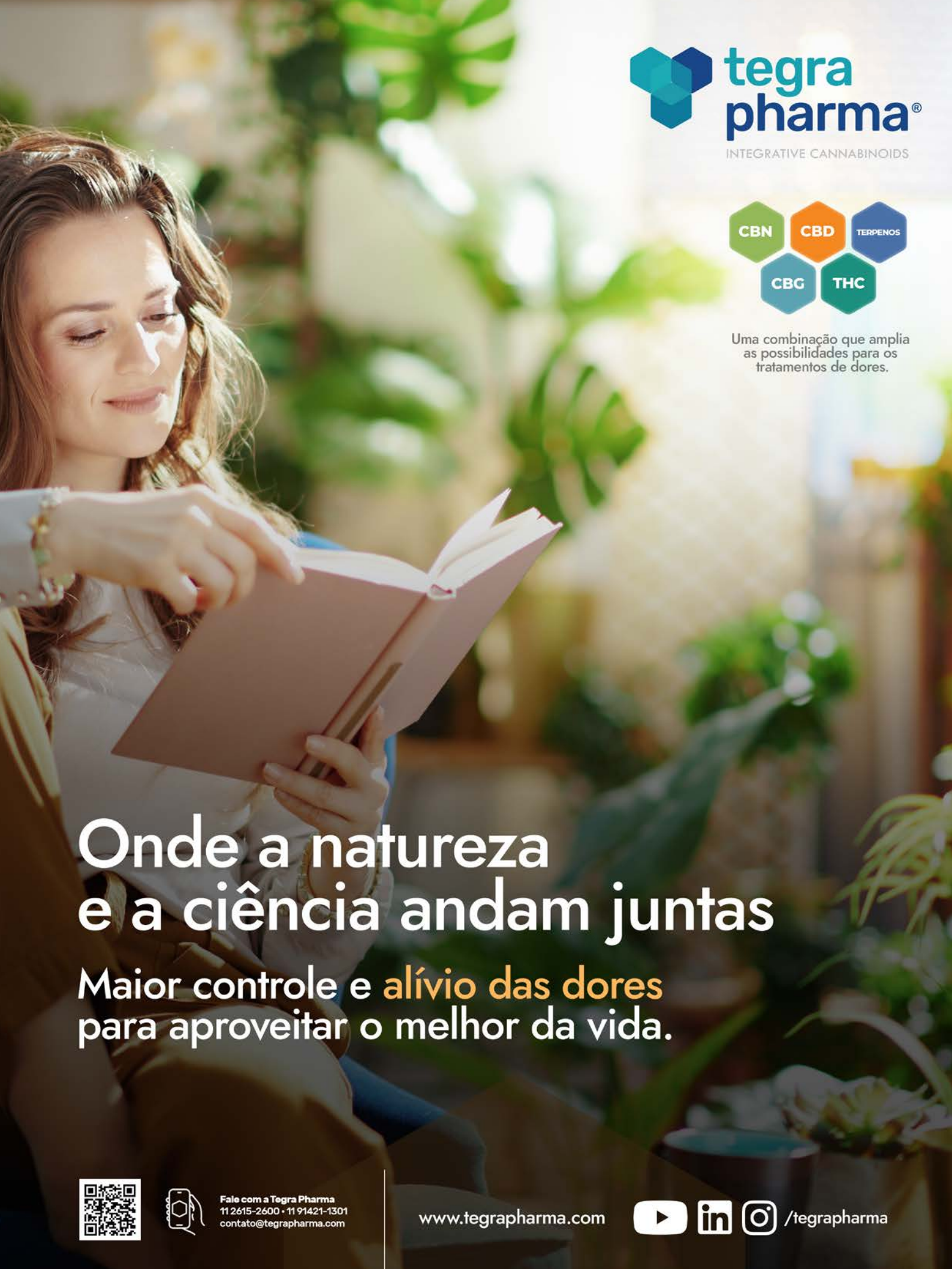
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# BrJP
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EDITORIAL

# Cannabinoids and the new horizons in the treatment of pain phenomenon

*Canabinoides e os novos horizontes no tratamento do fenômeno doloroso*

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Although the use and clinical practice are old around the cannabis plant, medicinal treatment has only recently achieved a prominent place by isolating the most important components of the plant and used as treatment products from the discovery of the endocannabinoid system.

Due to the scarcity of scientific evidence with relevance, we look forward to more publications and safe therapeutic combinations around this topic. Cannabinoid medicine is a reality in the current world context for various treatments, it is time to reflect and seek new treatment options, although many questions remain unanswered or are not ready by the scientific community, such as lack of relevant pain models, evaluation strategies limited by laws, differences between laboratory animals and humans, failures to perform analysis and interpretation of clinical trials, pharmacodynamics and pharmacokinetics of each of the cannabinoids, among other factors.

Probably, the most appropriate strategy is to perform reverse translational reasoning, verifying the occurrences with patients in daily clinical practice and, then, proposing pain models and evaluation methods consistent with the problem. On the other hand, we know that clinical decision-making must be based on randomized controlled trials and systematic reviews that drive experts to make decisions[1]. The road is long, but it is already being trodden.

I believe that this special issue of the Brazilian Journal of Pain on cannabinoids should have a strong cultural and political impact, in addition to the clinical relevance around "Cannabis" in the current Brazilian scenario, eager for information, contributing to a new reassessment of the current prohibitionist policies developed around the cannabis issue.

This is a huge responsibility, from a proposal made by professor Irimar de Paula Posso to the *Sociedade Brasileira para o Estudo da Dor* (SBED) Cannabis Committee in the previous administration. That's how it all started and, from paper, it became a reality. Embracing the cause, our current president Dr. José Oswaldo de Oliveira Jr continued with the efforts to publish one of the most controversial topics of our time. With a hard work of editing by the entire editorial board of SBED, especially by our Editor-in-Chief Dr. Josimari Melo DeSantana and extreme dedication of the authors regarding the themes entrusted to them.

In this supplement, we will provide a reliable source of information and updating for healthcare professionals and researchers in basic and clinical science and to everyone who is interested in the topic.

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# Painful behavior and medicinal cannabis

*Comportamento doloroso e cannabis medicinal*

Eduardo Aliende Perin[1], César Augusto de Paula Santos[2]

DOI 10.5935/2595-0118.20230006-en


## ABSTRACT

**BACKGKROUND AND OBJECTIVES**: Pain is defined as a complex sensory and emotional experience, and it is one of the most common causes for seeking health care, being the chronic pain one of the most prevalent health conditions in the world today, with millions of people debilitated by symptomatic conditions. The discovery of the endocannabinoid system and its organic effects on pain modulation, especially chronic pain, represented an unknown source of possibilities for the production of drugs that, theoretically, would have great potential to improve the quality of life of individuals with chronic pain. Given this, the general objective of this work was to search the literature for studies that investigated the use of medicinal cannabinoids for the treatment of chronic pain and pain behavior.
**CONTENTS**: This is a narrative review of the literature in which aspects of painful behavior are presented, such as cognitive distortions associated with the experience of pain, and the influence of trauma, stress and psychiatric comorbidities on pain outcomes. The endocannabinoid system influences the modulation of all these points and also the regulation of pain itself.
**CONCLUSION**: This study provides perspectives on painful behavior and how the endocannabinoid system can interfere with different aspects of pain and with the way the patient perceives pain. Further studies on this issue are extremely important.

**Keywords**: Cannabis, Chronic pain, Pain.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A dor é definida como uma experiência sensitiva e emocional complexa, e está entre as principais causas de busca por atendimento médico, sendo a dor crônica um dos problemas de saúde mais prevalentes no mundo atual, com milhões de pessoas debilitadas por condições sintomáticas. A descoberta do sistema endocanabinoide e seus efeitos orgânicos na modulação da dor, especialmente a crônica, representou uma fonte desconhecida de possibilidades para a produção de fármacos que, teoricamente, possuiriam grande potencial de melhorar a qualidade de vida de indivíduos portadores de dor crônica. Diante disso, o objetivo geral deste trabalho foi buscar na literatura estudos que investigaram o uso de canabinoides medicinais para o tratamento da dor crônica e do comportamento doloroso.
**CONTEÚDO**: Trata-se de um estudo de revisão narrativa da literatura em que são apresentados aspectos do comportamento doloroso, como as distorções cognitivas associadas à experiência de dor, e a influência do trauma, do estresse e de comorbidades psiquiátricas nos desfechos de dor. O sistema endocanabinoide tem influência na modulação de todos esses pontos e também na própria regulação da dor.
**CONCLUSÃO**: Este estudo traz perspectivas sobre o comportamento doloroso e de como o sistema endocanabinoide pode interferir em diversos aspectos da dor e da forma como o paciente percebe a dor. Mais estudos sobre o assunto são de extrema relevância.

**Descritores**: Cannabis, Dor, Dor crônica.

## INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1]. According to the IASP, "pain is always a personal experience influenced by various degrees of biological, psychological and social factors"[2]. Pain is among the main causes for seeking medical care, and chronic pain (CP) is one of the most prevalent health problems in the world today, with millions of people debilitated by symptomatic conditions[3].
The pharmacological therapy for CP proposed by the World Health Organization (WHO) includes the use of analgesics, anti-inflammatory drugs, adjuvant drugs, and opioids, which aim to act in nociceptive and mixed pain[4]. Opioids are considered excellent analgesics; however, their continuous use may present a high risk of tolerance, with the need for increasingly higher doses, which, in fact, increases the risk of adverse effects, use of high doses, and chemical dependence. Thus, seeking new pharmacological alternatives for the treatment of CP is necessary[5].

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**HIGHLIGHTS**
- Compounds formed in the cannabis secondary metabolism exhibit pharmacological properties of obvious interest.
- Specific errors called cognitive distortions were identified, such as selective abstraction, overgeneralization, personalization, and catastrophizing.
- Association between psychological factors, sleep, central sensitization, pain, and chronic neck, back, limb, and multiregional impairment.

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The discovery of the endocannabinoid system and its organic effects on pain modulation, especially chronic pain, represented an unknown source of possibilities for the production of drugs that, theoretically, would have great potential to improve the quality of life of individuals with CP[6].

Cannabis flowers are a fundamental raw material for the manufacture of the most diverse extracts known today. Several compounds formed in the secondary metabolism of cannabis have pharmacological properties of evident interest, notably the cannabinoids, especially tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), which, when converted into their neutral forms, tetrahydrocannabinol (THC) and cannabidiol (CBD), have paradoxical pharmacological effects on central nervous system (CNS)[8]. THC is psychoactive with euphoria properties, besides having antiemetic and analgesic effects, while CBD is depressant, with anticonvulsant and anxiolytic properties, with antipsychotic and anti-inflammatory effects[9].

The discovery of the cannabinoid receptors CB1 and CB2 guided the first researches on the subject, CB1 being well distributed in the CNS, which, in the presence of THC, leads to the inhibition of neurotransmitters, and can modulate pain pathways[10]. CB2 receptors also participate in the pain response, mainly by modulating dopamine release[11].

In fact, scientific research with cannabis provides evidence supporting its medicinal properties, therapeutic use in CP being one of them. Considering the growing incidence of problems associated with chronic pain and the need for the use of alternative therapies, understanding the aspects involved in the use of medicinal cannabis for pain treatment becomes something relevant. Given this, the general objective of this work was to search the literature for studies that addressed behavioral and cognitive aspects associated with CP and the use of medical cannabis.

## CONTENTS

### Pathological cognitions in pain

One aspect of pathological cognitions that has been extensively investigated in chronic pain is the field of cognitive distortions. The concept of cognitive distortion is borrowed from cognitive models of depression[12,13] and collectively refers to errors in the logic of interpreting situations. Beck et al. (1967) identified several specific errors called cognitive distortions, such as (1) selective abstraction – focusing on the negative aspects of an experience; (2) overgeneralization – assuming that the negative consequences of an experience apply to similar events in the future; (3) personalization – seeing oneself as personally responsible for negative situations; and (4) catastrophizing – expecting that the worst possible outcome will occur[13]. Catastrophizing, in particular, has been widely studied in chronic pain and it seems to imply not exactly the intensity of pain, but the degree of suffering and physical and mental disability imposed by pain[14].

The association of psychological factors with chronic low back pain was as–essed by a cross-sectional study of 472 participants. Of these, 125 participants had severe low back pain. Patients with catastrophizing cognitions had 2.21 (95% confidence interval = 1.30 – 3.77) greater odds of having severe pain and 2.72 times (CI = 1.75 – 4.23) greater odds of having severe functional limitation than patients without catastrophizing symptoms. Patients with maladaptive beliefs regarding rest were 2.75 (CI = 1.37 – 5.52) times more likely to have severe pain and 1.72 (CI = 1.04 – 2.83) times more likely to have severe functional limitation. Patients with movement phobia were 3.34 (CI = 1.36 – 8.24) times more likely to have severe pain and patients with social isolation were 1.98 (CI = 1.25 – 3.14) times more likely to have severe functional limitation[15].

The endogenous pain modulation assessed in humans by a protocol called Conditioned Pain Modulation (CPM) and catastrophizing were associated with the incidence and severity of acute pain after orthognathic surgery. The weaker the CPM and higher the levels of catastrophizing, higher the incidence and severity of acute postoperative pain[16].

A cross-sectional study of 172 orthopedic patients with foot and ankle CP (64% female, mean age 60.9 years, and mean body mass index – BMI – of 27.6 kg/m2) found a prevalence of depressive symptoms in 48%, central sensitization (CS) in 38%, and pain catastrophizing in 24% of cases. Interestingly, age, gender, and BMI accounted for 12% of the variance in pain scores, while psychological variables accounted for 28.2%. Catastrophizing was the largest independent predictor of pain severity, accounting for 14.4% of the variance, followed by BMI (10.7%) and depressive symptoms (2.3%)[17].

In a clinical trial, 78 patients (56 women) with CP had acceptance and commitment therapy (ACT) sessions, and before and after each session blood samples were collected and analyzed for interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF--alpha) levels. Pain interference and psychological inflexibility improved significantly during treatment, while pain intensity did not change. Psychological flexibility refers to the ability of individuals to engage in activities in spite of pain or distress, and therefore does not measure pain intensity, but rather reflects the interference of pain with daily life activities activities. IL-6 and TNF-alpha levels did not change with the course of treatment. Mean baseline levels of IL-6 and TNF-alpha weighted the improvement in psychological inflexibility during the course of treatment, but did not moderate changes in pain interference or pain intensity. In other words, basal inflammation level may be inversely proportional to greater psychological inflexibility, and probably also to low levels of inflammation would underlie variability in CP behavioral treatment[18]. Along this same line, another recent study of individuals with fibromyalgia who participated in a mindfulness-based stress reduction (MBSR) program, and showed that higher levels of pro and anti-inflammatory cytokines (IL-6/IL-10) were associated with lower improvements in psychological inflexibility during treatment[19].

### Trauma, stress and psychiatric comorbidities

Symptoms of depression, anxiety, and stress have a significant influence on musculoskeletal pain. Behavioral modification techniques are effective in managing these variables. A systematic review with meta-analysis that included 41 randomized

controlled trials evaluated the effectiveness of telematic behavioral modification techniques (e-BMT) for those psychological variables in patients with musculoskeletal CP. E-BMT achieved relevance, albeit with small effect size for depressive symptoms, and small to moderate effect size for anxiety in this population population, but was not effective for stress symptoms, with moderate level of evidence, perhaps due to the heterogeneity of stress measures, as well as traumatic situations within this population[20].

There is substantial evidence, primarily derived from cross-sectional studies, that women who have experienced intimate partner violence (IPV – both physical, sexual, psychological, and through controlling behaviors) have worse physical and mental health than those who have not[22,23] and that IPV among women is associated with a wide range of health problems, such as head trauma, convulsions, arthritis, migraine, CP, cardiovascular disease, chronic pelvic inflammatory disease, functional gastrointestinal disorders such as irritable bowel syndrome, suicidality, anxiety, and depression[21,23,24].

Violence affects health through physical injury, health risk behaviors initiated or escalated by managing emotions, or violence-related stress[25], in addition to the overload of activation of the hypothalamic-pituitary-adrenal (HPA) axis from chronic stress that causes physiological reactions (e.g., inflammatory, neuroendocrine, immunological) related to the development of chronic diseases such as depression, post-traumatic stress disorder (PTSD), and CP[26,27]. Improvement in the mental health of these women generally depends on the reduction or cessation of violence[28-30], with the greatest level of improvement soon after the violence has ended[31]. However, women may not fully recover their mental health[22,30,32,33]. In addition, the type and severity of abuse can impact these women's recovery[34-36].

A longitudinal study in Canada explored over four years the changes in women's mental health after separation from an abusive partner. Results showed that women improved their quality of life after separation, but remained with high levels of depression, PTSD symptoms, and disabling CP over the four-year follow-up. More severe abuse was associated with higher depression, PTSD, and CP scores unrelated to time elapsed after separation. The type and severity of abuse had a strong effect on these health outcomes over time, suggesting the existence of cumulative effects of abuse on health, resulting in long-term problems[37].

The association between psychological factors, sleep, central sensitization (CS), pain, and chronic neck, back, limb, and multiregional impairment was assessed in a survey with an online questionnaire applied to 1730 adolescents. CS can be defined as a state of increased responsiveness of nociceptive neurons in CNS, leading to a reduction in the activation threshold of these cells[38]. In addition, an amplification in pain processing due to an imbalance between inhibitory and facilitatory mechanisms may be present[39,40]. In this study, CS symptoms increased the chances of pain in the neck, back, and different regions. Depression, anxiety, and stress, as well as lack of physical activity, increased the chances of multiregional pain. Fear of moving increased levels of limb pain. A worse quality of sleep was associated with neck and upper limb impairment as well as multiregional pain. Fear of moving and CS symptoms were associated with multiregional pain and impairment[41].

There is substantial evidence that inadequate pain management in children is associated with neurological and behavioral problems, including increased pain sensitivity throughout life[42]. For example, children with sickle cell disease who have a high frequency of vasocclusive episodes are more likely to have a highly painful response during venipuncture[43]. Children with cancer, sickle cell disease, and other hematologic diseases undergo routine invasive procedures over months or years, and not surprisingly, pain caused by these diagnostic or therapeutic procedures is one of the most commonly reported physical complaints of children with cancer[44].

Sedation or analgesia can be used for pain control, although the risks of sedation, including hypoxia, outweigh the benefit in routine procedures. Therefore, identifying non-pharmacological interventions for pain management, such as distraction, which shifts the focus of attention from pain to pleasurable objects, images, or videos, may reduce the risks of neurological and behavioral problems[45,46].

Audio guided imagery (GI) and a 3D game in which children can be active players or simply watch passively (virtual reality – VR) were compared as distraction strategies in a randomized controlled crossover clinical trial in individuals aged 8 to 25 years (n=50) with hematologic or oncologic diseases and indication for blood or marrow transplantation, not sedated, and who would undergo an invasive procedure such as venipuncture. Those who had high catastrophizing scores reported less nervousness during the procedure with VR than with GI. State anxiety decreased between pre and post-intervention in VR group. Those with high trait anxiety had less pain during GI. In other words, children who had been scarred by stories and beliefs about pain had better response to VR, while those who had high baseline anxiety levels (trait anxiety) had better response with GI. The GI started with diaphragmatic breathing exercises, while VR did not, which may have contributed more to the individuals who already had higher trait anxiety[47].

## CONCLUSION

The behavior and cognitions associated with CP, especially catastrophizing, psychiatric comorbidities, obesity, as well as stress and activation of the HPA axis have substantial influence on the intensity of referred pain and especially on the degree of patient's functional disability.

No single treatment is able to modify so many variables, such as pain itself, depression, anxiety, sleep, HPA axis deactivation, CS, and appetite, as medical cannabis. There are still no studies proving that cannabis modifies cognitions associated with pain, but it is likely that it does, which tends to make it a very useful tool for the management of these patients in clinical practice.

## AUTHORS' CONTRIBUTIONS

**Eduardo Aliende Perin**

Data Collection, Conceptualization, Project Management, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Software, Supervision, Validation, Visualization

**Cesar Augusto de Paula Santos**

Data Collection, Conceptualization, Project Management, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Software, Supervision, Validation, Visualization

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# Medicinal cannabis law in the USA: history, movements, trends, and countertrends

*Legislação sobre cannabis medicinal nos Estados Unidos: histórico, movimentos, tendências e contra-tendências*

Clarissa Krieck Lee[1]

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: In recent decades, the United States (USA), after banning the use, possession, and commerce of the *CS* plant for medicinal and social purposes for nearly a century, has embarked on law reform processes and movements at the state level to legalize the plant, forging regulated markets to support these changes. The present study's objective was to describe the history of prohibition and eventual legalization, observing the social, political, and economic components that contributed to this paradigm shift.
**CONTENTS**: Qualitative research, using observation, literature review, and analysis of practical experience in advocacy processes, law reform, and building regulated markets to replace prohibition. The historical, social, and economic processes that made up the end of the prohibition of CS and its later regulation as a substance for medicinal and social use were described.
**CONCLUSION**: CS during the last century has been labeled as a drug with no medicinal potential for purely political and non-scientific reasons. A number of civil society movements in the US led to the legalization of CS due to its therapeutic properties. These movements have succeeded in redefining the plant as a medicine rather than a drug, while also taking into account the high social and economic costs of criminalizing it.

**Keywords:** Cannabis, Law Enforcement, Public Policy.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: Nas últimas décadas, os Estados Unidos (EUA), depois de proibir o uso, a posse e a comercialização da planta *CS* para fins medicinais e sociais por quase um século, embarcou em processos e movimentos de reforma de lei em nível estadual para legalizar a planta, forjando mercados regulamentados para amparar essas mudanças. O objetivo foi descrever o histórico da proibição e da eventual legalização, observando os componentes sociais, políticos e econômicos que contribuíram para essa mudança de paradigma.
**CONTEÚDO**: Utilizou-se de revisão de literatura, amparada por análise de experiência prática em processos de "*advocacy*" e construção de mercados regulamentados em substituição a proibição. Foram descritos os processos históricos, sociais e econômicos que compuseram o fim da proibição da *CS* e sua eventual regulamentação como substância para uso medicinal e social nos EUA.
**CONCLUSÃO**: Durante o último século, a *CS* foi rotulada como droga sem potencial medicinal por motivos puramente políticos e não científicos. Uma série de movimentos da sociedade civil nos EUA levou à legalização da *CS* devido a suas propriedades terapêuticas. Esses movimentos tiveram êxito ao redefinirem a planta como um remédio em vez de uma droga, levando em conta também o alto custo social e econômico de sua criminalização.

**Descritores:** Aplicação da Lei, Cannabis, Política Pública.

## INTRODUCTION

The Cannabis sativa (CS) plant permeates the history of American society since its colonial era[1], when the planting of its industrial hemp variety was not only encouraged, but required by some colonies, such as Virginia, for the production of rope, cloth for clothing, and ship sails. Presidents such as George Washington and Thomas Jefferson not only planted hemp on their estates but also promoted the practice widely[2].
At that time, using industrial hemp or even the traditional variation of the plant with other cannabinoids, such as tetrahydrocannabinol (THC), for medicinal purposes was not yet common in the United States (US), but already by the end of the 11th century, CS became a regular ingredient in many medicines offered in US pharmacies[3].
However, in the years 1900 and 1925, due to the great depression, the war with Mexico in 1910, and the huge wave of immigration of Mexicans to the US, society's perception to-

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**HIGHLIGHTS**
- History of CS prohibition in the United States.
- History of legalization and regulation in the United States.
- Description of trends and counter-trends in the new US economy.

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wards CS as a therapeutic agent or medicine changed. Due to the common social (formerly called recreational) use by this immigrant population, and the fear of mass unemployment by the USA citizens, the substance ended up being associated with xenophobic and prejudiced feelings, generating a political movement focused on banning the plant as a whole (including industrial hemp).

But the discrimination was not exclusive to Latinos. It was and still is perversely to black people as well. The "War on Drugs", as it was called, was a racist political tool to target black and brown people. Harry Anslinger, then director of the Federal Bureau of Narcotics coordinated a successful campaign to spread fallacies such as "people who use cannabis commit crimes", "people who make jazz and use cannabis have an evil character"; so much so that the FBI investigated the famous musician Louis Armstrong for his proclaimed medicinal use.

By 1931, 29 states had already banned CS. The use of cannabis as medicine greatly decreased in this period also due to the increasing popularity of synthetics and opium-derived drugs[4].

In 1937, a tax measure at the federal level, the Marijuana Tax Act of 1937, for the first time, through very high taxation, effectively banned the sale and possession of CS. The Marijuana Tax Act of 1937 was the measure that drove this trend that in the following decades characterized a series of laws and public policies focused on making CS an illicit drug, erasing for nearly 100 years from history its potential and therapeutic properties, and eventually preventing any possibility of scientific research in the area.

Between 1952 and 1956, laws called the Boggs Act and the Narcotics Control Act, respectively, began to impose severe criminal sentences for the possession of a variety of substances, including CS. In 1970, the US Congress passed the Controlled Substances Act, which created categories of different substances or drugs, as they were labeled, according to a totally unscientific and arbitrary assessment of their medicinal properties as well as their potential of abuse by the users of each substance. Category 1 drugs, which include CS, was characterized as agents with no medicinal application, and with a high level of abuse potential[5].

However, while governments and these eminent laws sought by all means to annihilate the medicinal properties in American memory and public opinion, other forces were at work in society. In 1972, the Shafer commission, a scientific study body created by President Nixon, recommended that the possession and use of CS no longer be considered a crime, and that it be removed from category 1 of the Controlled Substances Act, a recommendation that was rejected by the authorities, who kept (and still keep) the plant in this definition of an illegal drug with no medicinal properties at the federal level.

## CONTENTS

### The beginning of the end of prohibition

The Vietnam War was the focus of social debate in the 1970s, and the counter-culture movement that grew out of protests by young people against that war was symbolized by an entire generation that consumed CS and, through observation and experience, did not see that same harmful and dangerous effect dictated by the authorities. Starting with an incident in Ann Arbor, Michigan, in 1971, where student leader John Sinclair was sentenced to 10 years in prison for possession of two cigarettes of CS, society began to question these laws, first at the municipal level, then at the state level. Through advocacy, protests, public education, and plebiscites, many localities began to decriminalize the plant and its use and possession. In the 1970s, several states, such as Oregon, Alaska, and Maine followed this trend.

At this time, the first advocacy group focused on reforming the unjust laws governing CS, called the National Organization for the Reform of Marijuana Laws (NORML), emerged. NORML emerged as a force for change at the municipal and state levels, creating opportunities for activism, education, and transformation of these outdated laws. Other groups came later, such as Marijuana Policy Project, based in California and Americans for Safe Access and Drug Policy Alliance, both in Washington, DC. Drawing on the US constitutionalist legal concept of the autonomy of the states of the Union to change their local laws without the permission of the federal government, these groups joined with civil society used education to generate a change in public opinion about the plant, while using legal artifacts like plebiscites within the concept of state autonomy to change municipal laws as a way to leverage these processes. Decriminalizing was the first step, followed later by state-by-state regulations.

In the 1990s, in the midst of the AIDS crisis, following this trend, California passed the 1996 proposition 215, which provided access to CS for HIV-AIDS and cancer patients, creating the first state-level medicinal market in the US. Other states followed starting in 1998: Oregon, Washington, Nevada, and Alaska. In 1999 it was the turn of the state of Maine. And in 2000 Colorado and Hawaii. In the years that followed, a true domino effect caused several other states to follow the same trend, and medicinal use of the plant is now permitted in 38 states[6].

In the 2000s, in addition to this wave of medicinal regulation that took the US by storm, activists specifically focused on reintroducing the cultivation and use of industrial hemp in the US were able to advance that cause through the Hemp Farm Bill of 2005, through a series of litigation actions that culminated in the regulation of industrial hemp by the Farm Bill of 2018.

Hemp extract imported from Europe had been used as a source of raw material to obtain cannabidiol (CBD), which has been used to manufacture medicines on American soil for years. But the Americans wanted to grow hemp. This strategic decision to distinguish, for political purposes, industrial hemp from traditional CS, which by convention offers more than the 0.3% THC limit contained in hemp, although unscientific, was very successful because it allowed advances in industrial hemp law before society could even advance the laws on traditional CS, or rather the whole plant, like all its other cannabinoids. In any case, to science, hemp is a simple variation of the same plant, CS.

A few years later, in October 2009, the U.S. Department of Justice issued the Ogden memo, a directive directing prosecutors not to use federal public funds to arrest patients and medical cannabis providers who were in compliance with their states' medical laws[7]. By publicly pronouncing itself tolerant of these states' civil disobedience to the Union, the federal government had sent a message to the states: that they could proceed with this grand experiment as long as local laws were respected.
In 2012, motivated by the growth of medicinal markets, the states of Colorado and Washington became the first two states to regulate adult or formerly called recreational use via plebiscite. The idea was to regulate not only the use and possession by individuals over the age of 21, similar to the approach to alcohol, but also the production and commercialization through taxation. The main difference between these first two states was that Colorado's rules allowed any adult without a criminal record to also grow up to six plants at home for personal use. Other states followed: now there are 20 states with fully legalized and regulated markets for adult use.
Regulation of adult markets is extremely relevant for medicinal use because emerging cannabis science theorizes that all use is therapeutic. Whether for stress management, insomnia, chronic pain or anxiety, the US population, confronted by the opioid crisis, is increasingly turning to the CS plant as an alternative within the perspective of injury reduction. According to a Gallup poll, 68% of Americans support harme full legalization[8].
It was precisely this gradual and also drastic change in public opinion that contributed to this current complex scenario of law, in which 38 states allow medicinal use, of which 20 also allow adult use. Almost 78% of Americans have access to some form of legalized cannabis. But at the federal level it remains an illegal drug under Category 1 of the Controlled Substance Act, meaning, it has no medical use and has a high potential for abuse.
But what does this mean in practice? CS has become a widely available product in these markets, and in various forms, from the raw plant to edibles, beverages, tinctures, topical creams, concentrated extractions for vaporization purposes, dermal patches for muscle pain, capsules, and more. But due to federal illegality, patients, users, and the medical-scientific community remain limited and unable to conduct research to really understand in depth how the plant acts in the organism, the recommended dosages, the possible long-term effects of its use, the applications on the most diverse diseases, the pharmacological interactions, etc[10]. Even so, a simple search on the Pubmed database results in more than 20,000 articles on the subject. In recent years, Canada, by having legalized the drug federally in 2018, and Israel, by having a medicinal market committed to research, have been producing the clinical trials that the U.S. cannot yet freely produce.

**The new US economy**

Although the main motivation behind the regulation of CS was humane, there is no doubt that it only succeeded for economic reasons. For a long time, patients and activists visited the offices of federal legislators and senators to demand access to the plant, but it wasn't until the access to the first adult-use markets and socioeconomic data that their voices were heard. Instead of hearing the stories of overcoming families and their patients, what the politicians heard to when they finally act on and support proposed changes to the law, was the post-regulation economic data.

