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USO DE CANABINÓIDES SINTÉTICOS E FITOCANABINÓIDES NO TRATAMENTO DA DOR NEUROPÁTICA: UMA REVISÃO BASEADA EM ENSAIOS CLÍNICOS RANDOMIZADOS

USE OF SYNTHETIC AND PHYTOCANNABINOIDS IN THE TREATMENT OF NEUROPATHIC PAIN: A REVIEW BASED ON RANDOMIZED CLINICAL TRIALS

USO DE CANNABINOIDES SINTÉTICOS Y FITOCANNABINOIDES EN EL TRATAMIENTO DEL DOLOR NEUROPÁTICO: UNA REVISIÓN BASADA EN ENSAYOS CLÍNICOS ALEATORIZADOS

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RESUMO: A dor neuropática (DN) é uma condição altamente prevalente e incapacitante, frequentemente refratária aos tratamentos farmacológicos conservadores. Diante das limitações das terapias atualmente disponíveis, os canabinoides têm sido de interesse por suas propriedades neuroimunomoduladoras. Todavia, as evidências clínicas de eficácia são controversas. Esta revisão aborda as evidências de eficácia e segurança de canabinoides sintéticos e fitocanabinoides no tratamento da DN. Foram realizadas buscas nas bases Embase, Scopus, Web of Science, PubMed/MEDLINE e Cochrane Central Register of Controlled Trials, incluindo ensaios clínicos randomizados (ECR) publicados desde o ano 2000. Os estudos elegíveis avaliaram canabinoides como monoterapia ou como tratamento adjuvante para DN, com desfechos mensurados por instrumentos validados. Os dados foram analisados utilizando o sistema PICOT. Os resultados demonstraram heterogeneidade substancial quanto ao tipo de canabinoide, formulação, dose, via de administração, etiologia da dor e medidas de desfecho. Os canabinoides não foram superiores ao placebo quando utilizados como monoterapia; benefícios analgésicos modestos, melhora da qualidade do sono ou efeitos poupadores de opioides foram observados principalmente quando utilizados como terapia adjuvante ou administrados por via inalatória. As evidências atuais de ECR não sustentam o uso de canabinoides como monoterapia para DN.

Palavras-chave: Dor neuropática. Canabidiol. Fitocanabinoides. Tratamento.

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ABSTRACT: Neuropathic pain (NP) is a highly prevalent and disabling condition, often refractory to standard pharmacological treatments. Given the limitations of currently available therapies, cannabinoids have gained attention due to their and neuroimmunomodulatory properties. However, clinical evidence supporting their efficacy remains controversial. This paper reviews evidence on the efficacy and safety of synthetic and phytocannabinoids for the treatment of NP. We conducted a literature search in Embase, Scopus, Web of Science, PubMed/MEDLINE, and Cochrane Central Register of Controlled Trials, including randomized clinical trials (RCT) published since 2000. Eligible studies assessed cannabinoids as monotherapy or adjunctive treatment for NP, with outcomes evaluated using validated assessment tools. Data was analyzed using the PICOT framework. The results demonstrated substantial heterogeneity regarding cannabinoid type, formulation, dose, administration route, pain etiology, and outcome measures. Cannabinoids were not superior to placebo when used as monotherapy; modest analgesic benefits, improved sleep quality, or opioid-sparing effects were detected particularly when used as adjunctive therapy or administered via inhalation. Current evidence from RCT does not suggest the use of cannabinoids as monotherapy for NP. While selected patient subgroups may benefit from adjunctive cannabinoid-based therapies, the large heterogeneity of clinical protocols and assessments limit generalizable conclusions.

Keywords: Neuropathic pain. Cannabidiol. Phytocannabinoids. Treatment.

