# Neuropathies and the use of cannabinoids as a therapeutic strategy

*Neuropatias e o uso de canabinoides como estratégia terapêutica*

Helena Wohlers Sabo[1], Ana Gabriela Baptista[2]

DOI 10.5935/2595-0118.20230012-en


## 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.

Helena Wohlers Sabo – https://orcid.org/0000-0002-6903-5557;
Ana Gabriela Baptista – https://orcid.org/0000-0002-4888-0030.

1. Brasil Santo André Hospital, São Luiz Hospital, Clinic Neurophysiology, Santo André, SP, Brazil.
2. Albert Einstein Israeli Hospital, P&D Cannabinoid Therapy of Phytotherapic Products, São Paulo, SP, Brazil.

**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.

Submitted on June 01, 2022.
Accepted for publication on March 06, 2023.
Conflict of interests: none – Sponsoring sources: none.

**Correspondence to**:
Helena Wohlers Sabo
**E-mail**: helenaws39@gmail.com

## 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

## REFERENCES


1. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders? CNS Neurosci Ther. 2009;15(1):65-75.
2. Cao C, Li Y, Liu H, Bai G, Mayl J, Lin X, Sutherland K, Nabar N, Cai J. The potential therapeutic effects of THC on Alzheimer's disease. J Alzheimers Dis. 2014;42(3):973-84.
3. Rajesh M, Mukhopadhyay P, Bátkai S, Haskó G, Liaudet L, Drel VR, Obrosova IG, Pacher P. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. Am J Physiol Heart Circ Physiol. 2007;293(1):H610-9.
4. Ramer R, Bublitz K, Freimuth N, Merkord J, Rohde H, Haustein M, Borchert P, Schmuhl E, Linnebacher M, Hinz B. Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. FASEB J. 2012;26(4):1535-48.
5. Yao I, Stein ES, Maggio N. Cannabinoids, hippocampal excitability and efficacy for the treatment of epilepsy. Pharmacol Ther. 2019;202(1):32-9.
6. Calcutt NA. Diabetic neuropathy and neuropathic pain: a (con)fusion of pathogenic mechanisms. Pain. 2020;161(Suppl 1):S65-S86.
7. Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012;5(5):529-52.
8. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18(7):999-1012.
9. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164-73.
10. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299-306.
11. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4(1):2-8.
12. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5(5):400-11.
13. Gross F, Üçeyler N. Mechanisms of small nerve fiber pathology. Neurosci Lett. 2020;15;737:135316.