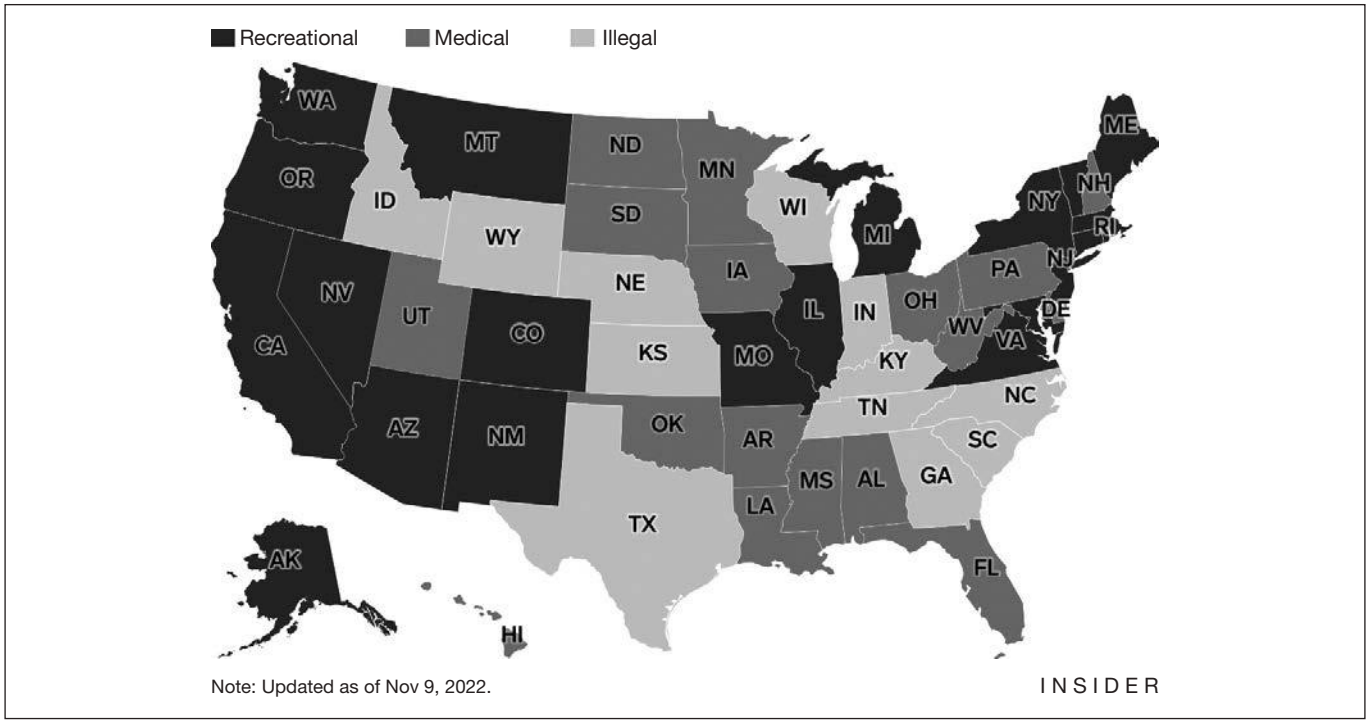


**Figure 1**. Map of Cannabis sativa legalization in the United States[9].

After each each year going by, officials saw more economic activity being generated by this new economy. In 2021, the legal cannabis industry totaled $25 billion in sales. The expectation by the end of 2022 is $33 billion, an annual increase of 32%, a growth percentage that has remained constant annually since legalization. The industry today has already created 520,000 jobs, and this number is expected to reach 800,000 by 2026[11].
Above all, regulated markets generate wealth for the public repository in the form of taxation. According to a study by New Frontier Data, federal legislation would result in $128.8 billion in taxes, and 1.6 million new jobs[12].
Representing the burgeoning cannabis industry, while bringing this economic data, activists were able to regulate full adult use in twenty states, a number that is likely to expand further, especially in states where a medicinal market already exists and where activists and society are organizing to change the laws.

**Trends and countertrends**

This complex legal scenario in the US is likely to remain the same for some years to come. Although the MORE Act, a bill proposing to legalize the plant at the federal level has passed the House of Representatives, and has the support of the industry at large, it is unlikely to pass the current Senate. Meanwhile, the global trend is for other countries to continue to evolve and reform their laws regarding CS, as the law reform in the US has caused other societies to question their laws due to the huge lack of access to medical cannabis for patients with a wide variety of illnesses.
The trend of existing medical markets in the US continues to expand their reach and implement adult-use models amidst federal illegality. Just as it was with the regulation of alcohol at the time of the great depression, it is important to highlight that not all states will regulate the use, be it medicinal or adult. States will follow the same concept of state autonomy in determining whether or not they want to expand or implement new regulatory systems to govern its use.
Regarding the industry, which was the main catalyst in changing the law at the state level, it is known that the large cannabis companies today do not want federal regulation because it would mean that traditional industries such as food and pharmaceuticals would swallow them up overnight.
Currently, these larger cannabis companies pay lobbyists to advance their own corporate interests, not those of the legalization cause. This characterizes the movement's biggest counter-trend: the industry's own actions to sabotage federal legalization.
The greatest economic benefit of federal legalization for both large and small and medium-sized businesses would be access to banking services and investment capital, both of which are still very limited. In addition, fairer taxation on their activities would allow for greater investments in their companies and employees. However, the economic trend is that a 30-40% annual growth in cannabis sales will continue without the industry having access to banking services, i.e. that it will continue to operate on a cash basis.
As far as what concerns the patients, access to research would be the greatest benefit of federal regulation, allowing one to embark on a new era of cannabis medicine, that of personalized medicine, in which, each individual, with his or her physician, could assess the unique needs of his or her endocannabinoid system, and determine which strains of plant and dose would be best suited for his or her specific condition. Tests that determine these specific deficiencies and needs for certain cannabinoids are already being tested in the marketplace.
One cannot forget the socioeconomic impact caused by the incarceration of people arrested daily for possession, purchase, or sale under federal illegality, the vast majority of whom are black and Latino individuals. Even though regulated states are not focused on arresting users and patients, 660,000 people are still arrested each year for possession of CS in the US. The trend of historical reparations will continue to dominate the law reform debates because, as it was observed and proven, prohibition and the war on drugs itself is a war based on racist precepts. Ironically, the legalization movement began with counties decriminalizing use and possession, yet to this day, even with multi-billion dollar markets in place, *CS* has yet to be decriminalized at a federal level.

## CONCLUSION

CS, for the past century, has been labeled as a drug with no medical potential for purely political rather than scientific reasons. A series of civil society movements in the US led to its legalization due to its therapeutic properties. These movements succeeded in redefining the plant as a medicine rather than a drug, also considering the high social and economic cost of its criminalization.

## AUTHOR CONTRIBUTION

**Clarissa Krieck Lee**
Writing - Preparation of the Original

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# Efficacy and analgesic potency of cannabinoids considering current available data

*A eficácia e o poder analgésico dos canabinoides à luz dos dados atuais disponíveis*

Marcus Vinicius Morais[1], Mauro Almeida[2], José Oswaldo de Oliveira Junior[1,3]

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Several studies have shown the growing interest and consumption of cannabinoids and medical cannabis (MC), with management of chronic pain being one of its main therapeutic recommendations. The objective of this study was to review and analyze the results of the most recent preclinical and clinical research on the application of MC and cannabinoids to understand their analgesic efficacy.

**CONTENTS**: A literature review was performed in Pubmed. Preclinical research has shown the role of the endocannabinoid system in pain pathways through the identification of its action sites and pain modulation mechanisms. Numerous clinical studies have endeavored to demonstrate the efficacy of CM and cannabinoids in the management of various pain syndromes. Some international guidelines have already incorporated the use of MC and cannabinoids, but as third or fourth-line treatment and, in most cases, with weak recommendation.

**CONCLUSION**: Despite the growing production of scientific knowledge, the data currently available still lack high-quality evidence to define the efficacy and analgesic potency of cannabinoids. Larger preclinical and clinical research are needed to understand the status of cannabinoids in pain management, as well as to generate high-quality evidence to include or not the use of MC and cannabinoids in guidelines for the management of the various pain syndromes.


**Keywords**: Cannabis, Cannabinoids, Medical marijuana, Pain, Pain management.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Diversos trabalhos têm constatado o crescente interesse e consumo de canabinoides e cannabis medicinal (CM), sendo o auxílio no manejo da dor crônica uma de suas principais indicações terapêuticas na atualidade. O objetivo deste estudo foi revisar e analisar os resultados das mais recentes pesquisas pré-clínicas e clínicas da aplicação da CM e dos canabinoides para compreensão de sua eficácia analgésica.

**CONTEÚDO**: Foi realizada uma revisão de literatura no sistema de busca Pubmed. Pesquisas pré-clínicas têm evidenciado o papel do sistema endocanabinoides nas vias da dor, através da identificação de seus locais de atuação e mecanismos de modulação da dor. Inúmeros estudos clínicos têm mostrado eficácia da CM e dos canabinoides para manejo de diversas síndromes dolorosas. Algumas diretrizes internacionais já incorporaram o uso de CM e canabinoides, mas como tratamento de terceira ou quarta linha e, na maioria dos casos, com poucas recomendações.

**CONCLUSÃO**: Apesar da crescente produção de conhecimento científico, os dados atualmente disponíveis ainda carecem de evidências de alta qualidade para definição da eficácia e poder analgésico dos canabinoides. São necessários maiores estudos pré-clínicos e clínicos para que se possa compreender melhor o status dos canabinoides no manejo da dor, assim como gerar evidências de alta qualidade para incluir ou não o uso da CM e dos canabinoides nos *guidelines* de manejo das diversas síndromes dolorosas.


**Descritores**: Canabinoides**,** Cannabis, Dor, Maconha medicinal, Manejo da dor.

## INTRODUCTION

Cannabinoids are chemical compounds called phytocannabinoids when derived from cannabis, such as Δ-9-tetrahydrocannabidinol (THC) and cannabidiol (CBD). They are further classified into synthetic ones, such as the drugs nabilone, dronabinol, and nabiximols, and endogenous ones, such as N-araquidonoiletanolamine (anandamide, AEA) and 2-araquidonoilglycerol (2-AG)[1], known as endocannabinoids. These, together with their receptors and the enzymes responsible for their metabolism, make up the endocannabinoid system (ECS)[2,3].

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**HIGHLIGHTS**

- The participation of the endocannabinoid system in nociceptive pathways has been postulated since the 19th century and is supported by robust evidence in medical literature.
- International guidelines have already incorporated the use of medical cannabis and cannabinoid drugs for the management of chronic pain, but as third or fourth-line treatments and, in most cases, with weak recommendations.
- Current evidence does not point to the use of cannabinoids in the management of acute and postoperative pain.

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The best characterized cannabinoid receptors are $CB_1$ (cannabinoid receptor$_1$) and $CB_2$ (cannabinoid receptor$_2$), which are G protein-coupled receptors (RAPG). Some of their functions are to inhibit the release of neurotransmitters[4] and to facilitate or inhibit the release of cytokines[5]. The highest concentration of $CB_1$ is in the central nervous system (CNS)[6,7] and $CB_2$ is in the immune system, and it can be up-regulated in response to injury and inflammation[8].

Among other assignments, the ECS is related to regulatory mechanisms of cell development and ontogenesis[9], mood, appetite, vomiting, neuronal activity, memory, immunity, cardiovascular system[10] and pain[11-13]. Endocannabinoids can activate both cannabinoid[14] and non-cannabinoid receptors[15], and the full agonist role of AEA in the transient potential receptor vanilloid subtype 1 (TRPV1)[16,17], which participates in pain pathways[18], is well documented.

Several studies have noted the growing interest and consumption of cannabinoids and medical cannabis (MC)[19-34], with the aid in chronic pain management being one of its main therapeutic indications nowadays, even standing out as the number one indication in some North American states[35,36].

The purpose of this study was to review and analyze the results of most recent preclinical and clinical research on MC and cannabinoids application to understand their current efficacy, analgesic power, and clinical status.

## CONTENTS

As methodology, the terms "cannabis AND pain", "cannabis AND pain guideline", "cannabis AND pain management", "cannabis based medicine AND pain", "cannabis based medicine AND pain guideline", "cannabis based medicine AND pain management", "cannabinoid AND pain", "cannabinoid AND pain guideline", and "cannabinoid AND pain management" were searched in the Pubmed search system, categorizing the papers into preclinical, clinical, and governmental and/or medical society recommendations articles. Texts not available in English were excluded. For the recommendations in each pain syndrome cited in this study, publications from the last 12 years were evaluated, with emphasis on the last five.

**Evidence from pre-clinical studies**

Pre-clinical studies, especially in animals, evidence the action of cannabinoids in pain pathways. Some of the first documented studies and discussions on the subject occurred as early as the 1890s[37], when it was shown that cannabinoids would reduce reactions of dogs to needle stings. In the 1970s, 1980s, and 1990s, several papers found that SCB is expressed through ascending and descending pain pathways at peripheral, spinal, and supraspinal sites, being found, among others, in nerve endings of primary afferent neurons, in the dorsal root ganglion, in superficial laminae of the spinal cord, and in encephalic locations such as the cortex, thalamus, hypothalamus, amygdala, periaqueductal gray matter (PAG), and rostral ventromedial bulb (RVM)[38-48]. In the same period, other researches also verified that cannabinoids could suppress behavioral reactions in inflammatory and nerve injury models, as well as act on pain by mechanical, chemical and thermal stimuli[49-55]. Their potency and efficacy is comparable to opioids[56], and they may surpass them in neuropathic pain models[57].

Endocannabinoids are expressed in the CNS in smaller quantities than the opioid system[58] and are less effective than the opioid system in acute pain when administered directly into RVM and PAG[59]. However, recent studies suggest that cannabinoids would be more effective than opioids for the management of chronic pain states[60,61].

Nevertheless, there is experimental evidence of interactions of these systems through heteromerization, resulting in simultaneous cannabinoid and opioid receptors, with potential for the development of hybrid ligands with analgesic purposes[62].

From the discoveries made in the last decades of the 20th century, it was postulated that cannabinoids would present, among other effects, high potency and high efficacy in reducing responses to painful stimuli, including from the behavioral and neurophysiological point of view. This action would be via $CB_1$ receptors with potential for inhibition of both wide dynamic range (WDR) neurons and specific neurons for nociception, suppression of the windup effect, action in medullary and thalamic neurons, and in modulation of descending pain pathways[63].

Recent research in rodents has observed possible new effects throughout the ECS, such as the analgesic action of endocannabinoids AEA and 2-AG on inflammatory and neuropathic pain, with AEA acting on $CB_1$ and TRPV 1 receptors[64,65]. Increased $CB_2$ expression has also been observed in the encephalon, dorsal root ganglion, and dorsal horn of the spinal cord under inflammatory and pathological conditions[66-76].

Also in rodents, there are indications that cannabinoid-mediated neuromodulation may be involved also in non-pharmacological analgesic therapies, such as transcutaneous electrical nerve stimulation (TENS)[77], analgesia induced by physical activity in inflammatory pain[78] and hot water immersion therapy[79]. A recent study further suggests that non-cannabinoid-based drugs, such as paracetamol (acetaminophen), may have their analgesic effect aided by stimulation of $CB_1$ receptors in RVM[80], as well as other compounds may interact with cannabinoid receptors in the CNS[81].

In models of chronic constriction injury (CCI) in rats, increased AEA and 2-AG were found in the PAG and RVM after 7 days of sciatic nerve constriction injury, when hyperalgesia and mechanical allodynia are at peak points[82]. Increased concentrations have also been noted in the spinal cord after induction of chronic pain in other models of CCI[82,83].

AEA has antihyperalgesic and anti-allodynia effects through mechanisms involving $CB_1$[84,85], while 2-AG leads to same effects through activation of peripheral $CB_1$ and $CB_2$[86]. CBD use significantly reduced allodynia in rats in the recent postoperative period of sciatic nerve ligation[87] and in the immediate postoperative period of trigeminal nerve constriction[88].

Similar results were obtained with the use of THC, which also showed ability to prevent the development of tolerance to morphine[89]. THC has more intense effects than CBD in pain reduction, but its use is limited by adverse effects. The joint adminis-

tration of THC and CBD maintains the high analgesic effect of THC, but significantly reduces its unwanted effects[90].

Some studies suggest that $CB_1$ expression protects against the development of cold allodynia[91], while $CB_2$ agonists suppress microglial activation and reduce neuropathic pain symptoms[92], presenting neuroprotective effects[73]. Studies with CCI models indicate that $CB_2$ selective agonists reduce thermal hyperalgesia[93], in addition to $CB_2$ receptor modulation of lymphocyte activity as an aid in reducing neuropathic pain[94].

Observed research has also postulated that cannabinoids can suppress C-fiber evoked responses of neurons in dorsal horn of the medulla in rodent models of neuropathic pain[95], in addition to reducing mechanical allodynia and anxiety-like behavior[96]. There is also evidence of chemotherapy-induced neuropathic pain reduction in rodents[97].

Numerous preclinical studies show reduction of inflammatory pain by cannabinoid receptor agonists, with the hot plate and tail withdrawal tests being the most commonly performed[98-101]. Reduction of local effects associated with inflammatory processes, such as edema, are also observed in rats subjected to local administration (in the hind paw) of AEA and $CB_1$ agonists[102]. Inflammation can be modulated via increased production of endocannabinoids or by up-regulation of cannabinoid receptor activity. Such effects lead to reduced joint injury in models of inflammatory pain that aim to mimic the processes of rheumatoid arthritis in humans[98,103].

In rodent models of inflammatory pain, the administration of $CB_1$ receptor antagonist in RVM and PAG reverses the analgesic effect, suggesting ECS participation in brain regions involved in analgesia produced by antiphlogistics[104]. Reduction of inflammatory pain also occurs when there is activation of encephalic $CB_2$ receptors[105]. Researches with rodents subjected to inflammatory pain induced by complete Freund's adjuvant (CFA), identified an important role of CBD in the attenuation of chronic pain[87]. In an *in vivo* study with *in vitro* checks, CBD increased serum levels of the anti-inflammatory factor IL-10 (interleukin 10) and decreased serum levels of the pro-inflammatory factors IL-6 (interleukin 6) and TNF-alpha (tumor necrosis factor alpha) was evidenced[106]. In another experiment, CBD administration led to improved inflammation in rodent models of autoimmune encephalomyelitis, and reduced axonal damage and T-cell recruitment in the spinal cord[107].

**Evidence of efficacy and analgesic power in clinical studies**

There are numerous reasons that lead patients to desire the use of MC and cannabinoids. Among those undergoing cancer treatment, some of the reasons are nausea, depression, irregular sleep, difficulty coping with stress and the disease itself, and, especially, insufficient pain control[33,108,109], as well as in patients with spinal cord injury. However, it is necessary to evaluate the currently available scientific evidence to establish appropriate and safe indications for MC and cannabinoids. Several systematic reviews and meta-analyses have been performed to answer such questions[21,110-135].

Some reviews are assertive about the lack of benefit in the use of cannabinoids for management of chronic oncologic and non-oncologic pain, either by inconsistent results in pain reduction or by lack of significant impact on physical and emotional functioning[114,121,128,130]. Such researches mention that the number needed to treat (NNT) is high and the number needed to harm (NNH) is low, and also point out that the evidence for sleep improvement and overall impression of patient improvement is of low quality[121]. The most recent evidence is broad and highly heterogeneous. Due to methodological limitations, the conclusions of current systematic reviews are summarized as "probably beneficial" or "unclear"[125]. Some authors advocate that MC and cannabinoid-based medicines (CBMs) are viable candidates for pain treatment and management as adjuvants or even as substitutes for some therapies. However, these papers explain that the available evidence in the literature is not conclusive[132,135].

Most modern systematic reviews reinforce that CBMs and MC can be effective in some cases of chronic pain, especially neuropathic pain. However, due to the limited degree of evidence[34,127], they should be recommended as third or fourth-line treatments[111]. The evidence is moderate on pain control within two weeks of therapy, and there is a progressive drop in confidence level over longer periods of treatment[116]. However, there is likelihood of a reduced opioid consumption in chronic pain when MC is associated with the treatment (it should be noted that the optimal dose for this purpose is still unknown)[119]. Finally, high-quality systematic reviews of randomized controlled trials published in 2021 reinforce that most of the available studies are not of sufficient quality to support decision making, and it is not possible to validate or disprove the medium and long-term efficacy and safety of CBMs and MC in pain management[120,136,137].

**Neuropathic pain**

Non-oncologic neuropathic pain is currently the main indication for the use of MC and CBM in cases of failure of pharmacological and non-pharmacological therapies already established in medical practice[131]. Importantly, as per the Cochrane review in 2018[124], there is no high-quality evidence attesting to the efficacy of CBM and MC in any chronic condition involving neuropathic pain.

In a double-blind, controlled, randomized study with 15 participants with chronic neuropathic radicular pain, there was a significant decrease in pain when using THC when compared to placebo. Through functional magnetic resonance imaging, a possible disconnection between pain-related affective areas (anterior cingulate cortex and dorsolateral prefrontal cortex) and the sensory-motor cortex was observed through the use of THC, including with the degree of connectivity reduction predicting the degree of pain reduction[138].

It has been observed that MC can relieve HIV-associated neuropathic pain[113] as well as reduce neuropathic pain and weight gain in a patient with diabetic cachexia neuropathy with a history of previous heroin abuse, according to a case report[139]. CBM can also be considered as adjuvants in patients with neuropathic pain undergoing treatment with spinal cord stimulation, with the possibility of pain reduction and improvement in quality of life, especially in relation to sleep[140]. Small analgesic effects have also been verified in the use of dronabinol, nabilone, and nabiximols. However, these are very heterogeneous studies[123,141]. In controlled, randomized studies with small samples, small analgesic effects have also been

found in the use of vaporized cannabis[142]. In one of these studies, it was found that inhaled cannabis can reduce chronic neuropathic pain in the short term in one out of every 5 to 6 patients (NNT 5.6)[143]. A systematic review with meta-analysis[144] showed a significant reduction of up to 30% in pain intensity with the use of CBMs, but noted that these data should be evaluated with caution as the evidence is of moderate to low quality. Analgesia of up to 30% is considered compatible with placebo effect[145].

**Musculoskeletal pain**

A systematic review[118] covering the terms "arthritis", "arthralgia" and "ankylosing spondylitis", found that about 20% of patients were using cannabis (not all for medical use as the primary purpose), reporting improvement in pain control. To date, few studies have been conducted or are in progress. Current evidence with vaporized cannabis and dronabinol points to possible reduction of opioid use in patients with chronic pain due to osteoarthritis[146]. MC has been indicated for musculoskeletal pain with failure or intolerance to first or second-line treatments[147]. However, the quality of current evidence does not allow recommendations to be made for routine clinical use[134].

Few studies targeting low back pain with MC and CBMs have been performed recently. The use of CBD in 100 patients with acute low back pain in a double-blind randomized controlled trial showed no superiority of the drug over placebo[148]. In a study involving participants with spinal surgery failure syndrome undergoing spinal cord stimulation, there was significant reduction in pain, mood, and sleep after the introduction of oral preparations with THC and CBD[149]. However, the available evidence is not of good enough quality to make a recommendation[122].

**Fibromyalgia**

The literature is still conflicting regarding the use of cannabinoids in fibromyalgia. While some reviews suggest that patients may benefit from the use of CBMs, especially in oral formulations[126], other reviews report that the current evidence that MC and CBMs constitute a safe and effective treatment of pain in fibromyalgia is weak, having serious methodological limitations that prevent the formation of indications and recommendations[150]. Despite the limited evidence, other authors report that emerging data point to a positive effect of cannabis and CBD in fibromyalgia. The use, however, should be carefully monitored due to psychiatric, cognitive, and addictive risks in these patients[151]. Whether patient improvement is directly related to pain improvement or due to an overall improvement in other symptoms associated with fibromyalgia, was also a question[151,152]. In a survey evaluating such symptoms, nabilone was far superior than amitriptyline for sleep improvement and marginally superior for feelings of mood and well-being[152]. Nabilone was also suggested for off label use in a study involving patients with fibromyalgia refractory to treatment already established by current guidelines (physical activity, physical therapy, psychotherapy, pharmacological treatment)[134].

**Oncologic pain**

As ECS modulators, MC and CBM may be a future option for patients who do not respond to conventional treatment[23]. Despite good preclinical evidence, current clinical trials have not shown pain improvement when MC or CBM were associated with patients with advanced disease and pain already refractory to high doses of opioids[21,153]. The use of nabiximols has not shown favorable results so far, but the drug lacks good quality evidence to define a recommendation[130]. However, some studies indicate minor analgesic effects with nabilone use[154], while others claim that MC is well tolerated and may lead to better pain control and reduced opioid consumption[155], contrary to a systematic literature review[156] that found high quality evidence in preclinical studies proving decreased opioid consumption, but without verifying the same effect in clinical studies with patients with chronic oncologic and non-oncologic pain.

**Acute and post-operative pain**

One study noted low-quality evidence that cannabinoids could be a safe alternative for a small reduction of acute pain on subjective scores[112]. However, contemporary medical literature and more recent systematic reviews indicate that cannabinoids have no role in acute pain management[129,157]. A recent qualitative and quantitative review[158] on the use of cannabinoids for postoperative pain management demonstrated limited role and clinical benefits in pain control, and also associated CBMs use with a possible increased risk of postoperative hypotension.

## CONCLUSION

Despite the increasing production of scientific knowledge, the data currently available still lack high-quality evidence to define the efficacy and analgesic power of cannabinoids[159]. Some international guidelines have already incorporated the use of MC and CBM, but as third or fourth-line treatments and, in most cases, with weak recommendations. More preclinical and clinical studies are needed to better comprehend the status of cannabinoids in pain management, as well as to generate high-quality evidence[160] to include or not the use of MC and CBM in the respective recommendations and guidelines for management of various pain syndromes.

## AUTHORS' CONTRIBUTIONS

**Marcus Vinicius Morais**
Data Collection, Writing - Preparation of the Original, Writing - Review and Editing
**Mauro Almeida**
Writing - Review and Editing
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Writing - Review and Editing, Supervision

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# The molecular machinery required to process endocannabinoids lipid signaling and their respective receptors

*A maquinaria molecular necessária para processar mensageiros lipídicos endocanabinoides e seus respectivos receptores*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Pharmaceutical preparations of cannabis have been used by mankind since long time ago, and recently they have been the pharmaceutical industry's focus. However, for proper therapeutic application, in-depth knowledge of the endocannabinoid system, which is made mainly by lipid signaling, is needed. The purpose of this study was to explore the current understanding of the players in this system, paying special attention to the molecular machinery required to process it.

**CONTENTS**: This is a narrative review of the current literature regarding major components of the endocannabinoid system, in particular: the receptors, main endogenous ligands, and the enzymes responsible for its components processing. The pharmacological and preclinical aspects were emphasized.

**CONCLUSION**: The better comprehension of the molecular structure of receptors and enzymes will be crucial to developing new pharmacological strategies. A detailed description of the machinery responsible for endocannabinoid lipid metabolization will pave the way for the discovery of new drugs that act on the endogenous system and that can be applied effectively in clinical practice.

**Keywords**: Cannabinoids, Membrane lipids, Pharmacology.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: Os preparados medicinais canabinoides são há muito utilizados pela humanidade e têm sido objeto de interesse da indústria farmacológica recente. Para a aplicação terapêutica adequada é necessário, no entanto, o conhecimento aprofundado do sistema canabinoide endógeno, o qual em sua grande parte é constituído por mensageiros lipídicos. O objetivo deste estudo foi explorar o conhecimento vigente a respeito dos constituintes desse sistema, com especial atenção à maquinaria molecular necessária para processá-los.

**CONTEÚDO**: Trata-se de uma revisão narrativa da literatura atual acerca dos integrantes do sistema canabinoide endógeno, notadamente: seus receptores, os principais ligantes endógenos e as enzimas responsáveis pelo processamento de seus componentes. Os aspectos farmacológicos e pré-clínicos foram enfatizados.

**CONCLUSÃO**: O melhor entendimento da ultraestrutura de receptores e enzimas contribuirá de forma decisiva para o desenvolvimento de novas estratégias farmacológicas. A partir da descrição pormenorizada da maquinaria responsável pela metabolização lipídica endocanabinoide é que se pavimentará o caminho para a descoberta de novos fármacos que atuem no sistema endógeno e que possam ser aplicados de forma eficaz na prática clínica.

**Descritores**: Canabinoides, Farmacologia, Lipídeos de membrana.

## INTRODUCTION

Medicinal preparations from the plant *Cannabis sativa* have been used throughout human history[1] as already mentioned in this special issue. However, only recently the psychoactive substance, Δ9-tetrahydrocannabinol (Δ9-THC), was discovered and isolated from hundreds of phytocannabinoids present in the plant[2,3]. This fundamental discovery led to the synthesis of several cannabinoids, which enabled the accumulation of pharmacological knowledge until, two decades after the discovery of THC, the first cannabinoid membrane receptor was identified and cloned, receiving the acronym CB1[4], followed quickly by the discovery of the second cannabinoid receptor CB2[5].

After the discovery of the receptors, it was possible to verify their first endogenous agonists. In 1992, the substance N-araquidonylethanolamine (AEA or anandamide)[6] was recognized. Subsequently, with the fact that AEA cannot completely reproduce the effects verifiable with THC, the second most important endocannabinoid (EC), 2-araquidonylglycerol (2-AG)[7,8], was ar-

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**HIGHLIGHTS**

- Emphasize the complexity of the endocannabinoid system and go beyond understanding direct pharmacological action.
- Comment regarding the interactions between the endocannabinoid system and other receptor families such as TRPs and PPARs.
- Point out potential promising targets for future research.

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rived at. Both derivatives of arachidonic acid (AA), were the first endogenous cannabinoid substances identified and remain the best studied. Some peptides and derivatives of AA metabolism that generate a cannabinoid-like effect have been recently described and are the target of intense research[9,10].

Thus, synthetically, there is a system formed by two membrane receptors (CB1 and CB2) and two families of lipid signalers that act as their ligands, which, together with the enzymes that synthesize and metabolize them, form the so-called endogenous cannabinoid system (ECs)[11]. This system has some characteristics that allow it to be distinguished from other classical neurotransmitter systems, especially in regard to nociception. Among them, a fundamentally important characteristic is the fact that the machinery related to the processing of lipid EC messengers is located in the synaptic terminals of the nociceptive pathway. Moreover, since ECs are not stored in synaptic vesicles, but produced on demand after intense neuronal activation, the probable ECs role is to brake neuronal signaling in response to its high activation[11]. In this review article, the intent was to explore this machinery components, detailing its constituents and elucidating its main aspects, with special focus on the relationship between ECs and their receptors.

## RECEPTORS

CB1 and CB2 receptors belong to the large family of G-protein-coupled receptors (GPCR). It is an extensive and diverse family of membrane receptors responsible for translating external signals (such as light, lipidic and proteinic particles, among others) into specific cellular responses[13]. Currently, the central contributions of these receptors in cell signaling have turned them into a key piece in drug discovery research[12,13]. They are composed of seven transmembrane α-helices with loops connecting them, being the N-terminal extracellular and C-terminal facing the intracellular side. Binding with a given substance leads to a conformational change in the receptor, leading to activation of the G protein docked on receptor's intracellular side, which initiates the specific cellular signaling process[14,15].

Following the International Union of Pharmacological Sciences taxonomic compatibility goals, it is possible to adopt a classification (to some extent minimalist, but widely accepted) of GPCR ligands that groups them into four categories according to their pharmacodynamic profile: agonists, antagonists, partial agonists, and inverse agonists.

In summary, agonists bind to receptors and activate the cellular response through conformational change. Antagonists bind to receptors and prevent the agonists from binding, generating no cellular response. The partial agonists works as a middle ground, binding to the receptors and generating an incomplete conformational response, but still allowing some cellular response, but blocking the receptors, preventing the full agonists from acting. So, ultimately, when both full and partial agonists are present, the partial agonists acts as competitive antagonists, decreasing the overall vector of receptor activation. The fourth group is represented by the inverse agonists, which induce a physiological response in the opposite direction to that expected from an agonist[12].

Although the idea that activation of a receptor only occurs when an agonist molecule binds to it is being spread, it is possible to find many examples that an appreciable level of activation can occur even in the absence of ligands[16].