RESUMEN: El dolor neuropático (DN) es una condición altamente prevalente e incapacitante, a menudo refractaria a los tratamientos farmacológicos convencionales. Dadas las limitaciones de las terapias actualmente disponibles, los cannabinoides han despertado interés debido a sus propiedades neuroinmunomoduladoras. Sin embargo, la evidencia clínica que respalda su eficacia sigue controvertida. Este trabajo revisa la evidencia de eficacia y seguridad de cannabinoides sintéticos y fitocannabinoides para el tratamiento de la DN. Se realizó una búsqueda en Embase, Scopus, Web of Science, PubMed/MEDLINE y Cochrane Central Register of Controlled Trials, incluyendo ensayos clínicos aleatorizados (ECA) publicados desde el año 2000. Los estudios elegibles evaluaron cannabinoides como monoterapia o tratamiento adyuvante para DN, con resultados medidos mediante instrumentos de evaluación validados. Los datos se analizaron utilizando el sistema PICOT. Los resultados mostraron una heterogeneidad cuanto al tipo de cannabinoide, formulación, dosis, vía de administración, etiología del dolor y medidas de resultado. Los cannabinoides no fueron superiores al placebo cuando se utilizaron como monoterapia; se observaron beneficios analgésicos modestos, mejora de la calidad del sueño o efectos ahorradores de opioides cuando se utilizaron como terapia adyuvante o por vía inhalatoria. La evidencia actual de ECA no respalda su uso como monoterapia para la DN.

Palabras clave: Dolor neuropático. Cannabidiol. Fitocannabinoides. Tratamiento.

INTRODUCTION

Pain consists in a negative sensory and emotional complex response to actual or potential tissue damage due to chemical, mechanical, or thermal causes; depending on its severity, persistence, and recurrence, pain may significantly impair functional capacity, limit the execution of routine activities and decrease quality of life (WALKER et al., 2025;

SCARLATTI et al., 2025). Clinically, pain episodes are classified as acute when lasting less than three months, whereas symptoms persisting beyond this period are defined as chronic. Currently, pain is categorized according to the predominant pathophysiological mechanism, which can be nociceptive (resulting from the activation of nociceptors in response to tissue injury), nociplastic (characterized by altered nociceptive processing in the absence of clear tissue or neural damage), or neuropathic (resulting from lesions or diseases affecting the somatosensory nervous system), being frequently associated with psychological disorders such as anxiety and depressive episodes regardless of the mechanism (SOUZA and DIAS-SOUZA, 2023; WILDERMAN et al., 2025).

Since the 11th revision of the International Classification of Diseases (ICD-11), pain is formally recognized as a disease in its acute and chronic forms (KORWISI et al., 2024). In this context, neuropathic pain (NP) is a clinically important component of chronic pain globally. Its prevalence estimates in the general population can range from 7% to 25%, and it has been associated with worse health-related quality of life and greater disability than other forms of chronic pain (POSSO et al., 2016; BOUHASSIRA, 2019; BASKOZOS et al., 2023). Currently, the therapeutic options used in NP rely on protocols for neuropsychiatric diseases, including gabapentin, pregabalin and amitriptyline (SILVA and DIAS-SOUZA, 2021). Opioids and non-steroidal anti-inflammatory drugs are also adopted as third-line options, mostly due to the severity of adverse effects in long treatments and efficiency in providing relief (BARBOSA et al., 2021). There is, therefore, a clear need for new therapies, for which cannabinoids have been considered one of the main alternatives.

Cannabinoids comprise a class of molecules originally isolated from *Cannabis sativa* extracts, of which cannabidiol (CBD) and tetrahydrocannabinol (THC), more adequately classified as phytocannabinoids, are the most studied compounds. Endocannabinoids are mediators produced by neurons and immune cells, and insights into their structure opened doors for the development of synthetic cannabinoids (HANEY et al., 2026; RASPINI et al., 2026; SOUZA and DIAS-SOUZA, 2023). Therefore, technically, “cannabinoids” encompasses the three categories. Cannabinoids have been associated with varied immunological and neurological properties, including modulation of pain, for which several molecular mechanisms of action have been described. These include agonism of cannabinoid receptors (CB_1/CB_2), vanilloid transient receptors potential channels, peroxisome proliferator-activated receptors (PPAR) and glycine receptors (SOUZA and DIAS-SOUZA, 2023).

Evidence from animal models suggests the potential of cannabinoids for treatments of NP. Intraperitoneal CBD prevented paclitaxel-induced peripheral neuropathy in female mice through a 5-HT_{1A} receptor-dependent agonism, without compromising chemotherapy efficacy (WARD et al., 2014). CBD microinjected into the prelimbic cortex reduced both mechanical allodynia and depression-like behavior in rats with chronic constriction injury by agonism of CB1 and 5-HT_{1A} receptors (MALVESTIO et al., 2021). More recently, CBD combined to β-caryophyllene effectively attenuated thermal and mechanical hyperalgesia/allodynia, restored nerve blood flow, and preserved intraepidermal nerve fiber density in male Sprague-Dawley rats with diabetic peripheral neuropathy through inhibition of the NLRP3 inflammasome and NF-κB pathway (KHAN et al., 2024). However, evidence for clinical use remains scarce and fragmented, despite the growing interest in this alternative.

