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].

Marcus Vinicius Morais – https://orcid.org/0000-0002-7926-2745;
Mauro Almeida – https://orcid.org/0000-0001-5275-7767;
José Oswaldo de Oliveira Junior – https://orcid.org/0000-0002-7130-8171.

1. Functional Neurosurgeon. AC Camargo Cancer Center, Pain and Stereotaxis Center, São Paulo, SP, Brazil.
2. Functional Neurosurgeon. M.e. Ophir Loyola Hospital, Department of Functional Neurosurgery, Belém, PA, Brazil.
3. Functional Neurosurgeon. D.r. State Public Servant Hospital, Neurosurgery Pain Specialist Group, São Paulo, SP, Brazil.

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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.

Correspondence to:
Marcus Vinicius Morais
E-mail: moraisneuro@gmail.com

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
José Oswaldo de Oliveira Junior
Writing - Review and Editing, Supervision

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