Naturally occurring receptors or those that have undergone mutations (spontaneous or induced) can cause activation scenarios in the absence of a ligand, that is, constitutive activation. The occurrence of such activation without agonist binding is found in studies of G-protein-coupled receptors, such as cannabinoids[16,17].

Most of the time, constitutive receptor activation does not present magnitude for clinical repercussion, however, in certain conditions in which a large increase in receptor expression occurs, there may be pathophysiological implications of relevance. Plenty of scientific documentation of this is shown in studies on receptors for beta-adrenoreceptors and receptors for cannabinoids[16-18]. Evidence accumulated over the last three decades has suggested a two-state model[19] in which receptors are in equilibrium between an inactive conformation (R) and a spontaneously active conformation (R*) that can couple to G-protein in the absence of ligands.

Classical agonists have high affinity for R* and increase R* concentration, while inverse agonists have high affinity for R and decrease R* concentration. Neutral competitive antagonists have equal affinity for R and R* and do not shift the equilibrium, but can competitively antagonize the effects of both agonists and inverse agonists.

The concept of a two-state model is important for comprehending the basic mechanisms of action in various classes of drugs, but it does not correspond to reality. The receptors are not restricted to these two options, possessing conformational flexibility and more numerous possibilities. The different conformations that receptors are capable of adopting can be preferentially stabilized by different ligands and can produce different functional effects by activating different signal transduction pathways. The most current redefinition suggests a more complex scheme that contemplates a multi-state model and constitutes a challenge in this area of study. A given G-protein-coupled receptor such as cannabinoid can generate a diverse range of signaling responses, highlighting the physiological and clinical relevance of this class of proteins[20,21]. It is important to note that the pharmacodynamic role is independent of the ligand's affinity to the receptor. For example, it is possible to have complete agonists with weak binding and partial agonists with strong affinity.

The conformational change generated by ligand-receptor binding leads to a change in the relative orientation of transmembrane portions 3 (TM3) and 6 (TM6), which leads to the exposure of G-protein complex binding sites previously hidden on the intracellular side[22,23]. The heterotrimeric G-protein complex is specific for a particular type of GPCR, which once activated leads to inhibition or activation of various effector enzymes or ion channels.

The molecular structure of cannabinoid receptors comprehension has increased with recent studies of their crystallization[24-29]. To date, only the synthetic cannabinoid receptor-ligand set has been crystallized[12]. The structures of human CB1 and CB2 re-

ceptors share an aminoacid similarity of approximately 44% and a 68% homology with respect to transmembrane helices (TM)[5,30]. It has been shown that the binding site for the cannabinoid receptor is located in the membrane's lipid bilayer, with action on the receptor through lateral insertion of the ligand, rather than directly from the outer side, through solution[12,31]. The main differences between both receptors reside in the sequences of second extracellular N-terminal loop, TM7 C-terminal helix and intracellular C-termination itself[29,32]. These structural differences are precisely what confer preference for a given ligand.

CB1 receptor is preferentially found in the central nervous system (CNS), being more expressed in the presynaptic axon termination of several structures (amygdala, hippocampus, cortex, cerebellum, and basal ganglia circuitry)[12,33-35], being strongly associated with GABAergic and glutamatergic neurons[34]. Its activation ultimately leads to increased activity of potassium and calcium ion channels, which leads to the belief that its action is to modulate neurotransmitter release in a dependent manner[12]. Despite its predominance in CNS, the CB1 receptor is also found in the peripheral nervous system (PNS), especially in sympathetic fibers[36] and in nociceptors, notably in the dorsal root ganglia, trigeminal and dermal peripheral nerve endings, where it acts by regulating nociceptive afference[37-39].

In turn, CB2 receptor is strongly related to the immune system, with its activation being associated with neuronal defense mechanisms and inflammation reduction[40]. CB2 receptors are expressed mainly in the CNS, immune system cells, astrocytes, and mycroglia[40]. Besides its presence as a membrane receptor in these locations, it has been described the intracellular presence of CB2 receptor in prefrontal cortex pyramidal neurons in murine model, exerting modulation of neuronal excitability through $Ca^{2+}$-activated $Cl^-$ channels[41,42], reinforcing that although its predominant expression is in the periphery, CB2R also has a role in neurological functions such as nociception, drug dependence, and neuroinflammation[43,44]. Although its presence in the CNS is up to 200 times less frequent than the CB1 receptor, there is an increase in its receptor transcription in situations of neurological insult such as chronic pain, stroke, and neuroinflammation[45,46].

As mentioned, the activity of both receptors, CB1 and CB2, is closely linked to the specific activation of G protein subunits. Classically, both receptors lead to suppression of adenylyl cyclase (AC) via $G_{i/o}$ signaling, which results in reduced levels of cyclic AMP (cAMP)[9,33,35,47]. However, as recently shown by a study[25], a difference in only one residue of the second intracellular loop (L222 in CB1 and P139 in CB2) may lead to coupling diversity between the cannabinoid receptor and the G protein family, with CB2 adopting a specificity only for $G_i$ (conferred by the presence of the P138-P139 pattern in ICL2, unique to CB2)[24], while CB1 can vary between $G_i$, $G_s$, and $G_q$. Thus, an explanation arises for certain experimental findings, in which, under certain circumstances (for example, when there is concomitant dopaminergic activation in striatal neuron cultures), there was AC stimulation by $G_s$ subunit after CB1 activation, leading to an increase in cAMP[48]. Added to this already complex scenario is the fact that there are also multiple possibilities of association between CB1 (through the $G_{\beta\gamma}$ subunit) and AC isoforms, generating predominance of stimulation (isoforms 2, 4, and 7) *versus* inhibition (1, 3, 5, 6, and 8)[9,49].

In addition to the orthosteric ligands, there is among the GPCR family receptors a modulation characteristic that allows them to broaden the spectrum of possibilities of conformational states and, therefore, of activation of intracellular signaling pathways: the interaction with *allosteric* ligands. Allosteric binding sites are those present in the receptor macromolecule, spatially distinct and not overlapping the so-called orthosteric site, but conformationally linked to it[50]. Allosteric modulators, when binding to the receptor in the absence of orthosteric ligand, can stimulate or inhibit the basal activity of this receptor, which was called *allo-agonism* and *allo-antagonism*, respectively. On the other hand, in the presence of the orthosteric ligand, allosteric modulation can alter the binding affinity of the former, as well as its efficiency in intracellular signaling[51].

Three features make these modulators especially interesting and potentially more effective than orthosteric binding: specificity, selectivity, and saturability[30,52-54]. Specificity is conferred by the greater frequency of variation in the aminoacid sequence making up the allosteric binding site (compared to the relative conservation in orthosteric domain sequence) and is thought to be the most important feature[52].

Selectivity in the target organ action is another relevant aspect. While the orthosteric ligand mostly affects receptor's signaling cascades in all tissues where it occurs, the allosteric modulation occurs mostly only in the tissue where the endogenous ligand was expressed in response to a particular stimulus[53]. Finally, saturation confers a ceiling effect, with no additional modulation expected apart from a certain threshold concentration of allosteric ligand, protecting against overdose[55]. Such characteristics, combined with the fact that drugs in clinical use, acting in ECs and based primarily on the orthosteric action of ligands, such as Dronabinol® and Cesamet®, generate considerable adverse effects (especially of psychoaffective order), have made the study on cannabinoid receptors' allosteric modulators an alternative for therapeutic application[52].

Inside the ECs, some ligands have been described as possessing allosteric modulatory activity. Lipoxin-4 (LXA4), an oxygenated derivative of AA, appears to act as a positive modulator of the CB1 receptor by strengthening anandamide affinity and activity[56]. Similarly, cholesterol and possibly other endogenous steroid derivatives such as pregnenolone have been verified in experimental models as possessing modulatory activity[25,57]. Some other endogenous allosteric modulators appear to exhibit positive function (PAM) for CB2 receptor and negative function (NAM) for CB1 receptor. Such is the case of pepcans (formerly hemopressins, endogenous cannabinoid peptides)[58,59].

The ECs, however, appears to have a much greater complexity than that dichotomized by these two receptors. Some authors have divided the receptors that bind to endogenous cannabinoids into three categories[60]: 1) receptors with extracellular binding site, represented mostly by GPCRs (such as the aforementioned CB1 and CB2); 2) receptors with intracellular EC binding site, such as those of transient receptor potential (TRP) family and 3) transcription factors, such as peroxisome proliferator-activated receptor (PPAR).

Besides the already studied GPCR, CB1 and CB2, it is worth mentioning that other receptors have been shown to have activation after binding with cannabinoids. It has been postulated that the orphan receptor GPR55 is a cannabinoid receptor, with authors already proposing its denomination as "CB3"[33,61,62]. The signaling pathway of this receptor involves multiple second messengers, which ultimately lead to increased intracellular $Ca^{2+}$. Interestingly, 2-AG exerts up to 200-fold greater potency as an agonist of GPR55 compared to its binding with the prototypical receptors (CB1 and CB2)[33,62]. However, these findings are not unanimous, with some authors not reproducing what has been found previously, failing to demonstrate ECs as activators of GPR55[61,63]. Thus, a more complete characterization of this receptor, with respect to its tissue distribution, subcellular localization, temporal pattern of expression, and the intracellular signaling pathways, is needed to lead to a greater comprehension of the ECs. Another orphan receptor that has also been listed as a possible cannabinoid receptor in the gastrointestinal tract is GPR119[64].

Robust evidence has been accumulated on the interaction between cannabinoids and transient receptor potential ion channels[33,60,65]. TRP receptors superfamily currently contains 28 known channels in mammals, subdivided into six subfamilies[66]. Among them, six channels (TRPV1-4, TRPA1 and TRPM8) have been shown to bind to cannabinoid substances (synthetic, vegetal and endocannabinoids), and they have been called *ionotropic cannabinoid receptors*[65]. These receptors are nothing more than true transmembrane pores, formed by tetramers (homo- or heteromerized). Each tetrameric subunit contains six transmembrane helices (S1-S6) that, when united, form an ion channel capable of regulating the entry of various cations in response to a stimulus[67]. When the action of ECs on these receptors was refined, so far only TRPV1, TRPV4, and TRPA1 showed consistent activation by endogenous ligands[65]. Anandamide has similar affinity to capsaicin in binding to TRPV1, but with less potent effect[68].

In 2003, a study showed activation of TRPV4 by prototypical ECs anandamide and 2-AG, being followed by other studies on the action of endogenous lipids such as N-acyl tryptophan and N-acyl tyrosine[69,70]. As for TRPA1, anandamide obtained a highly effective agonist action, about 59% higher than its prototypical agonist, mustard oil; TRPA1 was also activated by 2-AG[71]. In turn, TRPM8 seems to undergo antagonist action by anandamide[72]. It is due to the strong presence of these receptors (such as TRPV1 and TRPA1) in dorsal root nociceptor ganglia, the functional and clinical knowledge of their activation and the analgesic effect generated (such as application of topical capsaicin, for example) that the development of cannabinoid drugs for application in the treatment of chronic pain has been sought.

As a mechanism of action, it has been proposed that the modulation of these receptors by cannabinoids leads to immediate neuronal depolarization, followed subsequently by desensitization of these ion channels, which will remain in a silenced state, insensitive to the action of their ligands or thermal stimulation, which would precipitate a nociceptive stimulus[33]. Finally, PPARs are a family of heterodimeric nuclear hormone receptors, with three isoforms currently described (α, γ, and δ), which, when activated, bind to a DNA sequence (regions called *PPAR response elements*), leading to changes in the transcription of certain genes[73]. These target genes are listed in the regulation of metabolism, homeostasis, cell differentiation, and inflammation[74-76].

Since the 2000s, studies have shown that cannabinoid substances, among them ECs, bind to and activate such receptors[77]. Oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) activate PPARα, while anandamide and 2-AG also seem to show activity, although with less evidence, on α isoform and, more consistently, on γ isoform[78]. The activation of these receptors by PEA seems to exert an analgesic function *in vivo*, as has been observed in animal models of nociceptive behavior, either by testing PPARα inhibition through an antagonist or in knockout models[79-81]. However, the individual participation of these receptors in analgesia remains to be elucidated, as some authors find effects involving multiple receptors. One study, for example, identified that the analgesic effects of PEA on neuropathic pain involved CB1, TRPV1, and PPARγ receptors, but not its α isoform or CB2R[82].

## THE ENDOCANNABINOID PROCESSING MACHINERY AND ITS RELATIONSHIPS INSIDE THE ENDOGENOUS CANNABINOID SYSTEM

ECs are signaling lipid molecules comprised of two major groups: N-acylethanolamines (NAE) and monoacylglycerols (MAG)[11]. As mentioned, the two most studied ECs so far are anandamide and 2-AG, presenting different pharmacological characteristics. While anandamide seems to behave as a high-affinity partial agonist of the CB1 receptor, being almost inactive in CB2, 2-AG acts as a full agonist in both, but with low to moderate affinity[9,10,83]. Both are produced on demand, but synthesis, transport and inactivation occur differently according to the target tissue[9]. The basal levels of 2-AG are up to a thousand times higher than those of anandamide in the brain. Experimental studies that manipulated 2-AG metabolism (but not anandamide) had marked effects on endocannabinoid retrograde signaling. Thus, a consensus has been reached that 2-AG is the primary endogenous ligand of cannabinoid receptors in CNS[9-11,84,85].

As stated, ECs are produced on demand, and it should be kept in mind that they have a short half-life (approximately 15 minutes) and that metabolic enzymes and carrier molecules are responsible for their delivery to the target receptor in the exact and precise concentration[60]. Redundancy is a hallmark of the endocannabinoid biosynthesis and degradation system, with several pathways -including those that are responsible for the synthesis of other NAE and MAG – resulting in anandamide and 2-AG production[86,87]. Two enzymes, however, stand out: anandamide has N-acyl-phosphatidylethanolamine (NAPE) as its precursor form, synthesized by the enzyme NAPE-specific phospholipase D (NAPE-PLD)[9,88]; in turn, 2-AG is produced from diacylglycerol (DAG), by DAG lipases (DAGL) α or β – with studies evidencing that virtually all 2-AG involved in

adult brain's synaptic transmission is formed by DAGL α[9,85]. However, the limiting step in production of both is the formation of NAPE and DAG, which are converted from phosphatidylethanolamine by N-acyltransferase, and from phosphoinositides by phospholipase C, respectively[9,85,88].

Once synthesized and released into cytosol, ECs are unable to diffuse freely like other neurotransmitters, due to their hydrophobic nature. Thus, several mechanisms such as binding to certain carrier proteins, as well as endocytosis through the use of lipid "rafts"/caveolae have been studied and proposed as a means to transport anandamide and 2-AG, the latter being less elucidated, but probably sharing the system used by the former[9]. Heat shock protein (HSP) 70, albumin, fatty acid-binding proteins (FABPs) 5 and 7, and albumin itself have been listed[89-91]. As for the transport in extracellular medium, more specifically in the synaptic cleft, it seems to occur in microvesicles, instead of the transport occurring through a binding with transport proteins[92,93].

The ECs, as already pointed out, acts primarily as a suppressor of synaptic activity, regardless of the nature of the synapse or the transmission duration[89,94]. In most cases, endocannabinoid retrograde signaling starts with 2-AG production in postsynaptic neurons, in response to the increase of intracellular $Ca^{2+}$ or of receptors bound to $G_{q/11}$ unit. Transport across the synaptic cleft then occurs, and EC binds to CB1R located on the presynaptic membrane. In turn, the activated CB1R suppresses neurotransmitter release by two main mechanisms: 1) by inhibiting voltage-dependent $Ca^{2+}$ channels, thus decreasing the influx of presynaptic signaling cation; 2) by inhibiting AC and the subsequent cAMP/PKA pathway, which is involved in long-term depression (LTD)[89,94,95].

Anandamide also acts in a retrograde manner, but via multiple mechanisms, the main one being through TRPV1[96] receptors. The localization of the enzymes that synthesize ECs plays a crucial role in this context and seems to be associated with lipid sites inside the plasma membrane, called "rafts". The enzymatic machinery responsible for 2-AG production, for example, seems to concentrate in these microdomains[97]. These rafts also act effectively in AEA reuptake, as well as in the recycling of its metabolites, AA and ethanolamine, which are found in concentrated form in these membrane portions.

Anandamide is metabolized primarily by fatty acid amide hydrolase (FAAH), located mainly in postsynaptic neuron endoplasmic reticulum[98,99]. This enzyme also catabolizes other N-acylethanolamines, such as PEA and OEA, which despite having little biological activity on CB1 and CB2 receptors, can raise AEA levels indirectly, by competing as substrate for FAAH[100,101]. As degradation metabolites of anandamide, the aforementioned AA and ethanolamine remain. In turn, 2-AG is catabolized into AA and glycerol by monoacylglycerol lipase (MGL or MAGL), present in the presynaptic neuron[102,103]. Multiple other enzymes are also listed, such as FAAH itself[104,105] and enzymes in α/β hydrolases domain, such as ABHD2[106], 4[60], 6[107], and 12[108]. ECs can also undergo oxidation by AA cascade enzymes, such as cyclooxygenase 2 (COX-2) and by various lipoxygenases (LOXs)[109], with their oxidative by-products possessing their own biological activities in ECs, distinct from the ECs that generated them[110].

Based on the above it is clear that understanding lipid metabolism is fundamental to a complete ECs understanding. It is even more important to remember that there is a high diversity in the lipid membranes of eukaryotes[111] and that a large part of the enzymes belonging to ECs are membrane-bound proteins. Their activities and availability in the membrane can be affected by different lipids in the vicinity. In the case of FAAH, for example, it has been shown that cholesterol present in the membrane is responsible for stabilizing a dimeric form of the enzyme, as well as modulating its localization at subcellular level (i.e., in organelle membranes), and increasing its catalytic activity, which ultimately affects the extent to which EC signaling is propagated at the intracellular level and consequently its termination[112].

Similarly, the study of acyl chains composition in plasma membranes has gained relevance, demonstrating that the length and saturation degree of chains are crucial for intra and transmembrane trafficking and enzyme degradation processes[113]. Thus, although MAGL can hydrolyze several monoacylglycerols – all containing the same glycerol pole as 2-AG, but with distinct acyl chains – it is the length and saturation of their chains that will define the speed of hydrolysis rate, being up to 2x faster for 2-AG (longer and polyunsaturated chain) compared to its congener 2-PG (2-palmitoylglycerol, shorter and saturated chain)[113].

Interestingly, it has recently been shown that ABHD2 activity is progesterone-dependent in sperm, in which 2-AG acts as an endogenous inhibitor of a cation channel known as CatSper. In the presence of said hormone, this enzyme hydrolyzes 2-AG and leads to the CatSper channels opening, hyperactivating and ultimately making the sperm fertile[106]. The finding that the level of 2-AG is controlled by the stimulation of its degradation is of great relevance, since it casts questions on the current dogma of "production on demand" of the ECs, i.e., that ECs are produced only by controlling their biosynthesis in a stimulus-dependent manner from phospholipid precursors. At least in semen, 2-AG is "hydrolyzed on demand" from a preexisting pool[106] and finally adjusted by steroid hormones.

These examples show the ECs complexity, since the same cannabinoid receptor (e.g. CB1) or metabolic enzyme (e.g. FAAH), within the same cell, but under different lipid conditions, can culminate in different EC signaling and lead to different biological behaviors[60].

## CONCLUSION

The ECs components are widely expressed in different tissues and compose a lipid signaling system, playing a key role in the regulation of several physiological processes such as metabolism, mood, appetite, cardiovascular control, motor function, immune system, neurotransmission and nociception. The comprehension of its elements and a better understanding of receptors and enzymes ultrastructure will decisively contribute to the development of new pharmacological strategies that are not limited to CB1R

direct action, for example. Of the six enzymes involved in 2-AG metabolization, for example, only the MAGL structure is known. From the detailed description of the machinery responsible for endocannabinoid lipid metabolization, it will be possible to unlock the potential for the development of new drugs (such as analgesics without the CB1-mediated adverse effects) and their translation into clinical practice.

## AUTHORS' CONTRIBUTIONS

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Data Collection, Conceptualization, Writing - Preparation of the Original
**Leonardo Rafael Takahashi**
Writing - Review and Editing
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# Glia function in the endocanabinoid system: narrative review

*Função da glia no sistema endocanabinoide: revisão narrativa*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Evidence has highlighted a role of glial cell activation, and their interaction with different neural systems, especially the endocannabinoid system, in the mechanisms involved in the chronicity and maintenance of pain. The aim of this review is to bring an update on published data that demonstrate the interaction between glial cells and the endocannabinoid system in the pathophysiology of chronic pain and its treatment.

**CONTENTS**: A narrative review was performed based on a research in the Medline database, using the Keywords "endocannabinoid", "glial cells", "microglial", "astrocytes", "neuroinflammation".

**CONCLUSION**: Deepening the knowledge about the function of glial cells in the endocannabinoid system will open the possibility of acting on the pathophysiological origin of the pain chronification process, attenuating the mechanisms involved in central sensitization.


**Keywords**: Cannabinoids receptors, Neurogenic inflammation, Neuroglia, Pain.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A evidência científica tem ressaltado um papel da ativação das células da glia e de sua interação com diversos sistemas neurais, com destaque para o sistema endocanabinoide e mecanismos envolvidos na cronificação e manutenção da dor. O objetivo deste estudo foi atualizar os dados publicados que mostrem a interação entre as células da glia com o sistema endocanabinoide na fisiopatologia da dor crônica e seu tratamento.

**CONTEÚDO**: Foi realizada uma revisão narrativa baseada em pesquisa na base de dados Medline, com uso dos unitermos *"endocannabinoid", "glial cells", "microglial", "astrocytes", "neuroinflammation"*.

**CONCLUSÃO**: O aprofundamento do conhecimento acerca da função das células da glia no sistema endocanabinoide abrirá a possibilidade de atuação sobre a origem fisiopatológica do processo de cronificação de dor, atenuando os mecanismos envolvidos na sensibilização central.


**Descritores**: Dor, Inflamação neurogênica, Neuroglia, Receptores de canabinoides.

## INTRODUCTION

The evidence accumulated in the last years has highlighted the preponderant role of glia cell activation and its interaction with several neural systems in the mechanisms involved in pain chronification and maintenance[1]. Among the systems that exert and suffer influence from glia, the endocannabinoid system should be highlighted. This system is seen as a powerful regulator of synaptic function throughout the central nervous system (CNS), acting by reducing the release of neurotransmitters in the synaptic cleft, in a transient and long-lasting manner, and acting on the function of ion channels in the spinal cord and dorsal root ganglion (DRG)[2,3].

The chronification of pain can be synthesized as a process of maladaptive neuronal plasticity, which results in sensitization of pain pathways. As a result of these alterations, there is an imbalance between facilitation and inhibition of painful stimuli in the dorsal horn of the spinal cord, favoring the former[4]. This state of increased excitation in the CNS results in a pathological amplification of the stimuli entering and leaving the spinal cord[1,3]. As a consequence, the activation of glial cells occurs, leading to increased expression of several membrane receptors, intracellular proteins, and transcription factors that are implicated in the development and maintenance of chronic pain (CP). However, among the receptors that have their expression increased are the

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**HIGHLIGHTS**

- Mycroglia activation is strongly involved in the development of neuropathic pain secondary to peripheral nerve injury.
- The endocannabinoid system provides a pathway for attenuation of neurogenic inflammation, which is involved in the process of pain chronification.
- Mycroglia plays a central role in the interaction of the endocannabinoid system with the pathophysiology of chronic pain.

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cannabinoids CB1 and CB2, which, through their inhibitory actions, may serve as therapeutic targets to counterbalance this state of neuronal excitation[3].

The present review's objective was to update the published data showing interaction between glia cells with the endocannabinoid system in the pathophysiology of CP and its treatment.

## CONTENTS

### Glia cells and pain

The glia cells in the central nervous system (CNS) are the astrocytes, the microglia, and the oligodendrocytes. In the peripheral nervous system (PNS), glial satellite cells are found in the DRG and trigeminal ganglion, and Schwann cells in the peripheral nerves.

Mycroglia cells are CNS resident macrophages, originating from the monocyte lineage produced in the bone marrow. In the CNS, these cells are heterogeneously distributed, interacting dynamically with synapses to maintain brain homeostasis. Mycroglia can be activated as a result of insults to neural tissue. When this occurs, a rapid proliferation of these cells begins in the spinal cord, associated with changes in their morphology, adopting an ameboid shape[1].

Mycroglia activation is strongly involved in the development of neuropathic pain secondary to peripheral nerve injury and depends on the presence of mediators such as ATP, colony-stimulating factor 1 (CSF1), chemokines (CCL2 and CX3CL1), and proteases, from injured or activated sensory neurons. In parallel, there is increased expression of receptors for ATP and CX3CL1 (P2X4, P2X7, P2Y12, CX3CR1) in the spinal cord microglia itself[5].

Subsequent activation of these receptors leads to intracellular signaling mediated by phosphorylation of p38 protein kinase for increased production and release of inflammatory cytokines such as TNF-α, interleukins IL-1β, IL-18, brain-derived growth factor (BDNF) and cyclooxygenase (COX). These mediators are able to amplify synaptic transmission, and therefore potentiate pain transmission to the brain[5]. Some alterations in the microglia have the potential to produce prolonged effects. In a study evaluating enhancers in spinal microglia, persistent modifications near transcription-regulated genes were shown to exist. Enhancers are areas of open chromatin that define the binding point of cellular transcription factors. Changes in these regions may be implicated in the persistence of the facilitation state, which allows for the maintenance of CP[6].

Astrocytes are the greatest number of cells present in in the CNS, and although histologically they have a structural function as support cells, they are known to be involved in the development of acute and chronic neurological, neurodegenerative, neuropsychiatric diseases, and gliomas[1]. Differently from the other glial cells, astrocytes have a physical intercellular connection, determined by the communicating junctions, forming the blood-brain barrier, and performing other physiological functions, such as regulation of ionic concentration, modulation of synaptic transmission, among others[5]. Similarly to what happens to the microglia, astrocyte activation leads to a state of neuroinflammation, with participation in the pathophysiology and maintenance of CP[7].

Although both cells are involved in the development of CP, some differences mark the involvement of each of them. Astrocytes are involved in virtually all diseases that course with persistent pain, whereas microglia activation seems to occur in only a few specific situations. Peripheral nerve lesions exhibit participation of both cells, but in chemotherapy-induced neuropathy, only astrocyte participation has been identified. Similarly, only astrogliosis (not microgliosis) was observed in the dorsal root horn of patients with human immunodeficiency human related neuropathy. Models of neuropathic pain from bone cancer also show astrocyte involvement, but the participation of microglia in these cases is not yet definitive[7].

Finally, oligodentrocytes, cells in charge of myelin sheath production, have also been associated with the pain chronification process. It was shown that the expression of IL-33 derived from oligodendrocytes preponderantly contributed to the development of neuropathic pain after peripheral nerve injury. An interesting finding is that toxin-mediated ablation of these cells leads to the development of neuropathic pain symptoms, suggesting a protective role of oligodendrocytes in CP[5].

## ENDOCANNABINOID SYSTEM

The knowledge about the endocannabinoid system as a modulator of synapses in the CNS has been developed over the last 25 years, and robust evidence points to its action as a retrograde messenger, capable of suppressing the release of neurotransmitters in a transient and prolonged manner, both in excitatory and inhibitory synapses[2].

The endocannabinoid system is a complex biological network, consisting of the cannabinoid receptors (CB1 and CB2), their respective endogenous ligands, 2-araquidonoil glycerol (2-AG) and ethanolamine O-araquidonoil (AEA), as well as their synthesizing and degrading enzymes. Physiologically, it is related to the maintenance of homeostasis and, therefore, its components are found dispersed throughout the body, such as in the CNS, immune system cells, liver, as well as in the reproductive, respiratory, gastrointestinal, cardiovascular, and musculoskeletal systems[8,9].

The CB1 receptor is expressed primarily in the nervous system, with greater evidence for GABAergic axon endings. CB2, on the other hand, is present primarily on cells of the immune system, including microglia. However, this receptor is also present in the CNS, especially in the brainstem and mesencephalic dopaminergic pathways. Unlike CB1, which is among the G protein-coupled receptors with the highest expression in the CNS, CB2 has a reduced basal quantity and has a high inductivity when facing inflammatory stimulus[9].

In the glia, astrocytes express CB1 receptors, whose function is to regulate glutamine synthesis and, therefore, to control the amount of glutamate available in the synaptic cleft and the influx of calcium, modulating synapse strength. Mycroglia, on the other hand, expresses mainly CB2 and participates in the modulation between pro-inflammatory and anti-inflammatory states[8,9]. Both CB1 and CB2 are G protein-coupled receptors with inhibitory function, with their activation leading to blockade of sodium channels, activation of potassium channels, and inhibition of adenylyl cyclase[3].

The activation of cannabinoid receptors acts modulating the transmission of nociception, having already been shown the attenuation of pain behavior in animal models[10].

The main mechanism by which modulation of synaptic function occurs is retrograde signaling. This occurs when a postsynaptic activity leads to the production of endocannabinoids, which bind to CB1 expressed on the presynaptic membrane, leading to inhibition of neurotransmitter (glutamate) release. However, the endocannabinoid ligand can still act through the vanilloid receptor (TRPV1) and postsynaptic CB1 activation, as well as through activation of glia cells[2].

**Microglia and endocannabinoid signaling**

As already described, in situations where nociception is present, engagement of the microglia is expected from the activation of its cells, leading to the induction and perpetuation of neuroinflammation and a state of facilitation, which makes it conducive to the development of pain chronification. However, activation of CB2 receptors can profoundly modify the immune function of the microglia, converting it to an anti-inflammatory state, in which there is limited phagocytosis migration, increased production of anti-inflammatory mediators, and reduced production of pro-inflammatory ones[3].

With the activation of CB2, some changes are expected in the microglial response to injury. Reduced nitric oxide production, reduced synthesis of IL-1β, TNF-α, and BDNF can be observed as a result of attenuation of the p38 protein kinase pathway, and reduced ERK-mediated proliferation of mycroglia[3,11]. CB2 activation is also associated with increased release of IL-10, an anti-inflammatory cytokine[11]. A reduction in P2X4 purinergic receptor expression has also been shown following CB2 activation[12]. The switch to an anti-inflammatory state was also associated with reduced pain behavior[3].

Studies also suggest the presence of non-CB1 and non-CB2 receptors in the microglia, which are activated by cannabinoid ligands, and lead to a reduction in the release of IL-1α and TNF-α, pro-inflammatory cytokines[13,14].

Another pathway that has been gaining prominence is the palmitoylethanolamide (PEA) fatty acid, which, despite not binding to CB2, has anti-inflammatory and antinociceptive action indirectly mediated by this receptor. This could be observed from the reversal of its effect by a CB2 antagonist[15].

Microglia not only express cannabinoid receptors, but also produce endocannabinoids. With a production at least 20 times higher than that of other glia cells or neurons, the microglia is the major responsible for the production of endocannabinoids in the CNS3. The production of these ligands depends on signaling through the activation of purinergic receptors (P2X4 and P2X7), with a consequent increase in intracellular calcium[3]. In situations such as the presence of neuropathic pain, the microglia increases the production of endocannabinoids, as well as reduces the expression of its degrading enzyme, fatty acid amide hydrolase (FAAH)[3].

Besides the action of endocannabinoids on their receptors, other antinociceptive actions are observed from the action of these ligands in other systems. At the spinal level, there is inhibition of adenylate cyclase activity and reduction of cyclic AMP, which reduces nociceptive signaling to higher order neurons[3]. Endocannabinoids also inhibit the serotoninergic 5-HT3 pathway, reduce sodium influx, and block voltage-dependent (Cav3.2) presynaptic calcium channels[3].