In this narrative review we approach the use of synthetic and phytocannabinoids in the treatment of NP. We considered clinical trials (and a few preclinical studies) in order to provide useful discussions concerning the use in real-life conditions either as monotherapy or combined to clinically relevant drugs for the treatment of NP. Given the scarcity of studies in this field, this review becomes even more relevant in an increasingly challenging scenario for the development of therapeutic strategies for the treatment of NP.

METHODS

This review was prepared using randomized clinical trials published in english since the year 2000 on the use of synthetic and phytocannabinoids in the treatment of neuropathic pain, either as monotherapy or adjunctive treatment. Papers were retrieved from Embase, Scopus, Web of Science, PubMed/MEDLINE and Cochrane Central Register of Controlled Trials, using the keywords: *"neuropathic pain," "neuropathy," "cannabinoids," "cannabidiol," "CBD," "tetrahydrocannabinol," "THC," "medical cannabis"*, and *"synthetic cannabinoids"*. Studies involving patients under 18 years old, or mixed pain conditions only, or non-neuropathic pain only, or of treatment duration inferior to two weeks, or with patients allowed to use recreational *C. sativa*, or lacking a clear comparator, or assessed outcomes using instruments that were not validated, were excluded from this review.

We analyzed the selected papers using the PICOT framework (Patient, Intervention, Comparison, Outcomes, Time) to provide a better description of each study, especially concerning the methods and how the outcomes were assessed. During the literature search, we

noticed a complex scenario: clinical studies in this topic are both scarce and widely diverse concerning the treatment protocol. Due to this limitation, we applied no restriction to etiology of pain, administration route and element of comparison (placebo, standard care, or baseline conditions). Primary outcomes were pain intensity and pain relief, while secondary outcomes included quality of life, sleep, functional measures, and adverse events. Studies were organized in a timeline by administration routes and source of the cannabinoids (natural or synthetic), to make comparisons more reasonable.

RESULTS AND DISCUSSION

Orally administered *C. sativa*-based extracts and phytocompounds for NP

A study reported a treatment with *C. sativa* extracts aimed to provide pain relief and remission for patients (48 patients, 95% men) with an average age of 39 years (range 23-63 years) presenting central NP caused by brachial plexus avulsion, frequently resulting from traction injuries (BERMAN et al., 2004). Eligible participants were required to have at least one avulsed nerve root and an injury that had occurred more than 18 months prior to enrollment. Two *C. sativa* L. extracts were used, administered as oromucosal sprays: one containing THC/CBD in a 1:1 ratio (GW-1000-02/Sativex) and another containing THC only (GW-2000-02). The maximum dose was 8 sprays per administration (THC 21.6 mg or THC:CBD 21.6/20 mg) or up to 48 sprays within 24 hours (THC 129.6 mg or THC:CBD 129.6/120 mg), adjusted according to subjective clinical response and adverse events. Patients self-administered the treatments (including the placebo group) across three distinct treatment periods, each lasting between 14 and 20 days. Participants were allowed to continue their usual medications. Although the primary outcome measure did not reach the predefined threshold for clinical significance, the study found statistically significant improvements in pain severity and in sleep quality with medicinal cannabis extracts compared with placebo (GW-1000-02: $p = 0.005$; GW-2000-02: $p = 0.002$).

A double-blind, randomized, placebo-controlled, parallel-group study conducted by Langford et al. (2013) evaluated the efficacy of a nabiximols formulation (oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD/spray, maximum dose of 12 sprays/day) as an adjunct drug to conventional treatment in patients with central NP associated with multiple sclerosis (MS). The study was conducted across 33 international centers and randomized 339 participants, including 109 men (32.2%) and 230 women (67.8%). Participants had an average

age of 49 years, pain duration exceeding 5 years, and an average baseline pain intensity of 6.58 on the Numeric Rating Scale (NRS). The medication was added to the existing treatment regimen. Concomitant analgesic use (such as anticonvulsants and NSAIDs) was documented in over 90% of patients. The study was divided into two phases: Phase A (14 weeks), designed to assess efficacy, and Phase B (randomized withdrawal), designed to investigate maintenance of effect. In Phase A, the proportion of patients achieving a ≥30% reduction in pain did not reach statistical significance ($p = 0.234$). Similarly, no significant improvement in sleep quality was observed during this phase. In contrast, Phase B results favored nabiximols, with time to treatment failure being significantly longer in the active treatment group ($p = 0.04$). Additionally, during Phase B, reductions in pain intensity ($p = 0.028$) and improvements in sleep quality ($p = 0.015$) were statistically significant compared with placebo.