14. Hansson GK. Neuropathic pain: definition, diagnostic criteria, clinical phenomenology, and differential diagnostic issues. Pain. 2008;2008.
15. Pedowitz EJ, Abrams RMC, Simpson DM. Management of neuropathic pain in the geriatric population. Clin Geriatr Med. 2021;37(2):361-76.
16. Blanton HL, Brelsfoard J, DeTurk N, Pruitt K, Narasimhan M, Morgan DJ, Guindon J. Cannabinoids: current and future options to treat chronic and chemotherapy-induced neuropathic pain. Drugs. 2019;79(9):969-95.
17. Knezevic NN, Jovanovic F, Candido KD, Knezevic I. Oral pharmacotherapeutics for the management of peripheral neuropathic pain conditions – a review of clinical trials. Expert Opin Pharmacother. 2020;21(18):2231-48.
18. Lee G, Grovey B, Furnish T, Wallace M. Medical cannabis for neuropathic pain. Curr Pain Headache Rep. 2018;22(1):8.
19. Kogan NM, Lavi Y, Topping LM, Williams RO, McCann FE, Yekhtin Z, Feldmann M, Gallily R MRN. Novel CBG derivatives can reduce inflammation, pain, and obesity. Molecules. 2021;26:5601.
20. Sopacua M, Hoejimakers JGJ, Merkies ISJ, Lauria G, Waxman SG FC. Small fibre neuropathy: expanding the clinical pain universe. J Peripher Nerv Syst. 2019;24(1):19-23.
21. Alles SRA, Cain SM, Snutch TP. Pregabalin as a pain therapeutic: beyond calcium channels. Front Cell Neurosci. 2020;14:83.
22. Cipriani A. Review: selective serotonin reuptake inhibitors as effective as tricyclic antidepressants for major depression, and may have fewer adverse effects. Evid Based Ment Health. 2003;6(4):117.
23. Yeh CM, Ruan T, Lin YJ, Hsu TH. Activation of cannabinoid CB1 receptors suppresses the ROS-induced hypersensitivity of rat vagal lung C-fiber afferents. Pulm Pharmacol Ther. 2016 Oct;40:22-9.
24. O'Hearn S, Diaz P, Wan BA, DeAngelis C, Lao N, Malek L, Chow E, Blake A. Modulating the endocannabinoid pathway as treatment for peripheral neuropathic pain: a selected review of preclinical studies. Ann Palliat Med. 2017;6(Suppl 2):S209-S214.
25. Maldonado R, Baños JE, Cabañero D. The endocannabinoid system and neuropathic pain. Pain. 2016;157(Suppl 1):S23-S32.
26. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain. 2017;158(Suppl 1):S11-8.
27. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD; Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53-9.
28. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012;133(1):79-97.
29. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5(5):400-11.
30. Morera-Herreras T, Miguelez C, Aristieta A, Ruiz-Ortega JA, Ugedo L. Endocannabinoid modulation of dopaminergic motor circuits. Front Pharmacol. 2012;3:110.
31. Syed YY, McKeage K, Scott LJ. Delta-9-Tetrahydrocannabinol/cannabidiol (Sativex®): A review of its Use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs. 2014;74(5):563-78.
32. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260(4):984-97
33. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: A pilot study. Am J Phys Med Rehabil. 2010;89(10):840-8.
34. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-9.
35. Wallace MS, Marcotte TD, Atkinson JH, Padovano HT, Bonn-Miller M. A secondary analysis from a randomized trial on the effect of plasma tetrahydrocannabinol levels on pain reduction in painful diabetic peripheral neuropathy. J Pain. 2020;21(11-12):1175-86.
36. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136-48.
37. Almog S, Aharon-Peretz J, Vulfsons S, Ogintz M, Abalia H, Lupo T, Hayon Y, Eisenberg E. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. Eur J Pain. 2020;24(8):1505-16.
38. Murnion BP. Neuropathic pain: current definition and review of drug treatment. Aust Prescr. 2018;41(3):60-3.
39. Sadler A, Wilson J, Colvin L. Acute and chronic neuropathic pain in the hospital setting: use of screening tools. Clin J Pain. 2013;29(6):507-11.
40. Alshelh Z, Di Pietro F, Youssef AM, Reeves JM, Macey PM, Vickers ER, Peck CC, Murray GM, Henderson LA. Chronic neuropathic pain: it's about the rhythm. J Neurosci. 2016;36(3):1008-18.
41. Russo M, Naro A, Leo A, Sessa E, D'Aleo G, Bramanti P, Calabrò RS. Evaluating Sativex® in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. Pain Med. 2016;17(6):1145-54.
42. Starowicz K, Finn DP. Cannabinoids and pain: sites and mechanisms of action. Adv Pharmacol. 2017;80:437-475.
43. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17(1):21-9.
44. Hansen JS, Hansen RM, Petersen T, Gustavsen S, Oturai AB, Sellebjerg F, Sædder EA, Kasch H, Rasmussen PV, Finnerup NB, Svendsen KB. The effect of cannabis-based medicine on neuropathic pain and spasticity in patients with multiple sclerosis and spinal cord injury: study protocol of a national multicenter double-blinded, placebo--controlled trial. Brain Sci. 2021;11(9):1212.
45. Weizman L, Dayan L, Brill S, Nahman-Averbuch H, Hendler T, Jacob G, Sharon H. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. Neurology. 2018;91(14):e1285-e1294.