**Astrocytes and endocannabinoid signaling**

Astrocytes mainly express CB1 receptors, which are involved in neuronal homeostasis and control of metabolic functions[7]. However, experimental studies have brought to light evidence that the activation of this receptor plays a role in modulating neurogenic inflammation and nociception. This effect could be observed in a study that showed that the activation of CB1 led to attenuation of allodynia, persistent activation of astrocytes in the spinal cord, and the phosphorylation of p38 protein kinase in spinal astrocytes in a model of plantar incision[16].

**Interaction of glia and endocannabinoid system: perspectives**

The evidence for a central role of neurogenic inflammation in the pathophysiology of CP chronification and perpetuation has become increasingly robust[4]. And it is natural to search for mechanisms that are capable of alleviating or reversing these processes.

The data obtained, mostly from experimental studies about the influence that the endocannabinoid system exerts on neurogenic inflammation and on nociception pathways, brings an important direction towards this objective. These findings show us that, when stimulated, cannabinoid receptors, in particular CB2 receptors present in the microglia, prevent the development of an inflammatory state, both acute and long-lasting. In this way, central sensitization would also be prevented, a determining step in the development of CP.

Cannabinoids present great potential in the treatment of pain, including in preventing the processes involved in pain chronification. However, the efficacy and consequences of long-term use of these agents are still being checked in the literature. To date, entities such as the International Association for the Study of Pain (IASP) still do not place cannabinoids as the first line of treatment for CP[17]. Further studies are needed to ensure the efficacy and safety of these agents.

## CONCLUSION

The deepening of knowledge about the function of glia cells in the endocannabinoid system will open the possibility of acting on the physiopathological origin of the CP process, attenuating the mechanisms involved in central sensitization.

## AUTHORS' CONTRIBUTIONS

**José Osvaldo Barbosa-Neto**
Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Supervision
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# Anti-inflammatory effects of cannabinoids

*Efeitos anti-inflamatórios dos canabinoides*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: The use of cannabinoids for epileptic syndrome and control of side effects associated with chemotherapy is already widespread and supported by several well-controlled clinical trials. However, the use of these drugs in inflammatory pathologies is sometimes underestimated due to lack of scientific knowledge with a high degree of evidence, non-recognition of the endocannabinoid system as an active participant in these diseases, as well as fear of the stereotype surrounding the use of cannabis derivatives. The purpose of this study was to examine the anti-inflammatory and antioxidant effects of endogenous and exogenous cannabinoids on various physiological systems in which these ligands interact.

**CONTENTS**: Studies cited in this review were obtained by searching Pubmed, Medline, Google Scholar, Scielo, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and through the authors' familiarity with the published literature in this area of interest. Clinical, observational and intervention, experimental, qualitative studies and review articles were all included in the search. Articles were identified using the following descriptors: cannabis and tetrahydrocannabinol and cannabidiol and endocannabinoids and anti-inflammatory inflammation and oxidative stress. In addition, a manual revision of relevant references was also performed to capture articles that may not have been picked up through the initial search. The literature investigation was conducted from March 22 to May 2022.

**CONCLUSION**: Cannabinoids show to be a promising therapeutic option in the context of inflammatory diseases, given the complete and complex relationship between the endocannabinoid system and the immune system. The setback to be overcome in the use of cannabinoids as anti-inflammatory drugs includes the synthesis of non-psychoactive cannabinoid receptor agonists while maintaining potent anti-inflammatory activity. Further studies are needed to increase our understanding of cannabinoids and their intricate effects on immune system disorders.


**Keywords**: Anti-inflammatory agents, Cannabinoids. Inflammation, Pain.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: O uso de canabinoides para síndrome epiléptica e controle de efeitos adversos associados à quimioterapia já é amplamente difundido e apoiado por vários ensaios clínicos bem controlados. Entretanto, o uso destes fármacos em patologias inflamatórias é, por vezes, subestimado pela falta de conhecimento científico com alto grau de evidência, pelo não reconhecimento do sistema endocanabinoide como participante ativo destas doenças, bem como por receio do estereótipo que envolve o uso dos derivados da cannabis. O objetivo deste estudo foi analisar os efeitos anti-inflamatórios e antioxidantes de canabinoides endógenos e exógenos em vários sistemas fisiológicos nos quais esses ligantes interagem.

**CONTEÚDO**: Estudos citados nesta revisão foram obtidos por meio de buscas feitas nas bases de dados Pubmed, Medline, Google Acadêmico, Scielo, *Cochrane Central Register of Controlled Trials* (CENTRAL), LILACS, e através da familiaridade dos autores com a literatura publicada nesta área de interesse. Estudos clínicos, observacionais e de intervenção, experimentais, qualitativos e artigos de revisão foram todos incluídos na pesquisa. Os artigos foram identificados usando os seguintes descritores: cannabis e tetraidrocanabinol e canabidiol e endocanabinoides e inflamação anti-inflamatório e estresse oxidativo. Ademais, uma revisão manual nas referências relevantes também foi realizada para captura de artigos que podem não ter sido captados por meio da busca inicial. A investigação na literatura foi realizada no período de 22 de março a 17 de maio de 2022.

**CONCLUSÃO**: Os canabinoides demonstram ser uma opção terapêutica promissora no contexto das doenças inflamatórias, haja vista a completa e complexa relação entre o sistema endocanabinoide e o sistema imune. O revés a ser vencido no uso de ca-


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**HIGHLIGHTS**

- The cannabinoid system regulates a variety of cellular and physiological processes, and is thus related to regulatory processes including inflammation, metabolism regulation, energetic balance, thermogenesis, neural development, immune function, cardiovascular function, synaptic plasticity and learning, pain, memory, movement, psychomotor behavior, sleep/wake cycles, stress and emotion regulation, and digestion.
- The main anti-inflammatory mechanisms produced by cannabinoids are induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production, and induction of T-regulatory cells.
- Increased levels of anandamide decrease inflammatory responses, suggesting that endocannabinoids are physiologically involved in the attenuation of the immune system. However, there are still poorly understood and sometimes contradictory effects.

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nabinoides como fármacos anti-inflamatórios inclui a síntese de agonistas de receptores canabinoides que não sejam psicoativos, mantendo a potente atividade anti-inflamatória. Novos estudos são necessários para aumentar a compreensão dos canabinoides e seus efeitos intrincados sobre distúrbios do sistema imunológico.
**Descritores**: Anti-inflamatórios, Canabinoides, Dor, Inflamação.

## INTRODUCTION

The cannabis plant genus, a member of the Cannabaceae family, has three distinct primary species, varying in their biochemical constituents: *C. sativa* (Cs), *C. indica*, and *C. ruderalis*. Its anxiolytic and euphoric properties have been recorded in religious scriptures dating back several millennia, revealing that the use of Cs already held a strong and prominent position in ancient medicine. Its various benefits were documented in Sanskrit and Hindi literature as early as 2000-1400 B.C. and its medicinal use was described in more detail in the Indian Ayurvedic medical literature as early as 900 B.C. Between the centuries I and III, the Greek physicians Claudius Galen (131-201 A.D.) and Pedanius Dioscorides (40-90 A.D.) described medicinal indications.

However, the first scientific report on cannabis was published only in 1839 by the Irish physician William O'Shaughnessy, which marked the first traces of its popularization. By providing evidence of its therapeutic efficacy and safety for pathological conditions such as child convulsions and cholera, he was essential in laying the groundwork for medical research and use[1-8]. A major obstacle to the use of Cs was the fact that the active ingredient, cannabidiol (CBD), had not yet been described. It was first isolated from cannabis in 1940, and its structure was reported in 1963.

Nevertheless, the psychoactive effect of Cs overshadowed its possible therapeutic effects. The structure of the main psychoactive phytocannabinoid, Δ-9-tetrahydrocannabinol (THC), was determined in Israel by Mechoulam and Gaoni in 1964. Mechoulam's discovery promoted the exploration of a new receptor system, the endocannabinoid system. At the present time, this system comprises a few known endocannabinoids (mainly, N-amino acid ethanolamine [AEA] and 2-amino acid ethanolamine [2-AG]), possessing two primary cannabinoid receptors (CB1R and CB2R). Through these and receptors in other systems, endocannabinoids modulate the release of neurotransmitters and cytokines[9-15].

Regarding the function, the ubiquitous nature of the cannabinoid system regulates a variety of cellular and physiological processes, and is thus related to regulatory processes including inflammation, regulation of metabolism, energetic balance, thermogenesis, neural development, immune function, cardiovascular function, synaptic plasticity and learning, pain, memory, movement, psychomotor behavior, sleep/wake cycles, regulation of stress and emotion, and digestion. Studies to date indicate that the main potentials in the therapeutic use of the endocannabinoid system are linked to neuromodulation, modulation of the autonomic nervous system (ANS), immune system, and microcirculation[13,16-20].

The present study's objective was to examine the anti-inflammatory and antioxidant effects of endogenous and exogenous cannabinoids on various physiological systems in which these ligands interact.

## CONTENTS

The present narrative review was prepared as a comprehensive theoretical resource to achieve the described objectives. The use of cannabinoids for epileptic syndrome and control of adverse effects associated with chemotherapy is already widespread and supported by several well-controlled clinical trials. However, the use of these drugs in inflammatory diseases is sometimes underestimated due to lack of scientific knowledge with a high degree of evidence, non-recognition of the endocannabinoid system as an active participant in these diseases, and fear of the stereotype surrounding the use of cannabis derivatives. Therefore, the present study provides a basis to contribute to the scientific community by deepening the comprehension of the mechanisms involved in the anti-inflammatory effects promoted by cannabinoids and by providing substrate for the development of possible clinical and public health guidelines.

Studies mentioned in this review were obtained by searching the Pubmed, Medline, Google Scholar, Scielo, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS databases, as well as the authors' familiarity with the literature published in this area of interest. Clinical, observational and intervention, experimental, qualitative studies and review articles were all included in the search. Articles were identified using the following descriptors: cannabis and tetrahydrocannabinol and cannabidiol and endocannabinoids and inflammation and anti-inflammatory and oxidative stress. In addition, a manual search of relevant references was also performed to capture articles that may not have been picked up through the initial search. The literature search was conducted from March 22 to May 17, 2022.

### Endocannabinoid system

Endogenous cannabinoids act as natural ligands for cannabinoid receptors expressed in mammalian tissues, thus constituting an important lipid signaling system called the endocannabinoid system. Cannabinoid receptor agonists are very heterogeneous and can be divided into four groups, according to the difference in chemical and structural composition: classical, non-classical, aminoalkylindol and eicosanoids. The classical group consists of the phytocannabinoids (Δ-9-tetrahydrocannabinol [THC], cannabinol [CBN], cannabidiol [CBD], among others) and their synthetic analogues. The eicosanoid group is mainly made up of the endocannabinoids (arachidonylethanolamine [anandamide or AEA], 2-araquidonylglycerol [2-AG], among others), ligands of the cannabinoid system produced by human cells. The other two groups, non-classical and aminoalkylindol, consist of synthetic cannabinoids[21,22].

Endocannabinoids are derivatives of arachidonic acid combined with ethanolamine or glycerol. These products are synthesized on demand from phospholipid precursors that integrate the cell membrane in response to increased intracellular calcium levels. The prototypical endogenous cannabinoids are 2-AG and anandamide or AEA. Both are eicosanoids produced from arachidonic acid-containing phospholipids, such as phosphatidylinositol 4,5-biphosphate and phosphatidylethanolamine, respectively. These ligands have both complementary and divergent functions.

While 2-AG is a full agonist at both cannabinoid receptors (CB1R and CB2R), anandamide exerts partial agonism.

Other lesser known endocannabinoids include dopamine N-araquidonoil (NADA) and glycerol 2-araquidonoil ether (noladine), both of which bind strongly to CB1R. In addition, ethanolamine arachidonoil (virodamine) has been identified as a full CB2R agonist and possesses antagonistic activity on CB1R[23-28]. Exogenous cannabinoids, however, comprise both naturally occurring phytocannabinoids and synthetic cannabinoids. Exogenous cannabinoids are compounds isolated from the Cannabis genus and make up more than 100 chemicals, among which THC and CBD are the most abundant and most frequently used. THC has a high affinity for both CB1R and CB2R. In contrast, CBD has a higher affinity for CB2R. In addition, CBD possesses pain modulation effect by anti-inflammatory properties and may be able to counteract negative effects of THC on memory, mood and cognition[29-31].

In addition to the transmitters that serve as ligands for the cannabinoid receptors, the endocannabinoid family also comprises the enzymes for biosynthesis and degradation of the ligands. Enzymes known to hydrolyze the endocannabinoids include fatty acid amide hydrolase (FAAH), monoglyceride lipase, and N-acylethanolamine[12].

The cannabinoid receptors, CB1R and CB2R, are G-protein coupled heterotrimeric and both are expressed in the periphery and the central nervous system (CNS). However, CB1R expression is predominant in the CNS, especially in presynaptic nerves, while CB2R is mainly expressed in immune cells. Both are activated by endogenously produced lipophilic ligands. Nevertheless, CB1R and CB2R receptors are also coupled to a variety of ion channels in the cell membrane: inward rectifier potassium channels and calcium channels[11,32,33].

CB1R is highly expressed in most regions of the CNS, with densities that rival other neurotransmitter and neuromodulatory receptors. In addition to the CNS, CB1R expression has been reported in the somatic, sympathetic, parasympathetic, and enteric nervous systems. It is presented in both inhibitory GABAergic and excitatory glutamatergic neurons. The activation of this receptor, in a dose-dependent manner, can produce subsequent decrease of Ca2+ entry into the cell, without involvement of cyclic adenosine 3',5'-monophosphate (cAMP), producing its final effect, the reduction of neurotransmitter release. This mechanism may be related to the ability of CB1 receptor agonists to impair cognition and memory, and alter the control of motor function and nociception[34,35].

CB2R, on the other hand, is expressed at very low levels inside the central nervous system (CNS) under physiological conditions. However, pathological conditions characterized by a neuroinflammatory state have resulted in a positive regulation of CB2R levels in glia cells, such as microglia. This receptor is also expressed at high levels in immune cells and lymphoid tissues that participate in the innate and adaptive immune response. The presence of cannabinoid receptors is different on each immune cell, being expressed, from most abundant to scarcest, on B cells, natural killer (NK) cells, monocytes, neutrophils, CD8+ and CD4+ lymphocytes[36].

As a common mechanism, the cannabinoid receptors CB1 and CB2 also act to regulate the phosphorylation and activation of different members of the mitogen-activated protein kinase (MAPK) family, including kinases 1 and 2 regulated by extracellular signals. MAPK, in turn, controls gene expression related to cell proliferation, motility, adhesion and apoptosis, as well as glucose metabolism. Both receptors share the ability to modulate the release of chemical messengers. By acting on CB1 receptors, cannabinoids interact with various neurotransmitters in the CNS and can modulate their release, while controlling the release of inflammatory cytokines by acting on CB2R, regulating the immune system[37-40].

One of the non-CB1/CB2 receptors with cannabinoid binding capacity is the transient receptor vanilloid type 1 (TRPV1), also called the capsaicin receptor. This is a non-selective cation channel present in sensory neurons of the skin, heart, blood vessels, and lungs. TRPV1 is associated with the transmission and modulation of pain through primary afferent and perivascular sensory neurons[12,41,42]. In addition to this, additional pathway receptors have been shown to be involved in cannabinoid signal transduction. These include peroxisome proliferator-activated receptors (PPAR), G-protein receptor 55 (GPR55), as well as nicotinic receptors, serotoninergic receptor (5-HT1A) and adenosine A2A (Figure 1)[15,43].

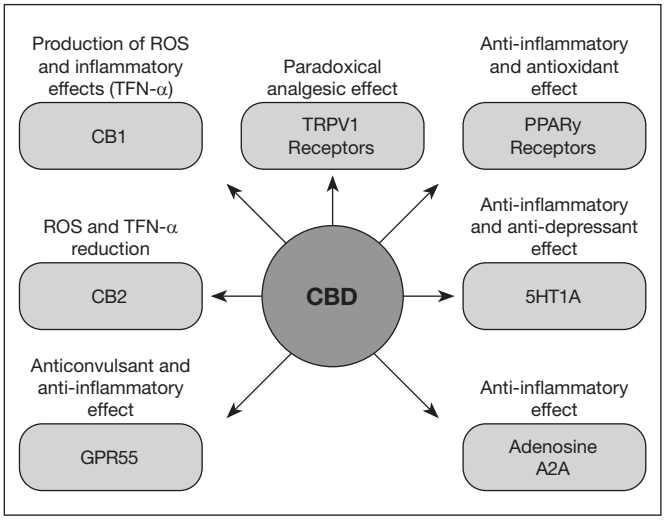


**Figure 1**. Main effects of cannabidiol on various membrane receptors

**Cannabinoids and inflammation**

Activation of glial CB1R and CB2R promote an anti-inflammatory state, elevating anti-inflammatory cytokines and also decreasing levels of pro-inflammatory cytokines. CB2R, present primarily in immune cells, plays an integral role in regulating humoral and cell-mediated immunity. Cannabinoids apparently act on inflammation through mechanisms different from those of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), thus free of the adverse effects associated with them.

Studies show that prenylated flavones, non-cannabinoid derivatives of the cannabis genus, are 30 times more potent than aspirin in inhibiting cyclooxygenase (COX), the well-established anti-inflammatory drug. THC is 80 times more potent than aspirin and twice as potent as hydrocortisone. Ajulemic acid (AJA), a

synthetic cannabinoid, is 50-100 times more potent than THC as an analgesic, having 12 times more affinity for CB2R than for CB1R, which makes it non-psychoactive in therapeutic doses[44].
Among the effects of cannabinoid derivatives, immune modulation referring to the suppression of tumor necrosis factor alpha (TNF-α) and other cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6), interferon-gamma (IFN-γ), and interleukin 12 (IL-12) produces a potent anti-inflammatory activity. CBD reduces TNF-α production and induces a reduction in FAAH activity while increasing the production of anandamide, an anti-inflammatory endocannabinoid. THC has been observed to produce anti-inflammatory effects by antagonizing with TNF-α[45-47].
The main anti-inflammatory mechanisms produced by cannabinoids are induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production, and induction of T-regulatory cells (Tregs).

**Induction of apoptosis**
Under normal conditions, apoptosis is necessary to maintain homeostasis and involves morphological changes (cell shrinkage, nuclear fragmentation, and pore formation in the plasma membrane) as well as molecular changes (induction of caspases and extravasation of cytochrome c)[48].
Both anandamide and THC, for example, induce apoptosis in T and B lymphocytes. However, THC, with greater immunosuppressive potency, promotes additional apoptosis in macrophages and antigen-presenting cells through regulation of BCL2 protein activity and caspases. Cannabidiol, on the other hand, induces apoptosis in T cells, CD4+ and CD8+, producing reactive oxygen species (ROS) and activating caspases 8 and 3[48-52]. In opposition to immune cells, cannabinoids can protect apoptosis in CNS cells, conferring neuroprotection. The mechanisms of immunosuppression by cannabinoids occur through partial activation of CB2R and probably also CB1R[53].

**Inhibition of cell proliferation**
Inhibition of lymphocyte proliferation may be induced by direct effects on immune cells, and not mediated by CB1R and CB2R. While low doses of THC stimulate T cells, high doses induce inhibition of the response to lipopolysaccharides (LPS), T cell mitogens, and anti-CD3 antibodies. THC can suppress immune functions and increase susceptibility to infections[54-56].

**Suppression of cytokine production**
Cytokines are the signaling proteins synthesized and secreted by stimulating immune cells. They are the modulating factors that balance the initiation and resolution of inflammation. Cannabinoids induce downregulation of cytokine production and disruption of the well-regulated immune response. In addition, cannabinoids can affect the host immune response and resistance by disrupting the balance between cytokines produced by T-helper, Th1 and Th2 subsets. Cannabinoids also exert their immunosuppressive effects by decreasing inflammatory products, including nitric oxide (NO), TNF-α, gamma interferon-induced protein 10 (CXCL10), chemokine CCL2, and chemokine CCL5. In addition, cannabinoids can regulate the migration and differentiation of monocytes into M1 or M2 macrophage phenotypes, as well as their ability to produce cytokines, chemokines, and other immune mediators[57-60].
Anandamide reduces the production of several interleukins (IL) such as IL-2, IL-6, IL-8, IL-12 and monocytes induced by LPS and also blocks LPS triggered activation of LPS and I-KB kinase of nuclear factor kappa B (NFkB), a protein complex that controls DNA transcription, cytokine production and cell survival[61]. Cannabidiol also reduces prostaglandin E2 and COX activity. THC, on the other hand, altered the Th1 destructive immunity by Th2 protective immunity, even less effectively than cannabidiol, and also showed immunosuppressive effects on dendritic cells. This occurs through suppression of IL-12p40 production and inhibition of expression of maturation markers such as MHCII, CD86 and CD4[51,62-65].
When AJA is in the peripheral blood, it reduces the production of the pro-inflammatory cytokine IL-1b, as well as the steady-state levels of IL-6 mRNA and its subsequent secretion by LPS-stimulated macrophages. IL-6 is a multifunctional cytokine that contributes to inflammation and tissue injury in a variety of diseases. However, AJA did not reduce TNF-α production in these studies[66]. Finally, increased levels of anandamide decrease inflammatory responses, suggesting that endocannabinoids are physiologically involved in attenuating the immune system[7]. However, there are still poorly understood and sometimes contradictory effects.

**Induction of regulatory T-cells**
Exogenous cannabinoids have been shown to suppress T-cell-mediated immune responses, mainly by inducing apoptosis and suppressing inflammatory cytokines and chemokines. THC can increase the number of Treg Foxp3+ cells, inducing them to inhibit cytokine production. This suggests that Treg cells, unlike other T cells, may be resistant to THC-induced apoptosis and can suppress the activation of T cells that eventually escape apoptosis. This further supports the notion that the endogenous cannabinoid system is protective against inflammatory changes[67,68].

**Cannabinoid system and oxidation**
Antioxidant activity of CBD has been shown in the redox state, direct or indirectly, through components of this system. The imbalance between oxidants and antioxidants leads to oxidative stress in lipids, nucleic acids, and proteins, which results in changes in the structure of these components, disrupting their molecular interactions and signal transduction pathways[69]. Oxidative modifications play an important role in the functioning of redox-sensitive transcription factors, such as nuclear factor erythroid 2 (NRF2) and NFkB. Therefore, they play a role in the regulation of pathological conditions characterized by imbalances in the redox system and inflammation, such as cancer, inflammatory diseases, and neurodegenerative diseases[70,71].
Like other antioxidants, CBD interrupts free radical chain reactions by capturing these molecules or transforming them into less active forms[8], also reducing oxidative conditions by preventing the formation of superoxide radicals, which are mainly ge-

nerated by xanthine oxidase (XO) and NADPH oxidase (NOX1 and NOX4). In experimental models of chronic inflammation, CBD promoted reduced NO levels[72].

CBD also reduces ROS production by chelating transition metal ions, thus decreasing amyloid formation in neurons[9]. It increases the mRNA level of superoxide dismutase (SOD) and the enzymatic activity of copper (Cu), zinc (Zn) and manganese-dependent superoxide dismutase (Mn-SOD), which are responsible for superoxide radical metabolism in experimental models[74].

When lowering ROS levels, CBD also protects non-enzymatic antioxidants through the prevention of their oxidation. This is relevant because glutathione cooperates with other low molecular weight compounds in antioxidant action, especially with vitamins such as A, E and C[75].

Repeated doses of CBD in inflammatory conditions increase peroxidase and glutathione reductase activity, resulting in decreased malonaldehyde levels[72]. The high affinity of CBDs for cysteine residues is a possible explanation for this observation[76]. It is known that under oxidative conditions, changes in enzyme activity can be caused by oxidative modifications of proteins, especially aromatic and sulfur amino acids[10]. CBD also aids in the action of antioxidant enzymes by preventing reduction in the levels of microelements, such as Zn or selenium [Sn], which are normally lowered under pathological conditions. These elements are necessary for the biological activity of some proteins, especially enzymes such as SOD or glutathione peroxidase[78].

Finally, it s possible to observe that cannabinoids can interact with the body's natural antioxidant system. This mechanism constitutes an accessory pathway by which the endocannabinoid system acts with anti-inflammatory effects.

## NON-CANNABINOID RECEPTORS AND INFLAMMATION

### TRP receptors

It has also been shown that CBD can affect redox balance and inflammation through modulation of mammalian transient receptor potential (TRP) channels[77,80]. CBD activates vanilloid receptors (TRPV), directly or indirectly, by increasing the level of endogenous AEA, one of the agonists of TRPV1[81]. This agonism causes desensitization, producing the "paradoxical analgesic activity" similar to that of capsaicin[72]. It has been suggested that there is a relationship between TRPV1 molecular signaling and oxidative stress[82] because ROS and the products of lipid peroxidation can regulate the physiological activity of TRPV1 by oxidizing its thiol groups[83]. Consequently, CBD not only activates TRP through a direct agonist-receptor interaction, but also by reducing the level of oxidative stress. In addition, it activates other vanilloid receptors, such as TRPV2 and the potential receptor subtype of ankarin protein 1 (TRPA1), while antagonizing the TRP-8 receptor (TRPM8)[79].

### PPAR receptors

PPARγ are members of a family of nuclear receptors that modify gene transcription in response to a variety of signaling pathways. They are expressed on immune system cells, such as monocytes and macrophages, and regulate inflammatory responses through inhibitory effects on the expression of inflammatory cytokines and eicosanoids. It participates in modulating inflammation by inducing proteosomal degradation by ubiquitination of p65, which causes inhibition of pro-inflammatory gene expression, such as cyclooxygenase-2 (COX2) expression and some pro-inflammatory mediators, such as TNF-α, IL-1β and IL-6, as well as inhibition of NFkB-mediated inflammatory signaling[84]. For this reason, acting through the PPARγ receptor, CBD shows anti-inflammatory and antioxidant properties.

Moreover, its direct activity is enhanced by the action of AEA and 2-AG, which are also PPARγ agonists and whose levels are elevated by these cannabinoids[85]. In addition to its ability to bind to CB2R, AJA binds to PPAR-γ, consequently suppressing the promoter activity of IL-8, a chemoattractant cytokine with specificity for the neutrophil, the main cell involved in acute inflammation.

### GPR55 Receptors

CBD acts as an antagonist of GPR55, which, when inactivated, reduces the intracellular level of calcium ions, and probable anticonvulsant effect[86]. Moreover, it has been shown that mice knockout for GPR55 have elevated levels of anti-inflammatory interleukins (IL-4, IL-10, and IFN-α)[87], while high expression of GPR55 reduces ROS production[88].

### 5-HT1A receptors

CBD has direct affinity for the human 5-HT1A receptor[89], and it also can indirectly induce this receptor by increasing the level of AEA[90]. When activated, the 5-HT1A receptor can act as a membrane antioxidant by capturing ROS[91]. Therefore, through activation of 5-HT1A, CBD can neutralize phospholipid peroxidation and thus participate in the protection of biomembranes against oxidative and, consequently, inflammatory modifications.

### Adenosine A2A receptors

CBD is also an agonist of the adenosine A2A[92] receptors. Adenosine and its agonists exhibit anti-inflammatory activity in vivo[93]. Therefore, adenosine release is one of the mechanisms of immunosuppression during inflammation[94], and adenosine receptor agonists reduce TNF-α[95,96] levels.

## CONCLUSION

Cannabinoids are a promising therapeutic option in the context of inflammatory diseases, given the complete and complex relationship between the endocannabinoid system and the immune system. The setback to be overcome in the use of cannabinoids as anti-inflammatory drugs includes the synthesis of cannabinoid receptor agonists that are non-psychoactive while maintaining potent anti-inflammatory activity. While most studies have focused on the effect of cannabinoids on cytokines, apoptosis and Th1 cells, further investigations into their effect on Th17 cells, dendritic cells, natural killer cells, B cells and Foxp3+ regulatory T cells are critical, as these cells play important roles in regulating and mediating the response to inflammatory or autoimmu-

ne diseases. Moreover, the interaction with adhesion molecules, co-stimulatory molecules, and chemokines, require further study to increase the comprehension of cannabinoids and their intricate effects on immune system disorders.

## AUTHORS' CONTRIBUTIONS

**Alexandre Magno da Nóbrega Marinho**
Project Management, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization
**Ricardo Wagner Gomes da Silva-Neto**
Methodology, Writing - Preparation of the original, Writing - Review and Editing, Visualization

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# Adverse effects of cannabinoid use: what is the safety paradigm?

*Efeitos adversos do uso dos canabinoides: qual o paradigma de segurança?*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** Interest in the use of marijuana (*Cannabis sativa*) for medicinal purposes has increased exponentially in recent decades, and the plant and its derivatives are becoming more frequently found in prescriptions for patients with chronic pain. All prescription drugs and illicit substances have adverse effects, even those from plants, fruits, and flowers, as has been well established with the use of tobacco, alcohol, and opium. Marijuana is no exception. The purpose of this study was to review and synthesize the evidence related to the adverse effects promoted by plant-derived cannabinoids, and the implications for the safety of using these substances in pain patients.
**CONTENTS:** A narrative review was conducted based on articles published in scientific journals indexed in Pubmed and Scielo between the years 2000 and 2022.
**CONCLUSION:** The evidence is still contradictory and weak on many aspects of adverse effects and clearly there is a need for further research and advances towards a more detailed elucidation of these effects for both non-medical and medical cannabis use. Screening and monitoring of such use, identifying situations of vulnerability to mental illness and dependence, with careful surveillance for adverse effects, is critical.


**Keywords:** Cannabis, Drug-related side effects and adverse reactions, Medical marijuana.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: O interesse na utilização da maconha (*Cannabis sativa*) com fins medicinais aumentou de forma exponencial nas últimas décadas e a planta e seus derivados vêm se tornando mais frequentemente encontrados nas prescrições médicas de pacientes com dor crônica. Todos os fármacos prescritos e substâncias ilícitas têm efeitos adversos, mesmo aquelas provenientes de plantas, frutas e flores, como já ficou bem estabelecido com o uso do tabaco, álcool e ópio. A maconha não é exceção. O objetivo deste estudo foi revisar e sintetizar as evidências relacionadas aos efeitos adversos promovidos pelos canabinoides derivados da planta, e às implicações sobre a segurança do uso destas substâncias em pacientes com dor.
**CONTEÚDO**: Foi realizada uma revisão narrativa baseada em artigos publicados em revistas científicas indexadas no Pubmed e Scielo, entre os anos de 2000 e 2022.
**CONCLUSÃO**: As evidências ainda são contraditórias e frágeis em relação a muitos aspectos dos efeitos adversos e claramente há a necessidade de mais pesquisas e avanços para uma elucidação mais detalhada destes efeitos tanto para o uso não medicinal quanto médico de cannabis. É fundamental uma triagem e monitoramento desse uso, identificando situações de vulnerabilidade a doenças mentais e dependência, com cuidadosa vigilância de efeitos adversos.