A nabiximols formulation was also evaluated in a double-blind, randomized, placebo-controlled, crossover pilot clinical trial with chemotherapy-induced NP patients (LYNCH et al., 2014). The study randomized 18 participants (3 men and 15 women, average age of 56 years), of whom 16 completed the protocol. All participants had a diagnosis of persistent neuropathic pain for at least three months. The product was administered with a progressive dose titration starting at 1-2 sprays/day (up to a maximum of 12 sprays daily), as an adjunctive therapy to conventional analgesic treatments, which were required to be at stable doses for 14 days prior to study initiation. The primary outcome was change in pain intensity, assessed using the NRS for Pain Intensity (NRS-PI, 0–10). No statistically significant difference was found between nabiximols and placebo treatment ($p = 0.29$). However, a responder analysis identified a subgroup of five participants who achieved a clinically meaningful reduction in pain (≥2-point decrease on the NRS-PI). Only in this subgroup was the improvement statistically significant compared with placebo ($p = 0.001$). Secondary outcomes, including quality of life measured by the SF-36 questionnaire, also did not show statistically significant improvement. The study reported a Number Needed to Treat (NNT) of 5.

A multicentric study was conducted to evaluate the efficacy and safety of a THC/CBD oromucosal spray in the treatment of peripheral NP (HOGGART et al., 2015). The trial involved 234 patients (average age of 57.8 years), and intervention consisted of an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD, administered up to 8 times every 3 hours, with a maximum of 24 sprays per day over 38 weeks. The study included two groups: one receiving the THC/CBD spray and one receiving placebo. Pain severity was measured using a

0–10 NRS, and daily spray dose. Sleep quality was also assessed. THC/CBD spray was effective in relieving NP (approximately 30% improvement, considered clinically significant), and improvements in sleep quality were maintained throughout the study period.

Russo et al. (2016) evaluated the effect of sublingual Sativex® spray (containing THC 2.7 mg and CBD 2.5 mg) on neuropathic pain in patients with multiple sclerosis (MS). The study included 20 patients (60% women), aged between 37 and 53 years, diagnosed with MS for at least six months. Two groups were included: MS patients with pain and MS patients without pain, both receiving Sativex® for 1 month. Treatment consisted of administration of up to 8 sprays per 3-hour period, with a maximum of 24 sprays per day. Pain was measured using a visual analog scale, and quality of life was assessed using the MSQoL-54 scale. Neurophysiological analysis was performed using magnetic stimulation and assessment of C-band power. The results showed that patients experienced a significant reduction in pain after 1 month of treatment, with improvements in both subjective and objective parameters of spasticity. MSQoL scores increased significantly in both groups, and C-band power increased significantly only in patients with MS-associated neuropathic pain. No significant changes were observed in electrophysiological parameters.

A trial investigated the benefits of an industrial formulation of Δ9-THC (Namisol®, single oral dose of 8 mg) for its analgesic efficacy, pharmacokinetics, and tolerability in patients with chronic abdominal pain due to pancreatitis (DE VRIES et al., 2016). The study involved 24 patients (average age was 52 years, 62.5% male), and pain had persisted for at least 8.3 years. The study compared Namisol® with placebo or diazepam (5 or 10 mg). Participants were stratified into opioid users and non-users, with each group receiving either Namisol® or placebo. Pain intensity was measured using a visual analog scale at rest and during movement. Plasma concentrations of THC and its metabolite 11-hydroxy-THC (11-OH-THC) were analyzed, and psychological effects were monitored using the Bond and Lader scales. Pharmacokinetics were investigated with consideration of polymorphisms in the CYP2C9 and CYP2C19 enzymes. Safety and tolerability were assessed through adverse events, vital signs, electrocardiography, and laboratory tests. There was no significant analgesic efficacy of Namisol® compared with placebo, and no differences were observed between opioid users and non-users. Plasma THC concentrations indicated adequate absorption and metabolism, with no significant differences associated with CYP polymorphisms. Namisol® induced euphoria, somnolence, and feelings of unreality, but without any effect on pain relief.

A randomized, double-blind, placebo-controlled clinical trial investigated the analgesic effects of THC in patients with chronic lumbar radicular NP (WIEZMAN et al., 2018). The study involved 17 male patients aged between 27 and 40 years with pain of moderate to high intensity (>40 on the Visual Analog Scale [VAS, 0–100]) lasting longer than six months. Patients had stable chronic pain without psychiatric comorbidities or use of substances that could interfere with study outcomes. The study lasted approximately six weeks, with two evaluation sessions. THC was administered sublingually using an oil formulation containing 0.2 mg/kg of THC per session (average dose 15.4 ± 2.2 mg) separated by a three-week washout period. The analgesic effect of THC was assessed using the visual analogic scale (VAS), while changes in functional brain connectivity were analyzed through resting-state functional magnetic resonance imaging, focusing on connectivity between the anterior cingulate cortex and the sensorimotor cortex. Assessment was performed approximately two hours after administration, corresponding to the observed peak plasma concentration of THC. There was a significant reduction in pain with a marked difference in VAS scores before and after THC administration. as well as changes in brain connectivity, suggest that the analgesic effect of THC is associated with alterations reflecting a reduction in functional brain connectivity.

An oral emulsified THC formulation (ECP002A) was designed for stable pharmacokinetics without high peak concentrations and was tested for its capacity of improving NP of patients with progressive multiple sclerosis (VAN AMERONGEN et al., 2018). A total of 24 patients with average disease duration of 11.5 years were treated following a protocol of single-day dose escalation (3 mg, 5 mg, 8 mg) and four weeks of treatment titrated to 24 mg/day. The effects were assessed concerning spasticity (Ashworth Scale, H/M reflex) and NP (Numeric Rating Scale [NRS], McGill Questionnaire). A post-hoc analysis in patients with baseline pain showed a significant early reduction in pain and improvement in spasticity ($p=0.0198$), with benefits in motor function and sleep quality (Pittsburgh Sleep Quality Index) emerging from the second week. These subjective improvements, however, were not consistently sustained in patient diaries, and no significant differences were found in objective spasticity measures versus placebo. The formulation demonstrated a favorable tolerability profile with predominantly mild adverse events (mainly dizziness and euphoric mood).

A randomized, double-blind, placebo-controlled, crossover trial investigated the efficacy of oral, purified cannabidivarin (CBDV), a non-psychoactive CBD analogue, for HIV-associated NP (EIBACH et al., 2021). The study enrolled 32 patients (96.9% men, aged 31-65

years) with persistent pain (average intensity 6.28 ± 1.37 on a 0–10 NRS). Participants were required to have hepatic, renal and cardiovascular functions preserved, with no severe comorbidities. CBDV was administered at a fixed dose of 400 mg/day (8 mL of a 50 mg/mL solution) for four weeks, and compared to placebo with a three-week washout period. The primary outcome was daily pain intensity (NRS recorded three times daily), and key secondary outcomes included the functional impact of pain, symptoms of anxiety and depression, global perception of improvement, and quality of life. Results demonstrated a lack of efficacy for CBDV: the average pain intensity during CBDV treatment was 0.62 points higher than with placebo, although not statistically significant (p=0.16). A responder analysis (defined as ≥20% pain reduction) showed that more patients responded to placebo (19 patients) than to CBDV (9 patients). CBDV also showed no significant benefit on any secondary outcome, including reduction in rescue analgesic use. CBDV provided no analgesic benefit for HIV-associated neuropathic pain and was inferior to placebo in the proportion of responders.

The analgesic effects of single oral doses of CBD (0, 200, 400, and 800 mg) was investigated in patients exposed to NP caused by temperature extremes (AROUT et al., 2022). This double-blind, placebo-controlled study included 17 healthy volunteers (47.1% men) aged between 21 and 50 years, with no history of chronic pain. Pain was experimentally induced using the cold pressor test (hand immersion in cold water at 4°C). A total of 47% of participants were weekly alcohol consumers but not smokers. The protocol consisted of four sessions, one for each dose (including (placebo), to assess pain threshold and tolerance, as well as subjective ratings of discomfort and pain using VAS. Pain response effects were analyzed at multiple time points between 0 and 6 hours after CBD administration, totalizing 360 minutes of monitoring/session. CBD did not produce consistent analgesia, and all three doses significantly increased subjecive ratings of pain intensity compared with placebo ($p < 0.01$). The study suggests that prolonged CBD treatment in a population with chronic pain may be more likely to produce effective analgesia than acute dosing in a pain-free population.