**Descritores**: Cannabis, Efeitos adversos e reações adversas relacionadas a medicamentos, Maconha medicinal.

## INTRODUCTION

Cannabinoids are a heterogeneous group of natural, endogenous or synthetic compounds, which are able to activate receptors that are part of the endocannabinoid system. The first compounds capable of producing clinical effects were obtained from marijuana (*cannabis sativa*), a plant from which about 60 substances classified as cannabinoids are produced, among which the most relevant is tetrahydrocannabinol (THC), but cannabidiol (CBD), cannabinol, and cannabigerol, among others, can also be found[1]. Later, with the discovery of the endocannabinoid system endogenous ligands such as 2-araquidonoil glycerol (2-AG) and ethanolamine O-araquidonoil (AEA) were identified, which act on cannabinoid receptors CB1 and CB2[2].
Cannabis products have been used by humans since prehistoric times, due to the plant's versatile uses, such as fiber, food, and medicine, as well as its adaptability to a wide variety of habitats. The first evidence of domestication, planting, and human medicinal use dates back 10.000 years, in Japan and other parts of

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**HIGHLIGHTS**
- The evidence is still contradictory and weak on many aspects of adverse effects.
- Increased knowledge about the extraction, purification, and synthesis of cannabinoids, as well as the pharmacology of these substances, has shed light on the mechanisms involved in their effects.
- There are an estimated 1 million and 10 million daily (or near-daily) cannabis users in Canada and the United States, respectively, making the issue a public health priority.

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the Asian continent[3]. In Brazil, its use was introduced by African slaves brought by the Portuguese, and it was named "*cânhamo*". It is not, therefore, a native plant of this country[4]. The therapeutic use of cannabis products has gained strength in Brazil and in the world, and they are now prescribed for various health problems. However, over the years, the scientific documentation of the hedonistic effects of cannabis use has started to become widespread. The non-medical use of cannabis, illicit in Brazil until now, started to be seen worldwide as a problem to be discussed, just like opium and coca, since the inclusion of the issue by the Brazilian and Egyptian representatives, in the II International Opium Conference, held in 1924, in Geneva, by the former League of Nations[4].

Increased knowledge about the extraction, purification, and synthesis of cannabinoids, as well as the pharmacokinetics and pharmacodynamics of these substances, has shed light on the mechanisms involved in their effects.

The purpose of this study was to synthesize the evidence regarding the adverse effects promoted by cannabinoid derivatives, and the implications for the safety of using these substances in pain patients.

## CONTENTS

A narrative review was conducted based on a search in Pubmed and Scielo databases, using different combinations of the keywords *"cannabinoids"; "cannabis"; "adverse effects"; "medicinal cannabis"; "cannabidiol"*, between the years 2000 and 2022.

Interest in the use of cannabis for medicinal purposes (*Cannabis sativa* L.) has increased exponentially in recent decades in several countries, and the plant is becoming more frequently found in prescriptions for patients with chronic pain. To illustrate this worldwide increase, statistics can be cited that 40% of cancer patients use cannabis for pain management in countries where access is legal, such as Canada, Germany, and Israel. However, herbal and plant-derived cannabis products are not monitored like traditional pharmaceuticals, which creates doubts and uncertainties about their true health risks to patients. Although synthetic cannabis presentations available for prescription have their contents explicit, a wide variety of plants and cannabis products contain different concentrations of THC and CBD, making the effects of exposure unpredictable[5].

According to US data, in states that have legalized cannabis, the prevalence of daily, weekly, and monthly cannabis use was much higher than in countries where it is still illegal. Evidence shows a tendency to increased consumption among adolescents, who are a particularly vulnerable age group for the onset of psychoactive substance use[6].

All prescribed drugs and illicit substances have adverse effects, even those from plants, fruits, and flowers, as has already been well established by the use of tobacco, alcohol, and opium. Marijuana is no exception. A scoping review of 72 systematic reviews on the effects of medical cannabis found that mild adverse effects were reported as frequent in half of the reviews included in the study, and in 36% of these, severe reactions were reported. The authors suggest that there is a possibility that the harms may outweigh the benefits[7].

Within the current context of the consideration of laws on cannabis use around the globe and increase of its use in various medical indications, it is of paramount importance, and a matter of public health, to provide clear and evidence-based information on the undesirable, acute and persistent effects, as well as being aware of the individuals most susceptible to complications when cannabis is used for medicinal purposes.

### Acute and intoxication

Cannabis use can lead to a range of behavioral or psychological changes with clinical impact, such as anxiety, euphoria, altered motor coordination, slowness, time distortion, sensory alterations, impaired judgment, and social isolation, which occur during or shortly after cannabis use and may be related to the dose that was used, the environment and previous experiences, and the individual's expectations. The most frequently observed adverse effects are panic attacks and other forms of anxiety, mainly reported by beginners[8].

Memory and attention are negatively impacted while impulsivity is increased. Authors have shown that acute cannabis use impaired working memory and verbal memory. A study correlating pharmacogenetics and neurocognition, in different types of cannabinoid derivative use (medicinal and non-medical), showed that working, verbal and visual memories were more impacted during acute intoxication in individuals with COMT Val allele, which is believed to be a link between cannabis and schizophrenia[9,10]. Acute cannabis toxicity is presented both with psychiatric symptoms (relaxation, time distortion, loss of inhibitions) and through physical effects (tachycardia, conjunctival edema, impairment in cognitive tasks and short-term memory), more common with higher THC ratios[11].

One little-known aspect of intoxication is that involving workers who handle the plants or are exposed to them, such as growers, police officers, or forensic technicians. Immediate respiratory symptoms in direct response to exposure are most common and are marked by congestion, rhinoconjunctivitis and/or chest symptoms such as coughing, wheezing, chest tightness or shortness of breath, related to bronchial hyperresponsiveness. Skin symptoms such as urticaria (contact urticaria), angioedema, and, rarely, late symptoms resembling dermatitis are also observed. Up to 20% of affected individuals may also experience anaphylactic-type reactions. Although rare, anaphylactic reactions have been reported in sensitized individuals, associated with the ingestion of hemp seeds, which are marketed as a protein health food[12].

### Psychiatric effects

*Psychosis and schizophrenia*

Studies have shown that regular cannabis users are twice as likely to develop psychosis, and for users with very high and frequent consumption, this likelihood increases to four times. Approximately one in four individuals with schizophrenia has a concomitant diagnosis of cannabis abuse. Overall, this use has been

shown to be associated with earlier onset of psychosis, increased symptom severity, higher relapse rates, longer hospitalizations, and poorer outcomes. Users who develop psychosis are more likely to develop the symptoms at a younger age than non-users, and are more associated with THC. An experimental study has shown that intravenous THC administration in healthy individuals can directly induce the development of psychosis subjective symptoms[13].

Despite the association that has been observed between cannabis use and schizophrenia, there is difficulty in proving a causal relationship. However, there is evidence that cannabis use affects the brain cannabinoid receptors affected by schizophrenia, cortical maturation, and mechanisms of addiction. There appears to be an overlapping genetic susceptibility to cannabis use and the development of schizophrenia, but this statement requires further investigation[14,15].

*Anxiety*

There are not a lot of studies on cannabis and anxiety, despite hypotheses that THC may provoke anxiety symptoms through its effects on serotonin and norepinephrine. There is a shortage of data, derived from the available studies, that allows for a longitudinal analysis, and therefore the available data does not reflect the potential for reverse causality. Cannabis use alone is not sufficient for the development of long-term anxiety and is at most a minor risk factor that may act in conjunction with other factors[16].

A genetic study about the effects of cannabis on anxiety symptoms in 1.424 adolescents over five years showed that cannabis use is associated with an increase in anxiety symptoms only in 5-HTTLPR gene short allele carriers, not a behavior observed in the general population[17].

*Depression and suicidal ideation*

There is a higher prevalence of cannabis use among patients with major depressive disorder compared to the general population. However, the evidence about the effects of cannabis on symptoms of depression is mixed. Some authors have reported that cannabis may be therapeutic for patients with depression, while others have shown that the substance may exacerbate symptoms. It is assumed that cannabis can both act as an outlet for depressive symptoms and can cause an increase in blunted emotions and anhedonia[18,19].

There are concerns about increased suicidal ideation or suicide attempts with acute or chronic cannabis use, although there is insufficient evidence to assert causality. Review studies with meta-analysis have demonstrated an association, although the included studies do not reflect current use patterns and have samples that are not representative of the general population[20,21].

In a nationally representative cohort of adults aged 20 to 59 in the United States, with data collected between 2005 and 2018, a significant association between cannabis use in the past 30 days and suicidal ideation was shown. Recent use was also associated with moderate to severe depression symptom profiles. These results generate further reflection on the topic and the need for additional care in individuals using the drug[22].

*Personality disorder*

Regarding this aspect, a study of 1.419 individuals with permanent DSM-IV diagnoses draws attention, showing that some personality disorders, such as antisocial and borderline, were strongly associated with cannabis use and abuse, indicating a possible genetic and phenotypic correlation. There should be an alert for this issue that is not always systematically addressed[18].

**Cardiovascular effects**

A possible increased risk of cardiovascular (CV) events associated with cannabis use has been reported and generated concern. Different mechanisms have been suggested as possible causes of cannabis-related CV risk, including direct reversible cerebral vasoconstriction (a possible mechanism of stroke), increased procoagulant proteins, ischemia by modulation of cannabinoid receptors in vascular smooth muscle and human cardiomyocytes, and arrhythmia. In a systematic review of 116 case reports and 29 observational studies, the authors concluded that although data are limited, there is a suggestion that cannabis use may have negative CV consequences[23,24].

A study that assessed the risk of cardiovascular emergency department visits and hospitalization in 18.653 adult patients authorized to use medical cannabis in Ontario, Canada from 2014 to 2017, noted that medical cannabis authorization was associated with an increased risk of emergency department visits or hospitalization for CV events, including stroke and acute coronary syndrome[25].

Recent cannabis use was associated with higher odds of a history of heart attack by an American study that evaluated 4.610 individuals between the ages of 18 and 44. The magnitude of this association increased among more frequent cannabis users. The large sample size, generalizability, and detailed data on cannabis use from this cross-sectional study provide unique insight into this growing public health problem[26].

**Effects of contaminants**

The non-medical community generally considers cannabis a relatively safe drug. There are, however, significant uncertainties surrounding the prevalence and effects of toxic contaminants associated with preparations, except for when good practices are employed. In addition to various factors that affect the pharmacokinetic and pharmacodynamic profile, contaminants, such as bioactive substances, can affect the absorption, distribution, metabolism, and excretion of phytocannabinoids and therefore potentially alter their effect. There is a shortage of formal research investigating this topic. There is a small case series (n=5) describing the effects of cholinergic adulteration on cannabis preparations. The results suggest that the addition of cholinergic compounds (nicotinic agonists, muscarinic antagonists, and anti-acetylcholinesterase substances) is associated with an increase in the effects of THC, serving to highlight that coadministered substances may interact with THC and other cannabinoids in a manner that modulates both their pharmacokinetics and clinical effect. More research is needed on the pharmacological effects of contaminants, especially in countries where non-rigorously controlled formulations are used by patients[27].

**Gastrointestinal effects**

Chronic cannabis use has the potential to alter and disrupt homeostasis in the gastrointestinal tract. TCH can increase food absorption and inhibit gastric motor activity via CB1 receptor activation. And despite the described antiemetic action of cannabinoids, there is the cannabinoid hyperemesis syndrome, which presents as a rare condition associated with cyclic nausea and vomiting, which can be induced by prolonged, non-medical cannabis abuse[28,29].

Thenowledge that agonism in cannabinoid receptors may possibly influence gastrointestinal motility has made the endocannabinoid system a new target for the treatment of some diseases, such as ulcerative colitis and Crohn's disease. It is worth mentioning that a major limitation for these therapies targeting the gastrointestinal tract with the use of cannabinoids are their potential adverse effects, which cannot be neglected[28].

**Effects on the respiratory system**

The possibility that smoking cannabis may have a negative effect on the respiratory system has generated an increased focus for this issue in recent years, considering also that smoking is one of the respiratory diseases cardinal points.

There is already consistent clinical evidence between the association of smoked cannabis with increased airway inflammation, which is similar to the impact of tobacco. From clinical studies it has been observed that cannabis smokers have higher percentages of chronic bronchitis symptoms, such as cough, bronchospasm, hyperinflation, and sputum production, when compared to tobacco users[30].

**Effects on the immune system**

Cannabis use was associated with statistically significant reductions in CD4 and CD8 T cells in individuals with and without acquired immunodeficiency syndrome (AIDS), yet cannabis exposure was not associated with an increased risk of progression to AIDS or increased oral HPV infection in patients with and without HIV. It is important to highlight that individuals who use cannabis daily have more severe symptoms of HIV infection and more adverse drug effects than users who use the substance less frequently[31,32].

**Cancer**

Mutagenicity of cannabis has been demonstrated *in vitro* and that smoking cannabis produces carcinogenic substances such as nitrosamines and polycyclic aromatic hydrocarbons, which are similar to those produced by individuals who smoke tobacco. In addition, cannabis smoke contains immunosuppressants and a mixture of potentially mutagenic chemicals. Despite these studies, cannabis, unlike tobacco and alcohol, has not yet been established as a risk factor for head and neck cancer, despite questions that need explanation and clarification on the subject in the coming years[33].

Authors have shown increased risks with any type of cannabis use, including at the time of the survey, for testicular germ cell tumors, especially in users with more than 10 years of use, which is worth warning for this population, as the increased risk result may be up to double[34].

**Reproductive system**

Chronic use of cannabis can cause altered reproductive system function. There is *in vivo* evidence to suggest that cannabis may negatively affect testosterone production and sperm motility in men. In animals, repeated treatment with cannabinoid agonists reduces testosterone secretion, alters sperm production and motility, and can inhibit ovulation. It appears, therefore, that long-term exposure, especially to THC, can result in infertility, most commonly observed in men[35,36].

Despite these reported associations between cannabis use and impaired fertility, there is currently insufficient concrete clinical evidence to comprehend the degree of risk of exposure to the substance in this specific respect. However, it is advisable that individuals avoid cannabis use when trying to conceive.

**Maternal-fetal binomial injuries**

In humans, cannabis use does not appear to be associated with low birth weight, premature delivery, or placental abruption. However, an increased risk of sudden infant death syndrome is reported in cases of cannabis use at conception, during pregnancy, and postnatally. In a study of postnatal growth, a dose-response relationship was found between head circumference and cannabis exposure, in which intense maternal exposure was associated with a smaller head circumference that persisted until 12 years of age[37,38].

CBD and other cannabinoids have been shown to cross the placental barrier and children who are exposed prenatally are more likely to experience numerous developmental changes, such as inattention, lower intelligence scores and poor academic performance. Exposure through lactation can delay developmental milestones in early childhood and affect communication early in life[39,40].

**Addiction**

Regular cannabis use can become an addiction in the same way as with other substances such as opioids or tobacco. The feeling of being "high" consequently generates the desire for repeated use and, for some users, this desire has the potential to become a disorder, with inappropriate use of the substance, especially in those who start this practice younger and those who have a higher frequency of exposure[41,42].

A research has shown that cannabis abuse is one of the most common addictions after cigarettes and alcohol in countries such as Australia, Canada, and the United States, although the rate of dependence is lower when compared to other drugs. However, this does not mean that it should be considered a trivial disease, because it is more prevalent in people who also abuse alcohol and other drugs. In recent years a steady increase in the number of users seeking assistance to control or quit cannabis use has been observed in several countries. This issue has to be looked at very closely in the coming years[41].

In US states that have implemented new laws regulating cannabis, there is potential for addiction to increase due to increased

availability. There are an estimated 1 million and 10 million daily (or near-daily) cannabis users in Canada and the United States, respectively, making the issue a public health priority[43].

## CONCLUSION

The understanding of cannabis use is rapidly changing, from new medical indications and legalization of use to the paradigm that it is not a harmless substance without consequences for those who use it, as is sometimes reported on the internet, on many websites and social media. Prolonged use has varied health implications, involving physical dependence and addiction, cognitive impairment, psychiatric changes, cardiovascular problems, infertility, and even cancer risk.

An important challenge is to compare the adverse effects of the non-medical use of cannabis, which is usually done by young adults who smoke cannabis, and the risks of medical use by older adults, usually by oral route. Screening and monitoring of this use is critical, identifying situations such as vulnerability to mental illness and dependence, with careful surveillance for adverse effects and doing dose titration, as well as close observation of the dose-response relationship before prescribing higher oral doses.

Literature reviews are still contradictory and weak on many aspects of adverse effects and clearly there is a need for further research and advancement for more detailed elucidation of these effects for both non-medical and medical cannabis use.

## AUTHORS' CONTRIBUTIONS

**João Batista Santos Garcia**
Conceptualization, Methodology, Writing - Review and Editing, Supervision
**José Osvaldo Barbosa Neto**
Data Collection, Methodology, Writing - Review and Editing

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# Cannabinoid therapy within the Unified Health System, perspectives in relation to pain treatment

*A terapia com canabinoides e perspectivas em relação ao tratamento da dor no Sistema Único de Saúde*

Hygor Kleber Cabral Silva[1], Rafaela Fernandes Lourenco[1]

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Pain is "an unpleasant sensory and emotional experience associated or not with real or potential tissue damage" which, when exceeding its protective function, beyond three months, is considered chronic pain, which in the long term can have its own clinical course. Given the scientific advances on the therapeutic effects of cannabinoids, the article brings a proposal for reflection as the Brazilian public health system (SUS – *Sistema Único de Saúde*), through medical cannabis, could offer better therapies for the treatment of conditions such as chronic pain.

**CONTENTS**: A narrative review was elaborated in databases such as Pubmed, Medline and Scielo. Considering the SUS Guidelines, the incorporation and access to medicinal cannabis can be understood as a strategy of social justice and reduction of inequities, because it is effective and safe in the treatment of chronic conditions, besides that the system already has strategies and policies aimed at regulating and distributing herbal medicines. Chronic pain is a prevalent condition, affects more than 2 billion people worldwide, and can be considered a global crisis. In Brazil, its prevalence varies between 23.02% and 76.17%, being higher in the elderly and female individuals. Despite this, in many cases, conventional treatments do not generate the analgesics effects expected, in addition to causing important adverse effects.

**CONCLUSION**: *Cannabis sativa* L. has great potential to become one of the best alternatives for chronic pain to be incorporated into herbal access programs around the country, such as in the SUS' *Farmácia Viva* project.


**Keywords**: Cannabinoids, Chronic pain, Complementary therapies, Delivery of health care, Phytotherapy.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A dor é "uma experiência sensitiva e emocional desagradável associada, ou semelhante àquela associada, a uma lesão tecidual real ou potencial", que, ao exceder sua função de proteção além de três meses é considerada dor crônica, e que em longo prazo pode ter seu próprio curso clínico. Diante dos avanços científicos acerca dos efeitos terapêuticos dos canabinoides, este artigo traz uma proposta de reflexão sobre como o Sistema Único de Saúde (SUS), por meio da medicina canábica, poderia ofertar melhores terapêuticas para o tratamento de condições que cursam com dor crônica.

**CONTEÚDO**: Foi elaborada uma revisão narrativa em bancos de dados como Pubmed, Medline e Scielo. Considerando as diretrizes do SUS, a incorporação e acesso a cannabis medicinal pode ser entendida como estratégia de justiça social e redução de inequidades, por ser eficaz e segura no tratamento de condições crônicas, além de que o sistema já conta com estratégias e políticas voltadas para regulamentação e distribuição de fitoterápicos. Dor crônica é uma condição prevalente, afeta mais de 2 bilhões de pessoas em todo o mundo e pode ser considerada uma crise global. No Brasil, sua prevalência varia entre 23,02% e 76,17%, sendo maior em idosos e em pessoas do sexo feminino. Apesar disso, em muitos casos, os tratamentos convencionais não geram os efeitos analgésicos esperados, além de causarem efeitos adversos importantes.

**CONCLUSÃO**: A *Cannabis sativa* L. tem um grande potencial de se tornar uma das melhores alternativas para dor crônica a ser incorporada nos programas de acesso a fitoterápicos no país, como no programa Farmácia Viva, do SUS.


**Descritores:** Canabinoides, Dor crônica, Fitoterapia, Prestação de cuidados de saúde, Terapias complementares.

## INTRODUCTION

Pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1], with a vital function in protecting the body. Pain exerts a protective function in animals, serving as an alert. This mechanism, with loss of its normal function, as in the case of post-surgical injuries, generates a painful symptom and re-

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**HIGHLIGHTS**
- Medical cannabis discussed from a public policy perspective;
- Efficacy and safety of cannabinoids in chronic pain;
- Challenges and expectations concerning the inclusion of *Cannabis sativa* L. as a phytotherapic in the *Farmácia Viva (*Living Pharmacy*)* project and the Brazilian public health system (SUS – *Sistema Único de Saúde*).

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quires therapeutic interventions. It is important to have efficient therapeutic tools to handle this condition[1].

Chronic pain (CP), for practical purposes, is considered to be pain that is persistent for more than three months. Thus, it loses its protective function and becomes a disease in itself. In the long term, it can also be the disease itself with its own clinical course[2,3]. It can also be independent of the causal event, without correlating in intensity with its causative agent, which may even be unknown[2,3].

Given the current scenario of indiscriminate use of opioids, data from 2018 already showed that around 30 million people abused these substances, causing many deaths. In the United States, this abuse is already considered an epidemic and a public health crisis and an alternative is increasingly needed to reduce this excessive consumption and avoid collateral damage. In this context, cannabis has significant relevance because it has a real potential to alleviate opioid withdrawal symptoms, reduce consumption, prevent relapse, and reduce overdose deaths[4].

## THE ENDOCANNABINOID SYSTEM AND PHYTOCANNABINOIDS

Currently, much emphasis has been given to clinical medicine and research on the therapeutic effects of phytocannabinoids present in *Cannabis sativa* L., a plant whose molecules called phytocannabinoids can act effectively as analgesics, anti-inflammatories, anticonvulsants, anxiolytics, and even neuromodulators. Cannabinoids act on the endocannabinoid system (ECS), an endogenous system recently discovered and described in the 1990's, which is responsible, among other functions, for homeostasis in vertebrate animals[5-7]. Many researches have directed their efforts to new pain treatments. One of the proposed mechanisms acts from the ECS modulation, in which exogenous cannabinoids coming from *Cannabis sativa* L also act. These discoveries were fundamental for elucidation of the phytocannabinoids mechanisms and places of action in pain modulation[8-10].

Cannabidiol (CBD) is one of the best known phytocannabinoids. It has proven to be extremely versatile pharmacologically, also showing an analgesic effect, with action that may be responsible for suppressing neuronal excitability and pain perception[11,12]. Moreover, the other predominant phytocannabinoid, tetrahydrocannabinol (THC), also acts as a positive allosteric modulator of opioid receptors, suggesting the involvement of these receptors in the antinociceptive effect (drugs with analgesic potential) of both phytocannabinoids[13-17].

### The dilemma of access to medical cannabis in Brazil

Access to medicinal cannabis in Brazil is still unequal, but it already happens for a small portion of the population, who seek this access through importation, patient associations, or even through judicial decisions for self-cultivation and artisanal production of the phytotherapeutic derivative. However, there is still the unofficial way, in which the majority still places themselves, assuming the risks inherent to the illegality of the substances, for lack of resources and the absence of the State in the regulation and distribution of the medicine[18,19].

Through medical prescription, the treatment with phytocannabinoids is already regulated in Brazil, based on decisions taken by the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA) in recent years. CBD, a phytocannabinoid whose therapeutic value arouses much scientific and commercial interest, was reclassified in 2015 and began to compose the class of controlled drugs on the C1 list of the Agency, subject to notification of special control prescription type B[20]. THC, the plant's psychotomimetic component, is still on the A3 list of psychotropic substances, subject to type "A" prescription notification[21,22].

Given the advances in scientific knowledge of the therapeutic effects of cannabinoids, especially CBD and THC, this article brings a proposal for reflection on the strategies that could be adopted by the Brazilian public health system (SUS – *Sistema Único de Saúde)* in order to promote the health of the population, prevent injuries and complications and ensure access to the best therapeutic tools for treatment of chronic diseases, including CP, through cannabis medicine. In Primary Health Care (PHC), via the Family Health Strategy (ESF) as the gateway to the SUS, incorporating strategies such as Farmácia Viva (FV) – a national program that aims to rescue the use and potential of medicinal plants – and the Integrative and Complementary Practices (PIC) – national policy that uses therapeutic resources for prevention and health promotion, integrating the human being with the environment and society[23-26] – it would be possible to open paths for access to medical cannabis for social classes underprivileged, as it has been shown to be an effective therapy in improving living conditions linked to various diseases.

## CONTENTS

This study carried out a narrative review, searching for descriptors in international and national databases (Pubmed, Medline and Scielo portals), presenting an open theme, a selective literature review, without using a rigid protocol. This technique allowed the construction of the article in a more critical way, in order to comprehend the theme from a contextual point of view[27].

## DISCUSSION

### SUS as a fair and universal public policy

During the 1980s in Brazil, after mobilizations around sanitary reform and the promulgation of the 1988 Constitution, SUS becomes the healthcare and sanitary model of public health. Art. 4 of Law n. 8,080 of 1990, which gives substance to public health policy in Brazil, defines it as "the set of health actions and services, provided by federal, state, and municipal public agencies and institutions, of the direct and indirect Administration, and foundations maintained by the Public Power"[28]. Among the services, actions, and interventions defined are care activities "for people, individually or collectively, aimed at the promotion and prevention, diagnosis, treatment, and rehabilitation of diseases and illnesses[29].

The incorporation and access to medical cannabis within SUS can be understood both as social justice and as a strategy to redu-

ce inequities, since it has already proven as effective and safe in the treatment of some diseases and very important in improving the life conditions of people such as those suffering from CP[23,25]. For a population that unequivocally can benefit from cannabinoid therapy, but that often tries it through unofficial or judicial means and without the accompaniment of a health professional, also because of the high cost of the products in Brazil, the access to medical cannabis by SUS becomes a fundamental action[19].

Strategies for access to herbal medicines are already a reality in Brazil through the National Policy on Integrative and Complementary Practices (PNPIC) and the National Policy on Medicinal Plants and Herbal Medicines (PNPMF) approved in 2006, which explore the medicinal power of the Brazilian flora, however without contemplating Cannabis sativa L. as a regulated plant for use in the SUS. All these practices offered by the SUS should preferably take place within the scope of the PHC and ESF, the gateway and organizational base of the Brazilian health system[30-32]. These are the foundations for implementation and regulation of medical cannabis, in order to guarantee access to services of promotion, protection, prevention, cure, rehabilitation, and palliative care throughout life, strategically prioritizing the main functions of the system aimed at individuals, families, and general population, effectively contributing to well-being and social insertion of citizens[19,33,34].

Regarding phytotherapy, PNPIC offers to SUS users, within APS, the possibility of therapeutic use of plants *in natura* or dried (plant drug) and herbal medicines manipulated and/or industrialized. The responsibility for approval, regulation, and surveillance of these plant products lies with ANVISA, which has been improving the health legislation in order to meet the PNPMF and favor safe and free access to users[35].

The use and distribution of medicinal plants and herbal medicines is subject to prescriptions from higher level health professionals, thus requiring continued education and preparation for them to use this therapeutic tool according to the Memento Phytotherapic of the Brazilian Pharmacopeia (*Memento Fitoterápico da Farmacopeia Brasileira* - MFFB), whose objective is to guide the prescription, oriented by scientific evidence, in addition to obtaining knowledge of identification, indications, posology, pharmaceutical presentation, precautions, and care with herbal medicines[31,36,37].

A project that emerged in the 1980s, created by Professor Francisco José de Abreu Matos, from the Federal University of Ceará (*Universidade Federal do Ceará* - UFC), became, through the Ordinance n.º 866 of April 20, 2010, the FV[38], creating a health service of pharmaceutical assistance linked to SUS to encourage and develop the practice of cultivation and distribution of herbal medicines. For it to work, the program needs agronomy professionals for cultivation and harvesting, pharmacy professionals to process, manipulate, and dispense the drugs, and professionals to prescribe it (doctors and dentists) who can guide the use[39]. Herbal medicines can enable the treatment for many of the diseases common in vulnerable communities, playing a very important role in public health[40].

These popular phytotherapy practices must be in line with good scientific practices in order to implement an effective and efficient model, with resoluteness and benefits, ensuring free, equitable, universal, and integral access to the Brazilian population. Health managers must also encourage and develop scientific research with a critical view on the use of medicinal plants in SUS, including *Cannabis sativa* L.[19,32,39].

### *Cannabis sativa* L. as a therapeutic tool against pain

CP affects about 2 billion people worldwide and is associated with impaired physical and emotional function, reduced participation in social and vocational activities, and lower perceived quality of life. CP prevalence varies within the medical literature, being estimated between 10% and 55% of the world population, with an average of 35%, predominantly in women, and whose most common locations are dorsal and lumbar spine[1].

In Brazil, a systematic review performed in 2021[2] confirms the trend presented by the International Association for the Study of Pain (IASP)[41], showing prevalence ranging from 23.02% to 76.17%, presenting a national average of 45.59%[43].

Data on the prevalence of CP in Brazil are scarce and can vary among regions; for example, 31% in Rio de Janeiro[4], 76% in Maranhão[2], 29.7% in São Paulo[45], 26% in Florianópolis[46], and 40% in Salvador[47]. Most studies show a higher prevalence in females, in people with advanced age (above 60% in people over 75 years old), being daily in almost 50% of the elderly, having moderate intensity for 45.8% of them and intense intensity for 46%, being associated with disabilities in daily and instrumental activities and with mobility alterations[43,48].

CP can be considered a global health crisis due to its high prevalence and the high risk of progression to physical and emotional disability. Low back pain and neck pain are among the 10 leading causes of disability and functional leave in the world, causing enormous socioeconomic impact[49]. Among the main causes of disabling CP are musculoskeletal disorders, such as osteoarthritis. In Brazil, low back pain is among the five leading causes of disability[50], with a prevalence around 40%, followed by pain in the upper and lower limbs and head and neck, and 15% report generalized pain. The high cost transferred to people and to State for the treatment of CP, associated with the functional and economic loss of people, justify the development of health policies for these cases, with scientific support and adapted to the epidemiological, socioeconomic, and cultural realities of each region[42,51].

Through a population survey, a cross-sectional study conducted in Brazil presented alarming data such as that up to 15% of the respondents with CP did not even know the cause[51]. Regarding the treatments performed, almost half of the studied population reported "no effect" and only 14.9% as "very good" or "excellent". Approximately 8% of the interviewees reported not having medical follow-up for the management of their pain.

Although acute pain can be considered adaptive, in some situations it evolves to chronic state, becoming a personal and public health problem. By generating a certain degree of physical and functional disability, temporary or permanent, dependence, and changes in family dynamics, the condition can bring high costs to health systems, with great impact on the patient and his family quality of life. Pain becomes the center of all ex-

periences, limiting decisions and behaviors. In addition, issues like social withdrawal, changes in libido, and feelings of hopelessness lead to other comorbidities such as anxiety, depression, and insomnia, among others[52].

However, even with the negative CP impact on people's quality of life and its high prevalence and disabling power, traditional therapeutic tools often do not generate the expected analgesic effect and many of the drugs used cause significant adverse effects. Therefore, it is necessary to consider and use new forms of analgesia in CP treatment[53,54].

The widely available analgesic agents are non-steroidal anti-inflammatory drugs (NSAIDs), COX inhibitors (cyclooxygenases), opioids, antidepressants, anticonvulsants, and anesthetics[55]. However, many of these drugs cause significant adverse effects, especially the opioids, which when used chronically can lead to increased tolerance, dependence, and risk of complications (even death from respiratory failure). Currently, opioids represent a major impact on mortality and morbidity, especially in the USA, where in recent years there has been an epidemic of indiscriminate use, with many associated deaths[56].

In CP patients, treatment with medical cannabis has been associated with improved pain-related outcomes, increased quality of life, improved function and reduced need for opioid analgesia[57]. But despite being described and used for thousands of years, phytocannabinoids have only recently gained a more technical and evidence-based approach to use as medicines. These days, the pain management field is largely tilted toward research on cannabis-based drugs, and investigations continue to explore their potential medical benefits in relation to both cannabidiol (CBD) and THC (tetrahydrocannabinol)[8,59].