More recently, Zubcevic et al. (2023) assessed the efficacy of CBD, THC and their combination in patients with NP due to polyneuropathy, postherpetic neuralgia, or peripheral nerve injury. A total of 115 participants were included, aged between 22 and 95 years. They had experienced chronic pain for more than 6 months and had failed at least one pharmacological treatment. The intervention consisted of oral capsules of CBD (5–50 mg), THC (2.5–25 mg), or a combination of both (CBD/THC 5 mg/2.5 mg–50 mg/25 mg), administered twice daily for

10 weeks (1-week baseline, 8 weeks of treatment, and 1-week tapering period). The study showed no significant differences between the treatment groups (CBD, THC, CBD/THC) and placebo in terms of pain reduction or impact on activities, mood, and sleep.

Smoked or inhaled *C. sativa* for NP treatment

The analgesic effects of smoked *C. sativa* were assessed in patients with chronic NP of central origin (due to spinal cord injury and multiple sclerosis) and peripheral origin (including diabetic neuropathy, traumatic neuropathy, and complex regional pain syndrome type I) in a randomized, placebo-controlled, crossover study (WILSEY et al., 2008). The sample included 38 participants, comprising 20 men (52.6%) and 18 women (47.4%), aged between 21 and 71 years, all with prior cannabis experience, which was discontinued 30 days before the study. Average pain intensity was 55 (±21) on a 100-point VAS, and the average duration of the condition was six years. During three experimental sessions lasting six hours each, participants received, in a crossover manner, cigarettes containing different concentrations of THC: placebo, low dose (3.5%), and high dose (7%), consuming nine inhalations per session under supervision. Administration by smoking reached an average THC consumption of 19 mg (low dose) and 34 mg (high dose). To further reduce unsystematic variation, participants were instructed to maintain their usual medication regimens throughout the 3- to 4-week study period. Both doses produced a statistically significant reduction in pain intensity over time compared with placebo ($p = 0.016$). Although an improvement trend was visible from 120 minutes onward (after the third puff), with an average relief of 0.35 points/minute on the VAS compared with placebo, a statistically significant difference at a specific time point was only observed at 240 minutes ($p = 0.02$). A limit effect was observed, as both the 3.5% and 7% THC doses resulted in nearly identical pain relief. Psychoactive effects were considered minimal and well tolerated.

Wallace et al. (2015) evaluated the benefits of inhaled vapor produced from *C. sativa* in patients diagnosed with moderately severe diabetic neuropathy for at least six months (one third presented obesity). A total of 16 patients aged 18 years or older, of both sexes, underwent four treatment sessions separated by two weeks, during which they inhaled vapor produced from 400 mg of *C. sativa* with THC concentrations of 1% (low), 4% (medium), or 7% (high), or placebo. The procedure consisted of four 5-second inhalations, with a 40-second rest period between inhalations. All patients received both inhaled *C. sativa* and placebo at different time points. The effects on pain relief were observed within minutes after inhalation. Pain intensity

was assessed using a 10-cm visual analog scale. The mixed-effects model indicated that, for each $1\log10$ unit of time, spontaneous pain intensity decreased by an average of 1.1 points. Spontaneous pain scores were significantly lower with *C. sativa* doses compared with placebo: 0.44 points for the low dose ($P = 0.031$), 0.42 points for the medium dose ($P = 0.04$), and 1.2 points for the high dose ($P < 0.001$). Although higher doses (4% and 7% THC) were more effective in relieving pain, they also caused significant cognitive deficits, whereas the 1% THC dose was more effective than placebo in reducing pain without causing measurable cognitive impairments.