## CONCLUSION

*Cannabis sativa* L. has potential to become one of the best therapeutic tools incorporated into programs to expand access to phytotherapics in Brazil through FV. The use of phytocannabinoids in clinical practice could expand the therapeutic arsenal of SUS professionals, so that it would be possible to reduce costs with production and/or supply of drugs in the public network, besides enabling a safe and efficient strategy to combat CP.

The incorporation of medical cannabis in SUS system can produce managerial and planning mechanisms for the promotion of health equity in groups which are in vulnerable situations, contributing to the institution of spaces for discussion on this topic. Although still very initial, with a conceptual and practical path to be followed, concerning strategies, policies and programs for its implementation, it is of fundamental importance that this theme be debated in all spheres of interest, from scientific development within academic institutions to political and governmental instances.

The insertion of medical cannabis in SUS system will require interdisciplinary articulations in order to promote health promotion, disease prevention, health surveillance, treatment and rehabilitation. Ensuring public funding for programs related to PIC, phytotherapies, and *farmácias vivas* ("living pharmacies"), continuing education for professionals, evaluation and monitoring of results, and social participation are vital processes for the full implementation, planning, and programming of offering medical cannabis in the public health system in Brazil.

## AUTHORS' CONTRIBUTIONS

**Hygor Kleber Cabral Silva**
Data Collection, Conceptualization, Research, Methodology, Writing - Preparation of the Original
**Rafaela Fernandes Lourenço**
Data Collection, Methodology, Writing - Review and Editing.

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# Integrative approach to the therapeutic use of cannabis for orofacial pain

*Abordagem integrativa do uso terapêutico da cannabis nas dores orofaciais*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Faced with the difficulty of treating chronic orofacial pain and seeking an approach that aims at the health and well-being of the patient in a broader way, cannabinoid therapy appears as an adjunct to pharmacological approaches.

**CONTENTS**: Cannabinoid therapy generates analgesia through the activation of the endocannabinoid system, as well as the use of palmitoylethanolamide (PEA), curcumin, grape seed extract, aromatherapy, acupuncture, laser therapy and the practice of physical exercise. In this way, these therapies allow a reduction in the use of analgesic drugs.

**CONCLUSION**: Cannabinoid therapy is part of this integrative approach and the combination of cannabinoids with other forms of activation of the endocannabinoid system contributes to a better therapeutic outcome and a better quality of life for countless patients suffering from chronic orofacial pain.

**Keywords**: Cannabidiol, Cannabis, Chronic pain, Endocannabinoids, Facial pain, Integrative dentistry.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: Diante da dificuldade de tratamento das dores orofaciais crônicas e buscando uma abordagem que vise a saúde e o bem-estar do paciente de uma forma mais ampla, surge a terapia canabinoide como coadjuvante nas abordagens farmacológicas.

**CONTEÚDO**: A terapia canabinoide promove analgesia através da ativação do sistema endocanabinoide, assim como o uso da palmitoiletanolamida (PEA), curcumina, extrato de semente de uva, aromaterapia, acupuntura, laserterapia e a prática de exercício físico. Desta forma, essas terapias permitem redução do uso de fármacos analgésicos.

**CONCLUSÃO**: A terapia canabinoide faz parte dessa abordagem integrativa e a combinação dos canabinoides com outras formas de ativação do sistema endocanabinoide contribui para melhores resultados terapêuticos e melhor qualidade de vida para inúmeros pacientes que sofrem de dores orofaciais crônicas.

**Descritores**: Canabidiol, Cannabis, Dor crônica, Dor facial, Endocanabinoides, Odontologia integrativa.

## INTRODUCTION

Pain is an unpleasant perception associated with the activation of the nociceptive pathway. The activation of the nociceptive pathway generates a nociception that corresponds to its sensory component, responsible for discriminating the intensity, location and duration of the nociceptive stimulus in the somatosensory cortex. On the other hand, the unpleasant perception corresponds to its emotional component, which involves the activation of several regions in the central nervous system involved in processing emotions.

Chronic pain (CP) is a much more complex experience than just pain that lasts longer than three months. It is often associated with maladaptive changes in the nervous system, as occurs in primary chronic pain, also called nociplastic pain. Pain is influenced by psychological, cognitive, behavioral, social, and neurophysiological factors[1,2].

Chronic orofacial pain, including temporomandibular disorders (TMD) and neuropathic pain, as well as chronic pain in general, present difficult treatment management. Among the possible causes of therapeutic failures are the exclusive focus on somatic complaints and neglect of psychosocial assessment, the variability of response to the same drug by different patients, the difficulty of its titration, its undesirable adverse effects (weight gain, decreased libido), and the need for the patient to change habits[3]. Recognizing the biopsychosocial model of CP, the need for a treatment with an integrative approach, seeking the health and

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**HIGHLIGHTS**
- Scientific evidence on the therapeutic use of cannabis in orofacial pain
- Integrative way of using phytocannabinoids in orofacial pain
- Different ways of activating the endocannabinoid system besides phytocannabinoids

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well-being of the patient with a view that goes beyond the somatic causes[4]. In this scenario, cannabinoids emerge as a possible therapeutic option.

## CONTENTS

**Getting to know cannabinoid therapy and the endocannabinoid system**

The treatment of chronic pain, the most mentioned reason for the use of medical cannabis, as well as research using cannabis and phytocannabinoids, has grown exponentially in the last decade[5]. The introduction of cannabinoids in a compassionate manner in the control of orofacial pain has gained prominence in scientific studies that show its therapeutic potential in its control[6,7]. The most studied phytocannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), are already part of the therapeutic arsenal for treating orofacial pain, since, besides reducing pain, they promote well-being and improve patients' quality of life.

The role of the endocannabinoid system (ECS) is determinant in the modulation of pain and inflammation, besides the maintenance of a series of homeostatic and physiological functions[8], such as temperature, cognition, emotional processing, modulation of inflammatory and immunological responses[9]. It is composed of endocannabinoids, the cannabinoid receptors (CR) CB1 and CB2, and enzymes responsible for the synthesis and degradation of endocannabinoids, as already detailed in other articles.

The receptors, together with the endocannabinoids, act by modulating the levels and activity of most other neurotransmitters[10]. Endocannabinoids are neuromodulatory fatty acids produced on demand by phospholipid precursors and released by postsynaptic neurons in response to physiological and pathological stimuli. After their signaling function, endocannabinoids are enzymatically degraded[11]. There are three types of cannabinoids: endocannabinoids such as 2-arachidonoylglycerol (2-A) and anandamide (AEA), produced endogenously; phytocannabinoids, which come from cannabigerolic acid (CBGA) produced by the Cannabis sativa plant; and synthetic cannabinoids (molecules synthesized in a laboratory).

Cannabinoids act mainly on G-protein-coupled CRs, widely distributed throughout the body[12]. CB1 and CB2 cannabinoid receptors are expressed in several regions involved in the transmission and modulation of orofacial pain, such as in trigeminal ganglion neurons, including those that innervate the masseter muscle[13]. CB1 receptors are also found in the trigeminal spinal tract nucleus[14] and in areas involved in descending pain modulation pathways[15] and pain perception, such as the prefrontal cortex[16]. Thus, cannabinoids can modulate orofacial pain both peripherally by acting on peripheral and central trigeminal nociceptive fibers, as well as in regions involved in endogenous analgesia mechanisms, as well as in the perception of pain.

Cannabinoids can also act on other non-cannabinoid receptors, such as TRPV1, also expressed in the trigeminal ganglion[17], and GPR18 and GPR55, found in areas of the nervous system which are involved in pain modulation[18].

CBD and THC are considered the major phytocannabinoids. They come from the phytocannabinoid CBGA, which serves as a substrate for the synthesis of the major cannabinoids. The minor phytocannabinoids have been studied in several diseases. Among them, one can mention cannabigerol (CBG), cannabinol (CBN), tetrahydrocannabivarin (THCV), and cannabichromene (CBC), the third most abundant in the plant, second only to CBD and THC.

Terpenes and flavonoids are a class of compounds produced by cannabis, contributing to its aroma and pigmentation, respectively[19]. They have a wide range of biological and pharmacological activities. The main terpenes produced by cannabis are myrcene, caryophyllene, humulene, pinene, linalool, limonemene, and terpinolene. Myrcene is the most prevalent in the plant, it has antipsychotic, antioxidant, analgesic, anti-inflammatory, sedative, myorelaxant and anticancerous properties[20-23]. The most important is β-caryophyllene. It is the only terpene known to interact with the body's endocannabinoid system (it selectively binds to the CB2 receptor)[24].

Flavonoids are secondary polyphenolic metabolites. They are divided into four main groups: flavonoids isoflavonoids, neoflavonoids, and anthocyanins. There are about 20 different pharmacologically active flavonoids identified in cannabis[19], indicating the medicinal benefits of cannaflavins found exclusively in cannabis.

All the components of the cannabis plant (phytocannabinoids, terpenes, flavonoids) together exert superior therapeutic effect than any of its single compounds. This cooperation between the different components of the plant is called the "entourage effect," as proposed by chemist Raphael Mechoulam[25].

There are three presentations of CBD: the full spectrum - which has all the components of cannabis (phytocannabinoids, terpenes, and flavonoids), the broad spectrum - which is similar to the full spectrum except that it does not contain the THC molecule, and the isolated - which may be only the CBD or THC molecule. For pain modulation, full spectrum presentations are always chosen, due to the following advantages: the entourage effect, less risk of an inverted U-shaped effect curve, lower dose to reach the therapeutic target[26].

THC produces analgesic and antihyperalgesic effects[27]. Studies have confirmed that CBD reduces levels of pro-inflammatory cytokines, inhibits T-cell proliferation, induces T-cell apoptosis, and reduces migration and adhesion of immune cells. Most clinical studies for the treatment of refractory CP have typically used a 1:1 combination (THC:CBD) often taken orally and well tolerated. Combining THC with CBD ameliorates the deleterious and psychoactive effects of administering THC alone. CBD:THC formulations have been effective in reducing mean pain scores in CP patients with multiple sclerosis, in reducing neurophysical measures in response to noxious stimuli, and in reducing refractory CP[28].

CBG is also known as a partial agonist for the CB1 and CB2 receptors, in addition to inhibiting anandamide reuptake[22]. One study[23] showed high efficacy of CBG, as most patients reported that their conditions were "much improved." Moreover, 73.9% claimed superiority of CBG-predominant cannabis over conventional CP drugs.

There is a consensus to consider cannabis for the treatment of neuropathic pain, inflammatory pain, nociplastic pain, and mixed pain[29]. Prescribers must titrate and manage the dose scheme

to achieve the patient's treatment goals, which can be varied and therefore individualized. Because each individual's SEC is unique, dosing does not follow a standard and must be personalized. One should always start with a low dosage and gradually increase it until the therapeutic target is reached.

In a paper published with consensus recommendations on dosage and administration of phytocannabinoids to modulate CP, three types of protocols were proposed: the conservative, the standard, and the rapid. For each protocol, a titration to a maximum daily dose recommendation was followed. The clinician may consider moving a patient between protocols to individualize the patient's treatment. CBD and THC are dosed until a therapeutic response in modulating CP is achieved.

Although limited, scientific evidence suggests that cannabinoids reduce pain associated with temporomandibular dysfunction (TMD), neuropathic and oncologic pain, and improve the patients' quality of life.

In a preclinical study using the formalin test on the temporomandibular joint (TMJ)[30], it was observed that a cannabinoid agonist reduced pain, via activation of the CB1 receptor, as much as morphine and more than ketamine and the anti-inflammatory drug indomethacin[31]. In another preclinical study mimicking the symptoms of muscular TMD, application of delta-9-tetrahydrocannabinol (THC)[6], cannabidiol (CBD), cannabinol (CBN) and the combination of CBD/CBN (1:1)[13] to the masseter muscle reduced neural growth factor (NGF)-induced mechanical sensitization. The analgesic effect of THC was via CB receptors16 and the CBD/CBN combination induced a reduction in mechanical sensitization which lasted longer than that induced by each of these substances alone[13], which is in agreement with the entourage effect of cannabinoids.

These studies suggest that THC, CBD and CBN could peripherally reduce muscle TMD without central adverse effects, which was later confirmed in a randomized, double-blind, controlled clinical trial[32]. A full-spectrum cannabidiol cream on the masseter muscle of patients with muscular TMD achieved reduced pain, as assessed by means of the Visual Analog Scale (70.2% compared with 9.81% in the placebo group), and masseter muscle electromyographic activity (11% in the right and 12.6% in the left, compared with 0.23% in the right and 3.3% in the left masseter in the placebo group)[32]. Therefore, according to the study, peripheral application of cannabinoids could be an effective strategy for reducing pain of TMD muscles without adverse effects.

Cannabinoids represent a genuine therapeutic strategy in neuropathic orofacial pain[33]. Full-spectrum cannabidiol-enriched oil has been shown to reduce allodynia in the neuropathic orofacial pain model of infraorbital nerve constriction[34]. In the absence of persuasive evidence, a group of pain physicians, psychiatrists, scientists, and patient representatives concluded through a multicriteria decision analysis that cannabinoids have a better benefit-safety profile than other drugs used to control peripheral neuropathic pain, especially since they contribute more to quality of life and have a more favorable side effect profile than other drugs[35].

In a clinical case report, the use of nabiximol (CBD 25 mg/mL + THC 27 mg/mL) for day 30 days eliminated trigeminal neuralgia secondary to multiple sclerosis and refractory to other drugs[36].

With the purpose of seeking new therapeutic options against the use of opioids in orofacial pain, many cancer patients make autonomous use of *Cannabis sativa* for pain relief. In Canada, for example, 18% of patients reported the use of cannabis, and 46% used the plant for pain relief[37]. Another study achieved improved pain intensity via the Numerical Pain Scale and worse nausea and vomiting with the use of THC/CBD in the form of the drug Sativex compared to placebo, but no significant changes with THC administration alone or opioid reduction[38].

The use of nabiximols as an oromucosal spray has also been studied in the adjuvant therapy of patients with oncologic CP. Given the poor quality of life of cancer patients, scientific findings in meta-analysis justify the use of cannabinoids as a possibility of managing the adverse effects of nausea and vomiting from chemotherapy, also evidencing the therapeutic antiemetic efficacy of THC and dronabinol when compared to placebo and neuroleptics, in addition to reports in the improvement of appetite loss[39]. The synthetic cannabinoid also showed antiemetic properties, reducing the severity of nausea from 2.5 to 1.5 in the intervention group[40].

Regarding the association of orofacial pain with headache conditions, fibromyalgia, and emotional symptoms, one analysis has shown that from a sample of 145 patients treated with cannabis for three years, 60% of them reported a long-term reduction in headache frequency[41]. Another trial compared treatments between nabilone and ibuprofen, concluding that the former was more effective in reducing pain intensity and reducing painkiller use[42].

As for fibromyalgia, favorable signs were obtained in the parameters of the questionnaire applied to Israeli patients sampled and treated with medicinal cannabis, showing few adverse effects in this treatment[43]. Another observational, prospective study with patients from a medical cannabis clinic in Israel showed that gradually titrated cannabinoids appear to be a promising treatment, especially in situations where traditional pharmacological methods fail with low compliance rates[44].

A review of the literature conducted in 2020 observed that components of *Cannabis sativa*, especially CBD, also exert anxiolytic properties, thus proving an alternative for improving the quality of life of patients suffering from such comorbidity along with orofacial pain. However, although there are still no safety protocols that can structure the administration of cannabis in the treatment of anxiety disorders, the development of such evidence in further studies is important to support the possibility of therapeutic alternatives to benzodiazepines[45].

**Integrative approach to cannabinoid therapy**

The combination of different ways of activating the endocannabinoid system makes it possible to reduce the consumption of analgesics and improve the quality of life for patients with chronic orofacial pain. There are several natural ways to activate the endocannabinoid system, for example with the use of palmitoylethanolamide (PEA), curcumin, grape seed extract, aromatherapy, acupuncture, laser therapy, and physical exercise.

PEA is a fatty acid derivative produced in the body and is present in eggs, milk, peanuts, and soybeans with anti-inflammatory and

analgesic properties, among others. Its therapeutic effects involve the activation and desensitization of vanilloid receptor channels and transient receptor potential 1 (TRPV1), activation of peroxisome proliferator-activated receptor alpha (PPAR-α), of CR coupled to G protein 55 (GPR55) and G 119 (GPR119), and indirect activation of CR via inhibition of anandamide endocannabinoid (AEA) degradation[46].

In the TMJ, PEA was shown to be more effective than the anti-inflammatory drug ibuprofen in reducing pain and increasing mouth opening[47]. In cases of burning mouth syndrome, ultramicronized PEA was more effective than placebo[48] and, in a clinical case report, it promoted symptom improvement when combined with gabapentin[49]. The combination of PEA with cannabinoids potentiates the analgesic effect of cannabinoids[50], suggesting the possibility of using lower doses of cannabinoids.

Turmeric is the main source of the polyphenol curcumin, known for its analgesic and anti-inflammatory effect[51], including in some types of pain in the orofacial area[52]. Although it has a low bioavailability, the addition to piperine, the main active component of black pepper, it solves the problem. The peripheral analgesic effect of curcumin involves the activation of the endocannabinoid and opioid system[53]. It is possible that curcumin acts directly on opioid and cannabinoid receptors expressed on nociceptors, causing antinociception through the inhibition of neuronal excitability and/or increasing the release of endogenous endocannabinoids and opioids.

Grape seed extract contributes to the reduction of CP such as orofacial pain and migraine[54] due to its ability to activate the endocannabinoid system. Grape seed extract supplementation inhibits pain signaling in an experimental model of migraine via activation of central cannabinoid receptors[55]. However, more clinical studies are still needed to confirm the potential of grape seed extract in reducing chronic orofacial pain.

Aromatherapy has presented analgesic effects in migraine[56] and muscular TMD[57]. In practice, essential oils can be used topically while massaging the pain are and vaporized to be inhaled. One of the mechanisms involved in aromatherapy-induced pain reduction is the activation of the endocannabinoid system, as shown with the use of beta-carophyllene, which is a CB2 receptor agonist and a major component of *copaíba* oil[58], lavender essential oil[59] and *Cedrus atlantica* essential oil[60]. Thus, future studies may lead to the development of promising phytotherapic drugs for the treatment of conditions involving dysregulation of the endocannabinoid system, including orofacial pain.

Another way to activate the endocannabinoid system is through acupuncture. Acupuncture is an ancient Chinese treatment with numerous therapeutic benefits, including pain reduction[61]. There are mechanisms involving the activation of these endogenous analgesia systems[62], including the endocannabinoid system, as shown by both acupuncture[63] and electroacupuncture[64].

Scientific studies have reinforced the clinical recommendations for physical exercise since it prevents and reduces CP[65]. Physical exercise is a natural way of activating the endocannabinoid system as it increases endocannabinoid levels[66], which contributes to its hypoalgesic effect as shown in the orofacial neuropathic pain model of infraorbital nerve constriction[67].

## CONCLUSION

Cannabinoids represent an important option for the control of chronic orofacial pain not only for their ability to reduce pain, but also to improve the quality of life of patients. Integrative treatment is undoubtedly the best way to go in the treatment of chronic pain in general, including orofacial pain.

Cannabinoid therapy is part of this integrative approach and the combination of cannabinoids with other forms of activation of the endocannabinoid system contributes to better therapeutic outcomes and improved quality of life for countless patients suffering from chronic orofacial pain. Considering that cannabinoids are relatively safe compared to other drugs used to control chronic orofacial pain, they should be included in the arsenal of the TMD and orofacial pain specialist as an effective adjunct treatment.

## AUTHORS' CONTRIBUTIONS

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# Neuropathies and the use of cannabinoids as a therapeutic strategy

*Neuropatias e o uso de canabinoides como estratégia terapêutica*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Prevalence of painful neuropathy is around 7%-10% in the entire population, also, it may have different histories and require integrated care. Challenges for patient care are concerning, most of them have not achieved satisfactory results with drugs for pain management, which are often disabling, in addition to associated comorbidities such as sleep disorders and mood swings. Most of the drugs currently being used for neuropathic pain (NP) have several adverse effects, which hinders adherence to treatment and makes it impossible to reach the doses that would be indicated for proper management. Given this scenario, studies are being done aiming at the endocannabinoid system present in the human body with the ability to modulate pain, sleep, and mood disorders, among other benefits. Drugs such as phytocannabinoids, mainly the molecules cannabidiol (CBD) and tetrahydrocannabidiol (THC), have been studied with significant potential for the treatment of painful neuropathy. This review aimed to describe the probable mechanisms of action of cannabinoids in NP and the results obtained so far with the use of these molecules.

**CONTENTS**: This study is a narrative review of the literature. Data were analyzed using the databases National Library of Medicine (NCBI), Academic Google, Medline and scientific database configurations by LILACS and Web of Science in a temporal search between 2004 and 2022. A total of 45 articles were counted.

**CONCLUSION**: THC modulates opioid effects in neuropathic pain. This is associated with a pharmacokinetic effect and has also been demonstrated by brain imaging. This significant performance can be associated with specific target sites and primary actors regarding Δ-9-THC and its binding to receptors associated with analgesia**.** Also, further studies with this component or associated with small cannabinoid variations are necessary to certify its role in neuropathic pain.


**Keywords**: Cannabidiol, Cannabinoids, Cannabis, Pain.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A neuropatia dolorosa tem prevalência estimada em toda a população em torno de 7% a 10%, pode ter diversas etiologias e requer cuidado integrado. O cuidado desses pacientes costuma ser desafiador, pois a maioria deles não obtém resultados satisfatórios com os fármacos disponíveis para manejo da dor que, muitas vezes, são incapacitantes, além das comorbidades associadas, como distúrbios do sono e alterações de humor. A maioria dos fármacos utilizados atualmente para o tratamento da dor neuropática (DN) apresenta diversos efeitos adversos, o que dificulta a adesão ao tratamento e impossibilita atingir as doses que seriam indicadas para o manejo adequado. Diante desse cenário, estudos estão sendo feitos visando o sistema endocanabinoide presente no corpo humano, que tem capacidade de modular a dor, sono e distúrbios do humor, entre outros benefícios. Fármacos como os fitocanabinoides, principalmente com as moléculas canabidiol (CBD) e tetrahidrocanabidiol (THC), têm sido estudados com potencial significativo para o tratamento da neuropatia dolorosa. Esta revisão teve o objetivo de descrever os mecanismos prováveis de ação dos canabinoides na DN e os resultados obtidos até o momento com a utilização dessas moléculas.

**CONTEÚDO**: Este estudo é uma revisão narrativa da literatura. Os dados foram analisados utilizando as bases de dados *National Library of Medicine* (NCBI), Google acadêmico, Medline e configurações de bases científicas pela LILACS e *Web of Science* em uma busca temporal entre 2004 e 2022. Foram contabilizados 45 artigos.

**CONCLUSÃO**: O THC modula os efeitos opioides na dor neuropática. Esta atuação é associada com efeito farmacocinético e foi demonstrada por imagens cerebrais. Esta atuação significativa pode ser associada com sítios alvo específicos e atuantes primários com relação ao Δ-9-THC e sua ligação a receptores associados à analgesia. Entretanto, mais estudos com este componente ou associado a pequenas variações canabinoides são necessários para afirmar a sua atuação na dor neuropática.


**Descritores:** Canabidiol, Canabinoides, Cannabis, Dor.

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**HIGHLIGHTS**

- Δ-9-THC has a prominent role in pain management.
- THC appears to act on pharmacodynamics and has a therapeutic window in neuropathic pain.
- The endocannabinoid system is differentiated from other treatments due to the fact that it has specific cannabinoid acting areas naturally in the human body.
- THC as a component has high prospects in pain management compared to conventional treatments.

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## INTRODUCTION

Cannabis sativa (CS) and its versatilities through its appropriation of phytocannabinoids and cannabinoid derivatives have been recommended for diverse clinical conditions for many centuries[1-5]. Historically, when it comes to pain management, the two therapeutic classes derived from plants and drugs are commonly used: opioids and anti-inflammatory drugs[6].

In this regard, the use of phytocannabinoids is of wide application7. Dronabinol is used to treat loss of appetite, nausea, vomiting, and in neuropathic pain (NP), mainly in conditions involved with multiple sclerosis[8]. In addition, it has been used in other conditions such as chronic noncancer pain and in other diseases such as fibromyalgia[9], allodynia[8] and chronic brachial plexus pain[10], promoting pain relief.

Despite relevant information on the effects of cannabinoids for pain treatment, little information has been accounted for regarding their actual effect on pain and especially whether they reduce the progression of synthetic opioids. With this, the present study's objective was to present cannabinoid therapeutics from the perspective of pain.

## CONTENTS

The design of the study was structured as a narrative type review article, as an appropriate way to describe and discuss the development of cannabinoids in the neuropathy therapeutic community from a contextual point of view. According to the authors[11], the structure of this research occurred in six steps: (1) explanation and (2) importance of this review, (3) literature search, (4) theoretical framework, (5) presentation of levels of evidence, and (6) important concluding points emphasizing the proposed objective.

About step 3, some criteria were defined, such as the investigation in a bibliographic presentation by means of scientific articles published in national and international scientific journals, which inform about the context of NP and the action of cannabinoids. Quality scientific bases were accessed according to the platforms of the National Library of Medicine (NCBI), Google Scholar, Medline, scientific base settings by LILACS and Web of Science and a temporal search between the years 2004 to 2022. For the search, the descriptors, divided into searches, presented in table 1 were used.

When evaluating the three different searches, as three main strategies using descriptors and Boolean descriptors, a total of 102 articles were obtained. This strategic step occurred in the period from April to May 2022. The inclusion criteria were filtered initially by article, title and abstract, after this first filtering, the selected articles were accessed in full-text form and/or in their entirety. Some exclusion criteria were used in the filtering in which they accounted for: (1) those that had no clarified methodology, (2) those that did not present the topic of phytocannabinoids and NP and those that were delimited to publications in years prior to 2011, with the purpose of limiting the most recent studies (at least 10 years until 2022), however, for this purpose, some articles from years prior to 2011 were considered because they were articles elected with great relevance in the scientific community and/or known as "gold standard".

**Table 1.** Descriptors used in the bibliographic search

| Search 1 |
|---|
| *(((cannabidiol) OR (cannabis)) OR (cannabinoids)) OR (tetrahydrocannabinol)) OR (THC)) OR (CBD)) OR (terpenes)) OR (canabidiol)) OR (Cannabis sativa)) AND (review[Filter])) AND (((neuropathy) OR (pain neuropathy)) OR (pain neuropathy)) OR (hyperalgesia)) OR (neuropathic pain)) OR (small fiber neuropathy)) OR (peripheral neuropathic pain)) OR (small fiber pathology)) OR (polyneuropathy)) OR (burning pain)) AND (review)))* = 24 articles |
| Search 2 |
| *(((“Neuropathy”) OR (“Neuropathies”) OR (“Neuropath*”) OR (“Neuropathic Pain”) AND ((“Dronabinol”) OR (“Cannabidiol”) OR (“CBD”) OR (“THC”) OR (“delta-9-tetra-hidrocanabinol”) OR (“Cannabis”))) → Human/EC* = 41 articles |
| Search 3 |
| *((“Neuropathic Pain”) AND ((“Dronabinol”) OR (“Cannabidiol”) OR (“CBD”) OR (“THC”) OR (“delta-9-tetra-hidrocanabinol”) OR (“Cannabis”))) → Human/EC* = 37 articles |

After collecting relevant articles and data, an analysis and interpretation was performed and the data were tabulated in Microsoft® Excel 2010 software in order to expose the action of cannabinoids in the context of neuropathy.

## PAINFUL NEUROPATHY

According to the International Association for the Study of Pain (IASP), NP occurs as a direct consequence of a disease or injury that affects the somatosensory system[12]. Literature data report the occurrence of NP in 7% to 10% of the general population[12,13], and 15% of people suffering from pain have NP. In diabetics, the number corresponds to the double of the general population (16%)[14]. In seniors, the estimated prevalence can reach up to 32%[15] and 40%-80% of cancer patients will develop NP after treatment with chemotherapy after 3 to 6 months of treatment[16].

The diagnosis of NP is based on at least three items: 1. type of pain and subjective symptoms, 2. objective clinical signs of nerve dysfunction or laboratory tests that demonstrate the changes, and 3. positive response to a treatment with drugs effective for treating NP[14].

NPs are alterations of the inhibitory interneurons and descending control systems that are responsible for the imbalance between descending inhibition and excitation seen at the level of neurons in the dorsal horn of the spinal cord[17].

Patients with NP usually express spontaneous pain sensations, which is indicative of activities of nociceptive afferent fibers in the absence of a known stimulus (allodynia). These ectopic discharges may originate from various parts of the injured nerve, such as the dorsal root ganglion, the axon, nerve endings, or a neuroma formed after injury. Apparently, nerves near the injured ones that are preserved can generate ectopic discharges as a result of ephaptic transmission[18].

The peripheral pain stimulus is processed to the central by entering the spinal cord and exciting second order neurons via glutamate, peptides such as substance P, and calcitonin gene-related peptides (CGRP). Second order neurons project information about the intensity and modality of painful stimuli via thalamus

to regions such as somatosensory, cingulate, and insular cortex, and receive inhibitory stimuli coming from the medulla and periaqueductal gray matter[13].

After nerve injury, inflammatory mediators such as CGRP and substance P promote increased vascular permeability. This results in localized edema and increased exposure of the nerve to prostaglandins, bradykinins, cytokines, and growth factors that are released from the damaged nerve endings and surrounding cells. Exposure to these inflammatory mediators increases chemical and mechanical neuronal sensitivity at the site of injury and in the posterior horn of the spinal cord, as well as the spinal cord itself, the latter generating central sensitization and promoting NP maintenance[18].

Alterations in the vanilloid channel expression (transient receptor potential-1 - TRPV-1) were observed in injured nerves and nearby C-fibers, which could lead to depolarization and spontaneous activity triggered by normal body temperature fluctuations. Emotional state and memory associations with pain play an important role. Serotoninergic, dopaminergic, noradrenergic, glycinergic, and GABAergic pathways originate in various supraspinal centers and project to the posterior horn of the medulla and modulate nociceptive signaling. In chronic pain, dysfunction of these modulatory pathways leads to reduced inhibition and may potentiate nociceptive signaling[18].

NP may be a consequence of central nervous system (CNS) or peripheral nervous system (PNS) lesions, such as diabetes mellitus neuropathy, post-herpetic neuropathy, degenerative spinal cord diseases, radiculopathies, cancer, chemotherapy, stroke, amputation (phantom limb pain), vitamin deficiency, alcohol or human immunodeficiency virus[19].

In addition, when there is impairment only of the fine fibers, autoimmune diseases, variants of sodium channel pathologies, B6 toxicity, kidney, liver or thyroid dysfunction, drugs and toxins, and idiopathic causes[13,18] must also be considered, besides hereditary causes. In peripheral neuropathies, the fibers that carry pain and temperature information are poorly myelinated (A delta) or amyelinated (C fibers) fibers, called thin fibers[18]. There may be concomitant involvement of the thick, myelinated fibers, which carry the information for deep sensation and motricity.

After a neurological lesion, there are changes in relation to the ion channels, both in the proximal (increased activity of the sodium channel) and distal (increased activity of the calcium channel) areas of the injured nerve, with a loss of potassium channels[18].

TRP channels are a family of non-selective cation permeability channels, which translate extracellular stimuli into acute and chronic neuronal responses via calcium influx. TRPA, TRPV and TRPM are modulated by endocannabinoids. There is evidence that dysfunction of these channels could contribute to NP in diabetes[6].

Regarding fine fibers, the main ion channels involved are voltage-dependent Na2+ channels[20].

**Current treatments**

Treatment is based on identifying reversible causes and promoting symptom control15. 15 However, there are several limitations, mainly the adverse effects of the available drugs, with a high intolerance rate, besides the refractoriness of symptoms. In the first line of pharmacological treatment are the calcium channel modulators (gabapentin and pregabalin) [15]. The main adverse effects include sedation, dizziness, ataxia, visual disturbances, cognitive impairment, and peripheral edema[21].

The second line of treatment encompasses tricyclic antidepressants (amitriptyline and nortriptyline) and dual norepinephrine and serotonin reuptake inhibitors (venlafaxine and duloxetine)[19]. The main adverse effects are nausea, constipation, hyperhidrosis, palpitations, dry mouth, hypertension, cognitive changes, and pharmacological interactions, with a risk of developing serotonergic syndrome[22].

In the third line are opioids and topical drugs, such as 8% capsaicin patch or cream and 4% or 5% lidocaine patch[23].

Other treatments include alpha lipoic acid, most commonly used in diabetic neuropathy, and the main adverse effects are nausea and vomiting[15].

Recently, cannabinoids have become increasingly prescribed and may be a good option for the treatment of NPs, with an increasing number of studies.

**Neuropathy and cannabinoids**

The endocannabinoid system consists of lipophilic ligands, mainly 2 arachidonoylglycerol (2-AG) and anandamide (AEA)[16,24]. It is a neuromodulation system that can act to modulate pain and inflammatory processes mediated by the immune system[18].

The two main targets of the action of these endocannabinoids are the CB-1 (receptor 1) and CB-2 (receptor 2) receptors[25]. Both are found in the presynaptic membrane of the CNS and peripheral neurons, and CB-1 is more concentrated than CB-2 in the CNS. In the PNS, on the other hand, there is distribution in the peripheral tissues and in different cells, especially defense cells[25]. CB-1 can be found in numerous organs, both central and peripheral, such as the spleen, lungs, thymus, and heart[25]. It predominates in the CNS, in areas responsible for pain modulation, such as the periaqueductal gray matter in the mesencephalon, the jelly substance in the posterior horn of the medulla, the ventroposterolateral nucleus of the thalamus, the ventromedial rostral bulb, the cortex, the hippocampus, and the amygdala[18,26-28]. The presynaptic localization of CB1 receptors allows cannabinoids to modulate the release of neurotransmitters such as dopamine, noradrenaline, glutamate, GABA, serotonin and acetylcholine[29].

The endogenous molecules AEA and 2-AG are metabolized by the enzymes FAAH (Fatty Acid Amide Hydrolase) and MAGL (Monoacylglycerol Lipase), respectively. Both amines reduce levels of endocannabinoids, leading to inhibition of signaling activity at CB-1 and CB-2 receptors. CBD acts as an inhibitor of FAAH[18,25], with a potential antinociceptive effect in preclinical studies and in animal models[18,30]. The adverse effects of CB1 receptor activation are challenging, despite analgesia, as they can generate sedation, psychotic behaviors, addiction, and cognitive impairment[30].

CB2 receptors predominate in cells of the hematopoietic system, including the immune system such as macrophages, dendritic cells and T cells in the periphery or microglia in the CNS[25,31,32]. Preclinical studies show that the CB2 receptor plays an important role in driving the neuroimmune response to the dorsal column of the spinal cord during NP, as well as potential to reduce motor impairment in neurodegenerative diseases[19,33].

CB2 receptors appear to contribute to analgesia by suppressing the release of inflammatory mediators in cells near nociceptive nerve terminals and blocking the transduction of pain signaling to the CNS[33]. Besides interacting with CB1 and CB2 receptors, cannabinoids also interact with μ (mu), (5-hydroxytryptamine-5HT1A), vanilloid (TRPV1) and GRP55 receptors[12,34].

5HT1A receptors are part of the serotonin pathway signaling, involved in the regulation of mood, appetite and sleep. TRPV1 receptors are involved in pain signaling in neurons and GPR55 receptors are found in the dorsal root ganglion of the spinal cord, although the detailed physiological pathway has not yet been identified. The phytocannabinoids (THC and CBD) also interact with receptors in the endocannabinoid system. THC has similar affinities to 2-AG, and is an agonist of CB-1, CB-2 and GPR55. It also performs neuromodulation and immunomodulation, probably responsible for the psychoactive and analgesic effects. However, CBD is an antagonist of CB-1, CB-2 and GPR55 receptors, but an agonist of TRPV1 and 5HT1A. Unlike THC, CBD has been shown to have antipsychotic, anxiolytic, and anti-inflammatory effects[19].

The most commonly described phytocannabinoids are THC, CBD, but also cannabinol (CBN), cannabigerol (CBG) and cannabichromene (CBC)[6,18,19]. THC is a chemical analog of N-arachidonoylethanolamine, and the effect is primarily through the activation of CB1 and CB2 receptors, especially CB1. The major adverse effects are cognitive dysfunction, loss of short-term memory sedimentation, and psychoactive effects[24].

CBD, on the other hand, is a weak agonist of CB1 receptors, but acts as a partial agonist in some signaling pathways of CB2 receptors[24], with sedative, anti-inflammatory, anticonvulsant, and antipsychotic effects. CBN (cannabinol) does modulate the CB2 receptor and has little affinity for CB1 compared to THC. CBC (cannabichromene) is a major cannabinoid and appears to have no affinity for CB1 and CB2 receptors. It has anti-inflammatory and antinociceptive effects through inhibition of the cyclooxygenase enzyme (COX) and prostaglandins[35].

CBG (cannabigerol) is the phytocannabinoid precursor to THC, CBD and CBC and is only produced in traces in cannabis. It has little affinity for CB receptors, but has the ability to reduce pain, erythema and inflammation through the peripheral inhibition of the lipo-oxygenase enzyme and by the central activation of the alpha-2-adrenergic receptor. It also has an antidepressant effect by being a potent inhibitor of anandamide uptake, as well as a moderate 5-HT1a antagonist[36,37]. CBG activates alpha 2-adrenoreceptors and interacts with other subtypes, such as TPRV, in addition to CB1 and CB2 receptors (the latter mainly) and has anti-inflammatory action although studies are still insufficient. There are new attempts of synthetic compounds similar to CBG being studied in rats and *in vitro*[24]. The complexity of cannabinoid interactions and their receptors *in vivo* may lead to synergistic effects, which has been described as the "entourage effect "[25].

## DISCUSSION

NP is known as a type of pain caused by a lesion or disease in the somatosensory nervous system. Currently, the management of NP considers the individual as a whole[38]. The management of NP is composed of two protocols as a graded form that includes anti-inflammatory, analgesic, opioid, and adjuvant drugs and, in the case of chronic NP, treatment with tricyclic antidepressants and antiepileptic drugs is also used[26,37].

It is known that NP is associated with CNS problems, however, the phenomenon of chronic pain is present in NP and contradicts acute neuropathic pain, which is a better known spectrum when compared to chronic NP and can often influence decision-making such as diagnosis[39], where the relevance of definitions between these different types of pain can help in levels of evidence in the management of NP. There is a compass between different oscillations in the NP in the area that encompasses the trigeminal spinal nucleus, with characteristics of regional homogeneity with local dispersion of the neural activity mediated through the activation of astrocytes, in which the analysis of neuronal mechanisms in levels of body dissemination may help in definitions of the development and/or maintenance of the NP[40].

In summary, NP is that which persists for more than three months, and when there is provable tissue damage, such as osteoarthritis, rheumatoid arthritis, fractures, and muscle stiffness. On the other hand, NP is known as a debilitating form of chronic pain, resulting from damage to the CNS or PNS, characterized by spontaneous pain at times when there is absence of any type of stimulus. In this situation, there is a sensation of numbness, needling, and burning, usually caused by diseases such as cancer, diabetes, drugs such as chemotherapy, immunological disorders, and physical trauma[27]. Several therapeutic applications of cannabinoids have been reported for years, such as anti-inflammatory, muscle relaxants, glaucoma indications, and analgesics[14,28,12,28,30].

Studies suggest that THC may assist in enhancing the analgesic effect of opioids by acting on *delta* and *kappa* opioid receptors and also on the synthesis and release of endogenous opioids. In addition, acute administration of CB1 receptor agonists results in actions such as catalepsy, hypothermia, decreased motor activity, and analgesia[31]. Investigations of the pharmacology of the use of cannabinoids have been indicated in areas of analgesic action, mainly in the spinal cord, brain, and peripheral areas, referring mainly to neuropathic[32,33,35,41] and systemic[36] pain.

The areas of analgesic action are one of the most evident points of cannabinoid action[42], initially due to the basic biological nature of CB1 and CB2 receptor areas in spinal, supraspinal and peripheral areas in which the analgesic action of cannabinoids is restricted peripherally in CB1R and CB2R agonists, or inhibitors of endocannabinoid catabolism. Recapture and modulation of other non-target $CB^1R$ and $CB^2R$ areas, in addition to acting on presynaptic neurotransmission and neuropeptide reuptake are some of the characteristics that attribute the efficacy of cannabinoids' analgesic action[42].

Among all the diseases associated with pain, it has been observed that there is a higher prevalence of the association of cannabinoids in the treatment of multiple sclerosis (MS)[34,41]. Study[16] presented the action of cannabinoids, especially in the form of inhalation in a context in which chemotherapy induces peripheral neuropathy and situations in which sensory nerve as well as motor deficits are evidenced, there is little or limited medicinal therapeutic action for these cases. With this, some antinocicep-

tive actions of both cannabinoids (THC and CBD) have been observed in experimental studies with the action of drugs such as cisplatin, oxaliplatin, vincristine, and paclitaxel. In a relevant clinical trial presented in this study, there was a reduction in pain intensity of over 50% using oromucosal spray at a milligram dose of 2.5 to 120 mg of Δ9-THC and 2.5 to 120 mg of CBD.
The study[43], still regarding activity in rehabilitation, specifically in the multiple sclerosis condition, spinal cord injury, brachial plexus injury and limb amputation due to neurofibrobromatosis, was conducted to investigate whether cannabinoids can treat intractable neurogenic symptoms. Each pharmacological performance consisted of the application of spray, which contained 2.5 mg of CBD/THC/24 hours over a period of 7 days[43].
In this context, the solution was associated with pain relief attributed to THC and CBD cannabinoids and the cannabis extract in its synergistic action improved bladder, muscle spasms and spasticity control.
The study[34] revealed that dronabinol (2.5 mg dose increased every 5 days and doses between 7.5 and 15 mg for 16 weeks of application) has sedative, anti-inflammatory, anxiolytic, and analgesic effects and these were significant in patients with multiple sclerosis (MS). Some results of cannabinoid use in individuals with MS are controversial[32,44].
In a randomized, double-blind, placebo-controlled, cross-sectional clinical trial[36], different doses were applied as different groups, divided into: medium doses of THC (3.53% of Δ-9-THC), low doses of THC (1.29% of Δ-9-THC) and control group in the treatment in central and peripheral NP prevalent in 39 patients, who obtained 30% reduction in pain intensity by vaporized cannabis. In cases of peripheral NP, the study[8] recruited 303 patients with peripheral NP associated with allodynia (change with which pain is felt), around 128 patients who were treated with a THC/CBD compound spray and, according to a questionnaire application, 30% of these patients with up to 24 daily applications obtained significant response to cannabinoid treatment compliance.
The authors[35] evaluated 60 patients with pain caused by diabetic neuropathy in a randomized, double-blind, cross-sectional, placebo-controlled study and assessed the analgesic response after application of doses of THC (4% and 7%) via aerosols. Still on this evaluation, a therapeutic window was evaluated in the sense of cannabis pharmacokinetic investigation, a blood sample was collected for plasma assay of total THC at 0, 15, 30, 45, 60, 150, and 240 minutes aiming secondary analyses, contemplated by associations between pain intensity, cognitive impairment, and THC plasma levels. It was observed that there are affirmative studies on the association between plasma THC levels and THC dose, confirmed by this same study, as the main result, showing that the therapeutic window in this case of pain in diabetes is between 16 ng/mL and 31 ng/mL in plasma THC levels.
On the other hand, in the study[37], 27 patients received a single inhalation of Δ-9-THC at a concentration of 0.5 mg, showed a reduction in chronic pain, which remained stable for 150 minutes, and there was also stability in the pharmacodynamics in THC plasma levels. THC seems to be the main component acting on pain and with some variations with CBD.

In order to relate brain activity and pain and the possible effects of THC, authors[45] have correlated the analgesia produced by the effect of THC with a reduction in the functional connectivity of the brain, specifically in the anterior cingulate cortex and sensorimotor cortex, attributing graphic theories that represent a reduction in connective (network) interactivity in areas involving the processing of pain[32,45]. Nevertheless, more studies about the interaction of cannabinoids and their respective effects on pain and its various types are needed.

## CONCLUSION

Painful neuropathy is a challenging disease to manage. Available drugs are generally insufficient for the control of pain and associated symptoms, both because of ineffective nociceptive control when adequate doses are used, and because of adverse effects that limit reaching these doses. Cannabinoids have potential for treating both pain and associated symptoms, improving sleep and mood disorders.
The current difficulty centers on the various routes of administration, lack of standardization of concentrations, and short monitoring time in clinical trials with small numbers of participants. More studies are needed, but it is possible to say that now there is an ally available for the treatment of painful neuropathy.

## AUTHORS' CONTRIBUTIONS

**Helena Wohlers Sabo**
Writing – Preparation of the original, Writing – Review and Editing
**Ana Gabriela Baptista**
Writing – Preparation of the original, Writing – Review and Editing

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# Use of cannabis medicine for the treatment of spasticity-associated pain

*O uso da medicina canábica para tratamento da dor associada à espasticidade*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Spasticity refers to the increase of resistance to joint passive movement according to its angular velocity. It is part of the triad of the pyramidal syndrome, along with the exacerbation of myotatic reflexes and muscle weakness, and is present in several lesions of the central nervous system, either in the spinal cord or brain. Pain associated with spasticity is caused by muscle spasms, activation of trigger points, joint deformities, interference with the position of body segments, and difficulty in movement control. For a more precise therapeutic intervention, the detailed physical examination of the locomotor system and spasticity can be completed by using specific spasticity evaluation scales. Multiple sclerosis (MS) is the clinical condition for which there are the greatest number of studies using cannabinoids to control spasticity. The objective of this study was to perform a literature review of the possible role of cannabinoid drugs in the control of spasticity and the pain associated with it.
**CONTENTS**: The literature shows moderate evidence that the combined use of 9-tetrahydrocannabinol and cannabidiol increases the number of people reporting improvement in spasticity.
**CONCLUSION**: It is possible to believe that the complaint of musculoskeletal pain associated with spasticity accompanies this improvement with the use of nabiximols, but there are still gaps in the literature for this specific topic.

**Keywords**: Cannabinoids, Muscle spasticity, Musculoskeletal pain, Rehabilitation, Treatment.


## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A espasticidade refere-se ao aumento da resistência ao movimento passivo articular conforme a sua velocidade angular. Ela faz parte da tríade da síndrome piramidal, junto com a exacerbação de reflexos miotáticos e fraqueza muscular, e está presente em diversas lesões do sistema nervoso central, de topografia medular ou encefálica. A dor associada à espasticidade é causada pelos espasmos musculares, ativação de pontos-gatilho, deformidades articulares, interferência na posição dos segmentos corporais e dificuldade para o controle do movimento. Para uma intervenção terapêutica mais precisa, o exame físico detalhado do aparelho locomotor e da espasticidade pode ser completado pelo uso de escalas de avaliação específicas. A esclerose múltipla é a condição clínica para a qual há maior número de estudos com uso de canabinoides para o controle da espasticidade. O objetivo deste estudo foi realizar uma revisão da literatura sobre o possível papel dos fármacos canabinoides no controle da espasticidade e da dor associada a ela.
**CONTEÚDO**: Há na literatura evidências moderadas de que o uso combinado de 9-tetrahidrocanabinol e canabidiol aumenta o número de pessoas que relatam melhora da espasticidade.
**CONCLUSÃO**: É possível acreditar que a queixa de dor musculoesquelética associada à espasticidade acompanhe essa melhora com uso de nabiximol, mas ainda há lacunas na literatura para esse tópico específico.

**Descritores**: Canabinoides, Dor musculoesquelética, Espasticidade, Reabilitação, Tratamento.

## INTRODUCTION

Spasticity is a motor sign associated with a neurological injury, characterized by increased muscle stretch reflexes. Typically, it is characterized by increased muscle resistance triggered by passive manipulation of a limb segment with high angular velocity[1]. The muscle activation resulting from the motor stimulus may be intermittent or sustained involuntarily. Spasticity usually occurs after spinal cord and/or brain injuries such as stroke (approximately 25% of patients)[2], traumatic brain injury (TBI)[3], spinal cord injury (SCI) (65-78% of patients)[4,5], MS (80% of patients at some stage of the disease)[6,7] and cerebral palsy (CP) (more than 90% of patients)[8].
Spasticity is typically associated with pyramidal tract lesions and is part of the pyramidal syndrome, appearing together with paresis and exacerbation of myotatic reflexes[9]. After an upper motor neuron lesion, three fundamental phenomena occur in the gene-

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**HIGHLIGHTS**
- Spasticity is a frequent complication of pyramidal system lesions, whose association with neuropathic pain contributes to compromised functionality.
- Musculoskeletal pain related to spasticity can refer to muscle spasm, trigger point activation, joint deformities, poor positioning or change in motion.
- The effectiveness of cannabinoids for controlling spasticity is further proven in multiple sclerosis.

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sis of spastic paresis. Initially, the corticospinal pathways lesion interrupts muscle commands, leading to immediate paresis, which can be defined as the lack of command to the agonist muscles when there is an attempt to generate force or movement. This insufficiency can result from a lack of adequate recruitment of motor units or a decrease in the frequency of discharges[9].

Second, in addition to the paresis itself, simultaneously to loss of movement and contraction, there is immobility of the affected region, which can facilitate the installation of muscle shortening in the body segment. The reduction in regional blood circulation due to paresis leads to relative hypoxia, which promotes fibroblast proliferation and accelerates the loss of muscle tissue. Consequently, there is a loss of performance and muscle shortening, in addition to reduced extensibility of connective tissues of musculoskeletal support (tendons, muscles, ligaments, joint capsule, fascia, vessels, and nerves). This process, which starts soon after the installation of immobility, is intensified over days or weeks if no preventive treatment is installed[9,10].

The third pathophysiological mechanism is related to adaptive changes in high brain centers and spinal cord, causing the recruitment of other descending pathways, such as rubroespinal, tectoespinal, reticuloespinal, and vestibuloespinal. These pathways may become uninhibited to compensate for corticospinal lesions, generating permanent muscle activity. In the spinal cord, there is a loss of inhibition of interneurons, creating mechanisms that lead to an abnormal or exaggerated increase in reflex pathways[11,12]. Associated with this phenomenon, clonus may occur, which is initiated by passive movements during activities, such as being dressed by the caregiver or being bathed by others, or by active movements, such as walking or grasping[3,12,13].

The dystonic spasticity can be defined as the chronic tonic muscle activity together with spasticity, that is, a muscle hyperactivity at rest, without triggering factors, which leads to postural and joint changes. Several of these postures can be recognized in hemiparetic patients after a stroke or TBI, such as the ankle in equinus and varus position, associated with hallux extension, internal rotation of the shoulder with flexion and pronation of the elbow and flexion of wrist and fingers. In the upper limb, these same patients commonly present an adducted shoulder, in internal rotation, with the elbow flexed and the forearm pronated[11-14].

Signs of spasticity are also observed with co-contraction, which is the exaggerated and unwanted contraction of the antagonist muscles during voluntary contractions, that is, two antagonist muscle groups contract simultaneously around a joint.

The co-contraction occurs in individuals with good voluntary motor control, but it decreases the precision of the movement, with consequent loss of functional capacity. Examples of this alteration are the contraction of the flexors that occurs during the attempt to extend the elbow, wrist, and fingers in the upper limb; the contraction of the hip extensors, which hinders its flexion during the swing phase, with reduced step amplitude; and, finally, the limitation of the ankle dorsiflexors, also during the swing phase of the gait, resulting in a tendency to plantar flexion and reaping pattern in hemiparesis. There are other types of muscle hyperactivity, such as dyskinesias, associated reactions and atetheses due to extrasecondary co-contractions, associated with excessive cutaneous or nociceptive response[15].

Muscle hyperactivity can vary during the day and by the position of the joints involved, including cervical positioning, and it is essential to dynamically evaluate the patient and listen carefully to him/her about in which positions or activities he/she has more functional difficulties. Other important factors involved in these changes are temperature, stress level, and nociceptive factors, such as urinary tract infections, wounds, onychomycosis, among others. The simple spasticity measurement at rest does not properly assess the individual's functional condition[16].

The purpose of this study was to conduct a review of the literature on the possible role of cannabinoid drugs in controlling spasticity and its associated pain.

## CONTENTS

**Pain associated with spasticity**

When the central nervous system injury results in inability to perform functional voluntary movements, spasticity keeps the affected limbs in vicious positions. The imbalance of the forces that act on joints in the segment with spastic paresis implies in the formation of joint contractures that can contribute to the appearance of secondary lesions[15]. Patients who develop spasticity of the toes flexor muscle groups can, for example, develop flexion contractures of the interphalangeal joints which result in claw deformities. On dorsal region of the clawed toe, painful calluses appear due to the friction of interphalangeal joints with the shoes; on the other hand, on the extremities of these toes, painful points may appear, associated to difficulty in the growth of the nail, which is pressed against the sole of the shoe[15].

The spastic contracture can be painful by itself, especially when the involved muscle group contains trigger points that can be triggered during the activation of movement. In this situation, the passive movement of a body segment in one direction can trigger the spasticity of the antagonist muscle group, causing pain. A good example is pain associated with the shoulder of spastic hemiplegic patients, which is triggered by the passive abduction movement during actions of washing the armpit or changing clothes, when this joint needs to be passively moved for arm elevation[17].

The improper positioning of the limb due to the movement incoordination caused by spasticity may cause musculoskeletal pain since it requires the body segment to discharge pressure at different points from those that are naturally prepared for this situation. For example, in the lower limbs, severe postures of hip and knee flexion and ankle plantar flexion deformity (equinus) may occur, hindering hygiene and positioning in bed and wheelchair, with increased risk of joint pain and formation of skin lesions by pressure[18].

In addition, the limb positioning inside ortheses can be compromised, with a pressure discharge in inappropriate places, causing pain and preventing the functional use of these instruments[3,19].

It is important to emphasize that the lack of spasticity control is associated with increased pain processes in the affected region, either by muscle spasm or by association with neuropathic changes and joint overloads. On the other hand, the increase in pain afference increases spasticity and forms a vicious cycle[10].

**Assessment of the spastic patient with pain**

A thorough clinical examination is essential for a better understanding of how muscle hyperactivity and spasticity act on functional activity. It is worth noting that neurological symptoms are present and must be evaluated in order to define the best strategies for the most effective treatment. This assessment is important because it makes it possible to check the rehabilitation treatment effectiveness[20,21].

A significant complication of spasticity treatment occurs because scales and tests are often subjective and of low sensitivity to reflect functional gains. To properly assess the patient with spasticity, regardless of etiology, the following measures obtained during the physical examination must be used[22]:

- passive joint amplitudes, seeking to quantify the totality of mobilization in all directions in which joint movement occurs. This test allows differentiating muscle retractions generated by immobility from the patterns associated with spasticity. This measure requires that the joint manipulation be done slowly and gradually to avoid increasing muscle hyperactivity[23];
- active joint amplitudes, when signs of muscle co-contraction and the presence of dystonic movements associated with functional loss can be better evaluated[23];
- the Modified Ashworth Scale (MAS) tries to quantify the resistance to passive mobilization with fast angular velocity, that is, with the triggering of spasticity. Despite being eminently subjective and influenced by muscle and joint conditions unrelated to spasticity, this measure is still the most clinically used and is the reference parameter in the literature on the subject. Table 1[24] describes the score levels used to describe the passive mobilization resistance in MAS;
- the presence of tonus, characterized by the repeated and involuntary contraction of a muscle group against a fast passive movement, is related to the severity of spasticity[23];
- the Tardieu scale compares the intensity of the muscle reaction to two modalities of muscle stretching: the slow stretching and the fastest possible stretching. This scale takes into consideration, besides the stretch velocity parameter (V) described above, the quality of the muscle reaction (X) and the angle of the muscle reaction (Y). For each muscle group, the response is measured at a specific speed in the two tested parameters, X and Y[25] (Table 2).

In addition, it is necessary to complete the functional assessment in order to better understand how muscle changes interfere with the performance of daily living and practice activities. The scales available in clinical practice are still not very sensitive to changes in muscle tone or, when they show quantitative changes, they are due to nonspecific modifications in functionality. More frequent use of the Functional Independence Measure (FIM)[26], Barthel's scale[20] or Spinal Cord Independence Measure (SCIM III)[27,28] may be recommended. In order to use more specific scales for the affected hemibody, the Fugl-Meyer scale and the block box test, among others, can be used, although they do not adequately measure the functional outcomes of spasticity treatment[20-22]. The quantitative or qualitative gait assessment or other parameters such as sensitivity and pain are also important for the best interpretation of the patients' functional difficulties[22].

**Table 1.** Modified Ashworth scale score[24]

| Score | Status |
|---|---|
| 0 | No increase in muscle tone |
| 1 | Slight increase in muscle tone, with minimal resistance in the last degrees of joint amplitude |
| 1+ | Slight increase in muscle tone, in less than half of the joint amplitude |
| 2 | Increased muscle tone over the full range of motion, but no difficulty in achieving full passive range of motion |
| 3 | Considerable increase in tone, making passive movement difficult |
| 4 | Muscle stiffness |

**Treatment**

The spasticity treatment must be interdisciplinary, since the therapeutic intervention of isolated health professionals tends to failure. The disabled person in the rehabilitation process has multiple needs, both physical and cognitive, emotional and social. Besides the medical team, representatives of physiotherapy, occupational therapy, nursing, social work, and speech therapy, as well as the patient's caregiver, should be part of the team[29].

**Table 2.** Tardieu Scale[25]

| Stretching Speed | | Action |
|---|---|---|
| V1 | As slow as possible | Measure the range of passive motion (maximum range of motion) |
| V2 | Speed at which the limb falls under the action of gravity | At these speeds it is possible to measure the interference of passive angular velocity on the range of motion and estimate spasticity |
| V3 | As fast as possible | |
| Muscle reaction quality | | |
| 0 | No resistance along the passive range | |
| 1 | Little resistance along the passive movement, without a clear lock at a specific angle | |
| 2 | Sure treatment of passive movement at a specific angle, stopping passive movement, but followed by relaxation | |
| 3 | Exhaustible bonus (< 10 seconds) at a specific angle | |
| 4 | Endless bonus (> 10 seconds) at a specific angle | |

It is noteworthy that spasticity treatment is not always mandatory if there is no functional impairment. However, the pain associated with spasticity requires therapeutic intervention and muscle tone control. A thorough clinical evaluation makes it possible to determine which affected areas impair functionality and cause pain, guiding the therapeutic intervention[1].

Initially, it is possible to structure, in a didactic way, the spastic patient's treatment in identifying, treating and preventing conditions that exacerbate spasticity[30]. The specific situations that make spasticity more intense include other sources of pain, either musculoskeletal or neuropathic (considering that spasticity already presupposes a central nervous lesion, either encephalic or medullary). It is necessary to turn the focus to skin lesions such as pressure ulcers, which have an intense nociceptive component, but may not be perceived as painful when the nerve lesion also compromises ascending pathways. Another source of nociceptive afference are infections (urinary tract, erysipelas, onychomycosis), besides pain of visceral origin (constipation, urolithiasis) and venous thrombosis[31].

The adequate patient positioning must be done from the earliest stages, during activities such as sitting and lying down, observing the trunk support and the adequate articular positioning in the segments where there is strength reduction. Special attention must be given to shoulder, because, due to the loss of movement, in a few weeks there may be retraction of the joint capsule, favoring the appearance of subluxation and pain that is difficult to control. Other frequent changes occur in the upper limb (tendency to elbow and wrist flexion, associated with hand claw) and in the lower limb (hip and knee flexion and ankle equinus positioning)[14,18,32].

To avoid these patterns, intensive joint movement should be instituted, coupled with the use of preventive orthoses (thermomoldable material positioners) tailored to the patient's shoulder, as well as the ankle and feet. It is important to remember that orthoses should be used with caution, because in spastic patients, when poorly positioned they lead to increased local irritation, which worsens spasticity and favors the appearance of skin lesions[31].

The direct spasticity treatment should be considered in several ways, depending on its severity and the functional impairment that it causes. The physical therapy techniques should be the basis for spasticity treatment and should be instituted early, although there is no consensus in literature about which technique is the most effective. Physical therapy is important to control muscle tone through muscle inhibition, prevention of secondary joint injuries and specific functional training. To these measures, the use of electrotherapy is associated, in the functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (TENS) modalities, the first being used as motor training with control of co-contractions and the second as a sensory stimulus useful in pain control, because it exacerbates spasticity. Heat and cold modalities are also useful in controlling spasticity[24,29]. The correctly molded orthoses have an important role in controlling the tonus, especially after pharmacological treatment[31].

The pharmacological therapy for spasticity should be instituted after the answer to the following three questions[32,33]: "is the muscle hyperactivity actively or passively problematic?", "Is spasticity the main cause of the patient's disability or is it one more cause?" and "Is spasticity limited to one or a few muscle groups or is it global?". The treatment through oral drugs, systemically, can currently be performed successfully using the following: baclofen, tizanidine, gabapentin, dantrolene, clonidine and benzodiazepines, but they all have systemic adverse effects that decrease muscle tone globally and cause drowsiness, which interfere with the rehabilitation process, besides being associated with toxicity and tolerance development[29,33,34] (Table 3).

For a more accurate and balanced control of focal spasticity, chemical blocks are used, with phenol or alcohol[35], or with botulinum toxin[1]. A useful way to assess the real action of spasticity on the limbs and their function is the use of transient nerve blocks, with trunk injection, or of the muscle motor points, with local anesthetics such as lidocaine or bupivacaine. These blocks cause transient paralysis for about 2 to 4 hours, depending on the agent used, which allows assessing the joint contractures and how the patient's function is with spasticity control, although there is not enough time to modify the motor patterns[35]. The blockades allow spasticity control

**Table 3.** Treatments for spasticity and adverse effects.

| Drugs | Mechanism | Dosage | Adverse Effects |
|---|---|---|---|
| Benzodiazepines | GABA-A Agonist | Variable | Sleepiness |
| Baclofen | GABA-B Agonist | 15 – 18 mg | Dizziness, weakness, possibility of withdrawal syndrome |
| Dantrolene | Derivative of hydantoin, which inhibits the release of calcium (acts directly on the skeletal muscle) | 25 – 300 mg | Dizziness, nausea, hepatotoxicity |
| Tizanidine | Alpha-2 presynaptic receptor agonist | 8 – 36 mg | Orthostatic hypotension, constipation, dry mouth, hepatotoxicity |
| Clonidine | Alpha-2 presynaptic receptor agonist | 0,1 – 2,4 mg | Dry mouth, hypotension and syncope |
| Gabapentin | Selective inhibitor of voltage-dependent calcium channels | 100 – 2400 mg | Dizziness, drowsiness |
| Lamotrigine | Calcium channel inhibition | 25 – 500 mg | Dizziness, exanthema |
| Cyproheptadine | Alters the activity of serotonin, histamine, and acetylcholine | 4 – 32 mg | Sedation |
| Tetrahidrocanabidiol | Acts on CB-1 and CB-2 receptors | Variable | Potential cognitive deficit and anxiety |

in more focal areas, with limited effect in extensive areas, as is the case of patients with spastic hemiparesis or very severe spastic tetraparesis, in which the quantity of regional procedures becomes very large, as well as the blocking agents dosage, which would exceed the recommended safety levels[24,36,37].

The treatment of spasticity with the use of cannabinoids began after reports of symptom relief in patients with MS who used inhaled cannabis, which led to studies with synthetic cannabinoids or their extracts[38]. It is important to emphasize that the presence of pain in spastic patients is frequent, but multifactorial, being linked to immobilism, increased muscle contracture and local neuropathic changes.

It is important to highlight that the spasticity symptoms accompany other neurological symptoms, such as altered sensitivity, altered consciousness, and the presence of pain, including chronic pain of central origin, and local neuropathic changes[1,11].

Neuropathic pain and pain associated with muscle spasms are common symptoms in MS. Animal models have suggested that activation of the cannabinoid-1 receptor (CB1) can reduce both types of pain. Systemic administration of cannabinoids produces analgesia in experimental models of acute and chronic pain. In animal models, the endocannabinoid system has shown a role in reducing spasticity[38].

Cannabinoids may act presynaptically in reducing glutamate release by activating CB1[33] receptors, and by reducing glutaminergic effects after exposure to 9-tetrahydrocannabinol (THC)[33-37]. There are also studies showing alteration of endocannabinoids and their receptors in animal models of MS. Furthermore, the use of cannabinoid antagonists worsens spasticity[37]. These studies showed that the use of CB-1 agonists and Delta-9-THC showed greater effectiveness in reducing and controlling spasticity[33-37], but the endocannabinoid system is complex and has not been fully elucidated.

## CANNABINOIDS IN THE TREATMENT OF SPASTICITY

Recently published reviews show the effect of cannabinoid use in controlling spasticity. One study covered 11 reviews on the treatment of spasticity in patients with MS (21 articles)[39]. The use of inhaled cannabis, THC, CBD, THC+CBD, dronabinol or nabilone, or oral cannabis extracts were evaluated. This review of the studies suggested that there is moderate evidence that cannabinoids, especially nabilone and nabiximol, reduce spasticity. The following year, the same group produced a new systematic review in which most articles used the Ashworth scale as the final outcome measure, associated with individual perception. The findings from smaller studies did not have their results reproduced in other studies with larger samples, which were mostly negative for changes in the Ashworth scale[38].

A problem reported by the cited studies is that this scale is not recommended for the assessment of patients with MS, in view of the variability of this group's disabilities. For pain control, the results of these two reviews were inconclusive[38,39]. These results were confirmed by a more recent review that included 25 randomized clinical trials that compared the use of placebo and synthetic cannabinoids by oral spray, adding up to 2290 patients between 18 and 60 years of age[40].

For spasticity control, the conclusion is that the formulation increases the amount of people who perceive a reduction in severity - odds ratio (OR) 2.51; 95% CI 1.25 to 4.04 - with moderate degree of certainty. Based on the previous argument about the interference of spasticity in the genesis of musculoskeletal pain, it is expected that these cannabinoids act similarly in controlling this pain modality. For the control of neuropathic pain, this review only identified one small study with a substantial relief effect in this group of patients compared to placebo (OR 4.23; 95% CI 1.11 to 16.17)[40,41].

In the pediatric population, there is only one randomized study, in which the administration of cannabinoids (CBD+-THC) did not imply spasticity reduction in children with cerebral palsy[42].

Adverse effects resulted in permanent discontinuation of treatment with nabiximol in 30% to 40% of patients. After prolonged use of the drug, a reduction in adverse events was seen, which were mainly fall-related injury (approximately 6%), dizziness (up to 4%), fatigue (up to 2.5%), nausea, and drowsiness (around 2% each). Psychotic events and suicidal thoughts were reported by 2.5 - 6.0% of patients. Abuse of the drug (doses greater than 12 sprays a day) triggered events such as anxiety, nausea, fatigue, and paranoia in 8% of patients[43-47].

Although the use of cannabinoids in chronic pain shows some benefit, its participation in patients with pain associated with spasticity is still unclear[45]. It is not yet known which cannabinoid could promote better effect, or what would be the best dose and period of use, and its adverse effects of long-term use are not fully comprehended. In a recent cost-benefit analysis, the use of nabiximol was recommended for controlling spasticity in patients with MS, some infantile convulsive syndromes and chronic pain, but these conclusions may be significantly modified according to clinical practice and health system characteristics, such as cost and frequency of multidisciplinary therapeutic care or surgical indications[48].

It is interesting to consider that the pain associated with spasticity does not depend on the spasticity intensity, which is clinically observed in the pain relief before the spasticity control after the introduction of the drugs[6,13]. This observation is also valid when the spasticity treatment is performed by procedures such as neuromuscular blockades with botulinum toxin. In this case, it is suggested that the pain reduction may have occurred prior to the spasticity reduction by the mechanical effect of muscle needling, similar to the acupuncture effect, since the motor points on which the botulinum toxin infiltrations are performed coincide 70% of the time with the acupuncture points of Traditional Chinese Medicine[38,47].

## CONCLUSION

Cannabinoid therapy has been shown to be an adjuvant in controlling spasticity and pain. Despite the greater pathophysiolo-

gical knowledge of the use of cannabinoids and the endocannabinoid system, there is still a need for further clinical studies to determine the best doses, blends and the therapy start timing.

## AUTHORS' CONTRIBUTIONS

**Eduardo de Melo Carvalho Rocha**
Project management, Writing - Document preparation
**Marcelo Riberto**
Project management, Writing - Proofreading and editing

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**ORCID.** ORCID (Open Researcher and Contributor ID) is a non-proprietary alphanumeric code for unique identification of scientists and their collaborators, providing persistent identity to humans, similar to what is created for content entities related to digital networks by digital object identifiers (DOIs). Your ORCID number must be entered on the title page. If you do not already have your ORCID, registration can be made in https://orcid.org/register.

**Highlights.** Highlights are mandatory for this journal as they help to increase the discoverability of an article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Highlights should be submitted in a separate page after the title page file. Please use 'Highlights' as a topic in the top of the page. Include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

**MAIN STRUCTURE OF ORIGINAL ARTICLES**
**Blinded manuscript** (no author details): main body of the paper (including references, figures, tables and any acknowledgements) should not include any identifying information, such as authors' names or affiliations.

**Abstract.** Abstracts should bring the main important information from the manuscript. Like the paper itself, abstracts should include all of the IMRaC elements: Introduction, Methods, Results, and Conclusion. Initially, on the introduction, authors should provide a broad overview of the entire study, write out the hypothesis or research question or problem it attempts to solve and why the reader should be interested. Two to three phrases may be enough to highlight the main idea, followed by the objective. Then, the methods section must inform the type of study, the procedure for collecting data, including descriptions of variables, instruments, software, or participants / groups of participants. Timeline measurements and analytical methods should also be presented. Main results

should be presented, comparing groups when necesssary, and presenting values between parenthesis. The discussion section explains the ultimate conclusion and its ramifications. The discussion section often goes beyond the scope of the project itself, including the implications of the research or what it adds to its field as a whole.

**Key-words.** Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes. Preferably, key-words must be selected from MeSH Database at https://www.ncbi.nlm.nih.gov/mesh.

**Introduction.** In this section, authors must sucintamente descrever o escopo e o conhecimento prévio baseado em evidência (state of the art) para o delineamento da pesquisa, tendo como base referências bibliográficas relacionadas ao tema, preferencialmente mais recentes conforme possível. Adicionalmente, a lacuna de conhecimento ou o problema em questão deve ser apresentado. Ao final, deve incluir o objetivo da pesquisa de forma clara e a relevância do assunto estudado.
**Methods.** Specific information about methods can be seen in the section of "Types of Article once each type of manuscript requires disctinct items. We must reinforce that report guidelines must be used to any type of article.
**Results.** devem ser descritos de forma objetiva, elucidados por figuras e tabelas quando necessário. Incluir análises realizadas e seus resultados.
**Discussion.** In this section, authors must discuss their results and three different phases to each conjunct of findings should be considered: interpretation of results, use of previous publication to confirm or refute findings and considerations of authors to each topic discussed. Previous information must be appropriately cited. Discussion can be optionally divided into subchapters. Limitations of the study, clinical implications (always when adequate), information about the importance / relevance, and perspectives for future researches are mandatoryly required.
**Conclusion.** Conclusions must be concise and directly repond to the objectives of the study. No extra commentaries are needed.
**Acknowledgments.** Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).
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If no funding has been provided for the research, please include the following sentence:
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**References.** References must follow Vancouver style (http://www.icmje.org).
**Figures and Tables.** They must be sent in the same file of the main manuscript just after references inserting break page between them.

**More information:**
**Summary.** When completing the submission process of their manuscript, authors must enter the text in Portuguese and English in a specific field on the platform, followed by the descriptors (from 3 to 6, which must be included in the Descriptors in Health (DeCs) or MeSH Database.
**Style.** Pattern manuscript style after the American Medical Association Manual of Style (10th edition). Stedman's Medical Dictionary (27th edition) and Merriam Webster's Collegiate Dictionary (10th edition) should be used as standard references. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc.

Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. In that case, supply the chemical name and a figure giving the chemical structure of the drug.
Capitalize the trade names of drugs and place them in parentheses after the generic names. Also, capitalize all equipments and apparatus used in the methods section. To comply with trademark law, include the name and location (city and state and country) of the manufacturer of any equipment mentioned in the manuscript followed by the symbol. Use the metric system to express units of measure and degrees Celsius to express temperatures, and use SI units rather than conventional units.
It is important that the file be saved in the native format of the word processor used. The text should be in single-column format.
When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts. Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

**Math formulae.** Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

**Footnotes.** Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

**Reference style.** Submissions should adhere to the BrJP® reference style, full details of which can be found in the information provided for each article type under section "Article Types" above. Authors are highly recommended to manage theirs references by using softwares such as Endnote, Mendeley or Zotero.
Cite literature references in the text should be presente as a superscript number as follows: "Pain pain pain pain pain pain pain[4]." For multiple references in the text, please use the format "Pain pain pain pain pain pain pain[4,5]." or "Pain pain pain pain pain pain pain[4-7,10]." (with a comma and no spaces).
- All references cited in the text must be listed at the end of the paper. They should be numbered, double spaced, and arranged alphabetically by first author last name.
- All authors must be listed in the references; the use of et al. is not acceptable.
- Journal titles should be abbreviated according to the National Library of Medicine's Index Medicus. Please refer to the NLM website's FAQ on how to find Index Medicus journals: www.nlm.nih.gov/services/aim.html.
- Unpublished data, personal communications, abstracts that cannot be retrieved by casual readers (e.g., meeting abstracts that require logging into a members-only site), and other inaccessible materials should not be listed as references. Unpublished materials may be cited in parentheses within the text.
**Figures.** BrJP has strict guidelines on image quality. You must ensure your figures follow these rules. Failure to supply files in the format specified below will result in the images being returned to you for re-formatting. This may lead to an associated delay in the review and publication of your manuscript.
A) Creating Digital Artwork
Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.
B) Digital Artwork Guideline Checklist
Here are the basics to have in place before submitting your digital art to BrJP:
Artwork should be saved as TIFF, PDF, Word Doc, PPT, or EPS files.

Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal to which you wish to submit. Measure the artwork typically shown and scale your image to match.)
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Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
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General points:
• Make sure you use uniform lettering and sizing of your original artwork.
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Please do not:
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• Supply files that are too low in resolution.
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**Color figures.** All figures will appear in a grey scale in both online and printed versions, according submitted by authorors and approved by the editotrial board/ reviewers.
**Figure legends.** Legends must be submitted for all figures. Provide each illustration with a title and an explanatory legend. The title should be part of the legend; do not reproduce the title and legend on the figure itself. They should be brief and specific and appear on a separate manuscript page after the references in the same file. Each legend should begin with a brief statement that identifies the figure. Each legend should be numbered consecutively with Arabic numerals (i.e., Fig. 1, Fig. 2, etc.), and should begin with the number of the illustration to which they refer. Explain all symbols and abbreviations used in the figure. Use scale markers in the image for electron micrographs and indicate the type of stain used for tissue, if this is the case.

**Tables.** Tables can be included within the manuscript document on a separate manuscript page after the references in the same file. Do not upload images of tables. All tabular matter must be editable (in Word). An image of a table, such as a scan, is not acceptable for publication. Tables, with their captions and legends, should be intelligible with minimal reference to the text. Tables of numerical data should each be typed (double spaced) on a separate page, numbered in sequence with Arabic numerals (i.e., Table 1, Table 2, etc.), provided with a title/heading, and referred to in the text as Table 1, Table 2, etc. Provide a detailed description of its contents and any footnotes below the body of the table.

**Social media promotion of individual articles.** At the revision stage, authors will be asked to enter a question at re-submission to be used for social media purposes. Please compose a question for which your paper's subject, topic, or title is an answer. We will take your question, attach your paper's web address, and use it for SBED´s social media promotion. Example of author composed question: What is the relationship between pain and fear in fibromyalgia patients? The answer is the title of author´s paper, such as in this example "Fear is a predictor to increase pain in fibromyalgia patients," which the BrJP® editorial office will translate to a bit.ly URL (a shortened web address) and attach it to the question. The final product, the question, and the shortened web address, is the message we will promote on social media, to boost awareness and drive traffic to the published content. What everyone will see on social media: What is the relationship between pain and fear in fibromyalgia patients? http://bit.ly/vvXvxV, for example.

**ARTICLE TYPES**
The journal will only consider publication of work that includes information that is sufficient to permit replication by other laboratories or groups. Manuscripts reporting data from novel chemical probes will not be considered unless the structure and pharmacological characterization, including selectivity and relevant formulation, are reported or directly described in a prior peer-reviewed publication.
Brazilian Journal of Pain (BrJP) publishes original research articles, reviews, and brief communications on topics related to distinct areas of pain.
Our Editorial Board is committed to disseminate high-quality research in the field of pain.
BrJP follows principles of publication ethics included in the code of conduct of the Committee on Publication Ethics (COPE).
BrJP accepts submission of manuscripts with up to 4,000 words (excluding title page, abstract, references, tables, figures and legends). Information contained in any appendices will be included in the total number of words allowed for publication.
A total of six (6) either tables and/or figures is allowed.
The following types of study can be considered for publication, if directly related to the journals scope. Click on the article type to see details on manuscript formatting.
The below article types are considered for publication in BrJP.
a) **Intervention studies** (clinical trials): studies that investigate the effect(s) of one or more treatment interventions on outcomes directly related to pain. World Health Organization defines a clinical trial as any research study that prospectively allocates human participants to one or more health-related interventions to evaluate the effect(s) on health outcome(s). Clinical trials include single-case experimental studies, case series, nonrandomized controlled trials, and randomized controlled trials.
Randomized clinical trials (RCTs) must follow Consolidated Standards of Reporting Trials (CONSORT) available at http://www.consort-statement.org/. In the manuscript, authors must provide the CONSORT Checklist and the CONSORT Flow Diagram which illustrates the progress of patients through the trial, including all phases, at the endo f the manuscript in the same file.
Registration of clinical trials Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors recommendations. Trials must register at or before the onset of patient enrolment. Clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes.
Moreover, CONSORT-Abstract must be used in an attempt that authors provide a minimum list of itens in the abstract section (see https://bit.ly/3OG1IUS). For the RCTs, title must consider information from the PICOT strategy (P: population; I: intervention: C: comparation; O: outcome; T: time).
RCTs must provide registration that satisfies the requirements of the International Committee of Medical Journal Editors (ICMJE), e.g. http://clinicaltrials.gov/ and / or http://www.anzctr.org.au. The complete list of all clinical trial registries can be found at: http://www.who.int/ictrp/network/primary/en/index.html. We suggest that all authors register clinical trials prospectively via websites such as http://www.clinicaltrials.gov or https://ensaiosclinicos.gov.br/. Note: We accept single case studies and series of cases (i.e. clinical trials without a comparison group) in a low proportion if they are really interesting in the area of interest.
Template for Intervention Description and Replication (TIDieR) checklist and guide must also be used to promote a complete description of both pharmacological and non-pharmacological interventions, in an attempt that clinicians and patients can reliably implement interventions that are shown to be useful, and other researchers can replicate or build on research findings. The TIDieR guide provides, for each item, an explanation, elaboration, and examples of good

reporting and can be found at https://www.equator-network.org/wp-content/uploads/2014/03/TIDieR-Checklist-PDF.pdf. TIDieR checklist must be submitted at the end of the manuscript in the same file.

The resultant 12 item TIDieR checklist is an extension of the CONSORT 2010 statement (item 5). For authors of reports of randomised trials, it is recommended that TIDieR is used in conjunction with the CONSORT checklist: when authors complete item 5 of the CONSORT checklist, they should insert "refer to TIDieR checklist" and provide a separate completed TIDieR checklist.

Sample size must be presente in all details in all manuscripts which are clinical trials. P value and confidence interval will be required as well.

In line with the position of the International Committee of Medical Journal Editors, BrJP will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of the manuscript.

b) **Observational studies**: studies that investigate the relationship(s) between variables of interest related to pain. Observational studies include transversal or longitudinal cross-sectional studies, cohort studies, and case-control studies. All observational studies must be reported following the recommendation from Strengthening the reporting of observational studies in epidemiology (STROBE) statement (http://strobe-statement.org/index.php?id=strobe-home). STROBE checklist must be submitted at the end of the manuscript in the same file.

c) **Qualitative studies**: studies that focus on understanding needs, motivations, perceptions, opinions, experiences, and human behavior. The object of a qualitative study is guided by in-depth analysis of a topic, including opinions, attitudes, motivations, and behavioral patterns without quantification. All qualitative studies must be reported following the recommendation from Standards for Reporting Qualitative Research (SRQR) statement (https://www.equator-network.org/reporting-guidelines/srqr/). SRQR checklist must be submitted at the end of the manuscript in the same file.

d) **Systematic reviews**: studies that analyze and/or synthesize the literature on a topic related to the scope of pain. Systematic reviews that include meta-analysis will have priority over other systematic reviews. Those that have an insufficient number of articles or articles with low quality in the methods section and do not include an assertive and valid discussion/conclusion about the topic will be evaluated with caution. Authors must follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to presente a systematic reviews. This checklist is available at http://prisma-statement.org/prismastatement/Checklist.aspx and must be filled in and submitted with the manuscript. PRISMA checklist must be submitted at the end of the manuscript in the same file.

The risk of bias analysis should be performed, according to the authors' choice, using the Risk Analysis tools of the Cochrane RoB2 Collaboration (https://bit.ly/31PpnOW) or PeDro Scale (https://bit .ly/3zR7FY0).

GRADE is a systematic approach to classifying the certainty of evidence in systematic reviews and other evidence syntheses and should be used in systematic reviews. The checklist covers the key determinants for each of the five factors (risk of bias, inconsistency, indirect evidence, imprecision, publication bias) that can lead to reduced quality in the system. Check information about GRADE at https://bit.ly/3qkwwjV.

e) **Studies on the translation and cross-cultural adaptation of questionnaires or assessment tools**: studies that aim to translate and/or cross-culturally adapt questionnaires from other countries to a language other than that of the original version of existing assessment instruments. Authors must use the checklist (in Appendix) to format this type of paper and adhere to the other recommendations of the BrJP. Answers to the checklist must be submitted with the manuscript at the end of the manuscript in the same file. At the time of submission, authors must also include written permission from the authors of the original manuscript that whose instrument was translated and/or cross-culturally adapted.

f) **Methodological studies**: studies related to the development and/or evaluation of clinimetric properties and characteristics of assessment instruments. Authors are required to use the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) to format methodological papers, in addition to following BrJP instructions, which can be found at https://bit.ly/3KODxBE.

g) **Clinical trial protocols**: BrJP welcomes the publication of pain-related clinical trial protocols. We only accept trial protocols that are substantially funded, have ethics approval, have been prospectively registered and of very high quality. We expect that clinical trial protocols must be novel and with a large sample size. Finally, authors have to provide that the clinical trial is on its first stages of recruitment. Authors must use Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement while formatting the manuscript (http://www.spirit-statement.org).

h) **Animal pre-clinical studies**: Animal experiments should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978), Federal Law 11.794/08 (Lei Arouca), Brazilian practice guideline for the care and use of animals for scientific and teaching purposes (DBPA). Authors should clearly indicate in the manuscript that such guidelines have been followed. Authors must use Animal Research: Reporting of In Vivo Experiments (ARRIVE) statement while formatting the manuscript (https://www.equator-network.org/reporting-guidelines/improving-bioscience-research-reporting-the-arrive-guidelines-for-reporting-animal-research/).

All experiments involving animals should be approved by a local Animal Care Committee and should be in accordance with the guidelines of the corresponding country. If guidelines are not available in the country where the research is being performed, we recommend following the guidelines described by the National Institutes of Health, USA. We propose that the following general guidelines be followed to establish reliability and robustness of the data presented.

Pharmacological studies. General pharmacological principles such as dose-response curves and testing an antagonist against its agonist, which indicate receptor-mediated interactions and specificity of the proposed drug, are recommended. In a few cases, there are well-established doses of pharmacological drugs that can be used but these should be justified by appropriate literature. Vehicle control data are needed.

Behavioral studies. To perform unbiased studies, it is essential that the following principles be used in behavioral studies: blinding of the behavioral tester (preferably to the condition, but essentially to the drug/genotype/manipulation or vehicle, phenotype, etc.) and also randomization of animals to groups. It is also recommended that when possible behavioral studies should be performed by the same tester, or interrater reliability should be performed and reported between multiple testors. Details on the randomization procedures and blinding should be included in the methods.

Genetic studies or usage of gene delivery tools. Studies on genetically-modified mice should employ control mice of the corresponding genetic background as controls. When viral tools are used for gene delivery, virions expressing a functionally-neutral gene, such as GFP, should be included as controls. In RNAi experiments, scrambled/sense/functionally-neutral constructs should be included as controls.

Animals. Age, sex, species, and source of animals should be reported. The number of replicates and animals used per experiment and group should be clearly outlined in the methods. We recommend use of both male and female animals in experiments where appropriate and possible.

Sham controls for surgical and other interventions are recommended.

Drug formulation. All drugs used in the study should be listed with the vendor for which it was purchased, dosing, how the drug was dissolved, site (city, state and country, route of administration and symbol of trade mark.

Studies involving molecular profiling data, i.e. 'Omics'. Descriptive data from Omics approaches on animal models or clinical groups, such as transcriptomics, genomics, proteomics, microRNA profiling etc., should be accompanied by secondary validation of data sets, such as by quantitative PCR. The analysis of functional implications of the genes, proteins or microRNAs identified via such approaches is recommended.

Statistics. Care should be taken that the statistical measures adopted are appropriate for the data sets being analyzed. For example, while comparing multiple groups or time points, application of a t-test is inappropriate. ANOVA and post-t-hoc tests that enable multiple comparisons (e.g., Bonferroni) should be used. The choice of one-way or two-way ANOVA is dependent upon the number of independent variables being tested such as treatment, time, sex or other. If the authors are unsure about which statistical measures to implement, receiving help from a statistician is recommended.

Secondary analyses of data. BrJP abides by the ICMJE guidelines regarding manuscripts based on secondary analyses of data. Such manuscripts should address

a novel, distinct, and impactful aspect of the data that could not be presented in the primary manuscript/analysis. A manuscript derived from secondary analyses must clearly cite the primary publication(s) (as well as additional secondary publications), and state that it contains secondary analyses/results. We strongly discourage unnecessary division of datasets into multiple manuscripts.

i) **Diagnostic/prognostic studies**: studies related to biological effects and / or mechanisms of action of pharmacological and non-pharmacological interventions to pain. Authors must use STAndards for the Reporting of Diagnostic accuracy studies (STARD) statement while formatting the manuscript (https://www.equator-network.org/reporting-guidelines/stard/).

j) **Short communications**: BrJP will publish one short communication per issue (up to six a year) in a format similar to that of the original articles, containing 1200 words and up to two figures, one table, and ten references.

k) **Masterclass articles**: this type of article presents the state of art of any topic that is important to the field of pain. All masterclass articles will be invited manuscripts and authors must be recognized experts in a specific field of pain. However, authors can send e-mails to the editor in chief expressing the interest to submit a masterclass article to the BrJP.

l) **Letter to editor.** A Letter to the Editor raises issues of importance regarding an article recently published in BrJP. If accepted, the letter is sent to the authors of the article who have an opportunity to respond. Word count should be around 500-750. File format should be Microsoft Word, and manuscript pages should be numbered.

m) **Clinical notes/case reports**: a single case or a series of cases related to either acute or chronic pain can be presented here. Only very interesting cases will be considered for publication. Thus, authors should include a justification to show why that/those case(s) are relevant to be published and what this publication would add to the literature in the title page. This type of publication requires approval in the institutional Ethics Committee and informed consente signed by participant(s), which must be mentioned in the text. The maximum of words is 1800. Results must be clearly presented and discussed based on the sicnetific literature, citing references. A maximum of three authors can be included. Main strutcture should contain: introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow-up and outcomes, patient perspective, discussion, acknowledgments and references. More information about how to write case reports must follow Case REport Reporting Guideline (CARE) which can be found at https://bit.ly/3lM1crJ. A checklist must be included in the manuscript file after to presenting figures and tables, when adequate. Figures and tables can be included.

Title page. The title page should include the following: (i) complete title (preferably no chemical formulas or arbitrary abbreviations); (ii) full names of all authors; (iii) complete affiliations of all authors; (iv) the number of text pages of the entire manuscript (including pages containing figures and tables) and the actual number of figures and tables; (v) the author to whom correspondence should be sent and this author's complete mailing address, telephone number, and e-mail address, and, if available, institutional URL.

Acknowledgments. Place acknowledgments at the end of the text before the reference list and should specify thefollowing: (1) contributions that need acknowledging but do not justify authorship; (2) acknowledgments of technical help; (3) acknowledgments of financial and material support, specifying the nature of the support; (4) financial arrangements that may represent a possible conflict of interest.

This would also include any of the following arrangements, such as if any of the authors have a financial relationship to the work; have received any government or company grants or research support; are employees of a company; are consultants for a company; are stockholders of the company; are members of a speakers bureau; or have received any other form of financial support.

Conflict of Interest. A Conflict of Interest statement must be included for all manuscripts within the Acknowledgments section. Even if there are no conflicts of interest, please explicitly state this.

## FINAL PROOFREADING AND APPROVAL FOR PUBLICATION

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Include responses to the Reviewers' Response Letter. Please use this proof only to check the typing, editing, completeness and correction of text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with the permission of the Editor-in-Chief.

We will do everything we can to get your article published quickly and accurately. It is important to ensure that all fixes are sent back to us in a single communication. Check carefully before responding, as the inclusion of any subsequent fixes cannot be guaranteed. The review is the sole responsibility of the authors.

## EDITORIAL FLOW

More intuitively, we communicate to the authors the sequential steps by which an article is processed in the editorial process developed by BrJP, from submission to decision-making by the editor-in-chief (Figure 1).

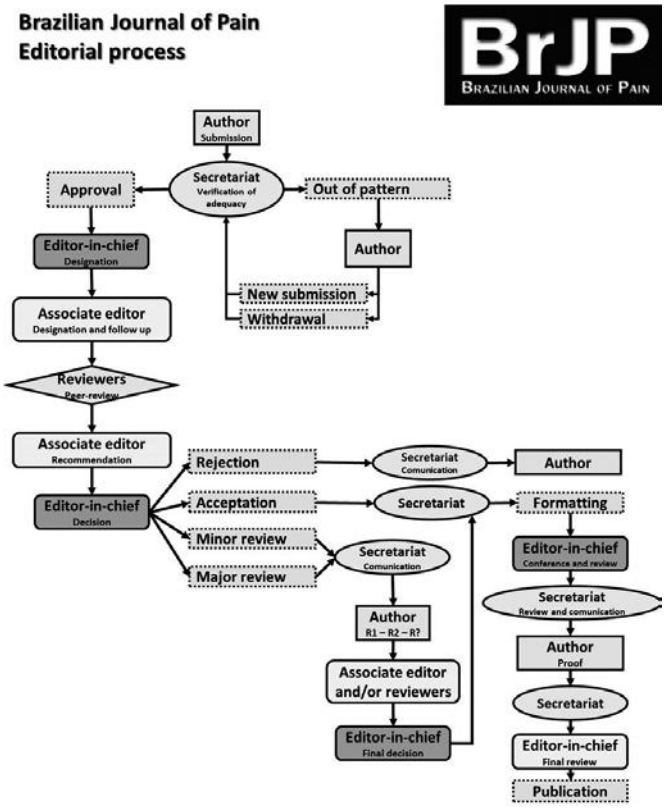


**Figure 1**. Flow of the editorial process of the Brazilian Journal of Pain.

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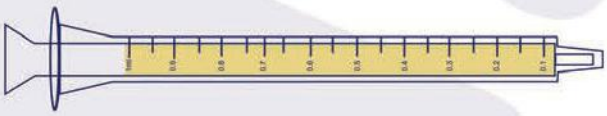
**NABIX® 10.000** (frasco 100ml): **cada ml contém 100mg CBD + 3mg THC.**
**NABIX® 1.500** (frasco 30ml): **cada ml contém 50mg CBD + 1,5mg THC.**

**NABIX® T-free** é o único produto de Cannabis, Broad Spectrum, no mercado brasileiro que apresenta dose fixa de CBD com **isenção de THC** em sua formulação, preservando todos os outros componentes da planta.

**NABIX® T-free** é uma das mais seguras e eficazes opções terapêuticas de uso compassivo para o tratamento da dor crônica refratária em diferentes níveis, principalmente em pacientes não compatíveis com o uso de THC (pediatria, desordens psiquiátricas graves etc.).

**NABIX® T-free** (frasco 30ml): **cada ml contém 200mg CBD em alta concentração**

Os produtos da linha Nabix são os únicos no mercado brasileiro que apresentam:

- Seringa dosadora de precisão;
- Produção em grau farmacêutico;
- Certificado de análise completa em todos os lotes, incluindo quantificação de todos os componentes da formulação, microbiologia e micro toxinas


**NABIX® Sport** é a primeira e única fita de uso tópico que associa canabinoides (full spectrum) + Lidocaína + Mentol, com liberação prolongada (12horas) no mercado brasileiro.

A combinação de ingredientes ativos chaves, faz do **NABIX® Sport** uma opção terapêutica no uso compassivo para o tratamento de lesões musculares, e/ou, dor crônica refratárias.

O paciente tem a opção de se recuperar mantendo-se em plena atividade no dia a dia, tornando-se uma poderosa opção terapêutica adjuvante aos tratamentos tradicionais.

Atenção: os ativos do **NABIX® Sport** não chegam à corrente sanguínea. Sua ação é tópica, acessando o sistema endocanabinoide presente na pele humana.

**NABIX® Sport**: cada fita (25cm comprimento X 5 cm largura), libera progressivamente, por unidade aplicada, 30mg CBD + 20 mg Lidocaína + 40mg Mentol.

Os produtos possuem certificados de análise em todos os lotes, garantindo a segurança e a dosagem correta dos ativos presentes no tape.

**IMPORTANTE:** Produtos de cannabis não possuem comprovação clínica comprovada, e/ou, pesquisas clínicas concluídas. Seu uso segue a RDC 660/2022 da ANVISA e o acesso do paciente deve ser somente através de prescrição por profissional da saúde habilitado, em uso compassivo. O uso de qualquer produto canábico deve ser sempre acompanhado de supervisão permanente de um profissional legal. Para maiores informações consulte o seu médico. Material exclusivo para profissionais da saúde habilitados.