An exploratory placebo-controlled study evaluated the analgesic effects of vaporized cannabis in patients with NP due to spinal cord injury or neural disease (WILSEY et al., 2016). A total of 42 patients (aged 18-70) with chronic pain intensity ≥4/10 (VAS scale) used a Volcano Vaporizer in three eight-hour sessions (placebo, 2.9% and 6.7% THC), each involving four standardized inhalations followed by optional additional puffs after three hours. Exclusion criteria included severe psychiatric disorders (such as schizophrenia, severe depression) due to suicide risk, and comorbidities such as coronary artery disease, severe COPD, severe liver or renal disease. Patients maintained stable baseline medications. A dose-dependent reduction in pain was found compared to placebo ($p < 0.0001$), with onset at one hour ($p < 0.05$) and sustained effect. There was no significant difference in neurocognitive performance between active doses and placebo.

The clinical benefits of inhaled *C. sativa* for analgesia in women with fibromyalgia was investigated in a randomized, placebo-controlled study (VAN DE DONK et al., 2019). A total of 20 patients with average pain intensity 7.2/10 (VAS scale) were treated in four experimental sessions, in which three preparations were vaporized (Bedrocan: 22.4 mg THC/<1 mg CBD; Bediol: 13.4 mg THC/17.8 mg CBD; Bedrolite: 18.4 mg CBD/<1 mg THC), and the placebo. Key exclusion criteria were recent opioid use, history of severe psychiatric disorders, or prior recreational use of *C. sativa*. No active treatment was superior to placebo; however, a responder analysis showed a significantly higher proportion of patients achieved ≥30% spontaneous pain reduction with Bediol preparation versus placebo (90% vs. 55%, p=0.01). A complex cannabinoid interaction was described: CBD in Bediol increased plasma THC concentrations, but concurrently reduced THC's analgesic effect.

A study investigated the pharmacokinetics, analgesic efficacy, cognitive performance, and safety of different doses of inhaled THC in patients with moderate to severe chronic pain due to painful radiculopathy, diabetic neuropathy and complex regional pain syndrome

(ALMOG et al., 2020). A total of 27 participants (70.37% men), with an average age of 48.3 years (18–67 years), and pain intensity ≥6 (VAS scale) underwent three sessions separated by a minimum interval of two days, receiving, in random order, a single inhalation of 0.5 or 1 mg THC, or placebo, with follow-up for up to 150 minutes after administration. Pain intensity was assessed using the VAS scale at multiple time points after inhalation, along with adverse events, vital signs, and cognitive performance. Serial blood samples were collected for analysis of plasma THC levels. The 1 mg dose produced greater pain reduction (average decrease of 2.95 points on VAS scale) compared with the 0.5 mg dose (1.95 points) and placebo. No consistent cognitive impairments were observed, and adverse events were mild and self-limited.

Orally administered synthetic cannabinoids for NP

Karts et al. (2003) conducted a randomized, double-blind, placebo-controlled crossover study to investigate the efficacy of CT-3 (1′,1′Dimethylheptyl-Δ^8-tetrahydrocannabinol-11-oic acid) as an adjunctive therapy for patients with chronic NP due to varied neural lesions, including brachial plexus injury, traumatic injury of the trigeminal and maxillary nerves, lumbar disc herniation, post-discectomy spinal scarring and traumatic spinal cord injury. The sample consisted in 21 patients (61.9% men) aged between 29 and 65 years and presenting hyperalgesia, with a subgroup presenting allodynia. Treatment consisted of a daily dose of 40 mg of CT-3 for the first four days, increased to 80 mg/day for the following three days, compared with placebo. Pain was assessed using the VAS scale and the Verbal Rating Scale (VRS). Patients were allowed to continue their prescribed analgesic medications if doses had been stable for at least two months. Around 50% of the patients regularly used opioids (morphine, tramadol, oxycodone), analgesics (metamizole), anticonvulsants (gabapentin), anxiolytics (diazepam), hypnotics (zolpidem), and antidepressants (amitriptyline). Patients treated with CT-3 showed a statistically significant reduction in pain intensity three hours after administration compared with placebo ($p = 0.02$), with the effect becoming less pronounced after eight hours.

A randomized, double-blind, crossover study compared the use of nabilone to the use of dihydrocodeine in patients with refractory chronic NP due to cervical radiculopathy, complex regional pain syndrome, diabetic neuropathy, postherpetic neuralgia, and postsurgical neuropathic pain (FRANK et al., 2008). A total of 96 patients with pain intensity of 69.6 mm on VAS scale (0-100) were treated in two 6-week periods separated by a 2-week washout.

Medications were administered orally and titrated to a maximum tolerated dose (nabilone: 0.25–2 mg/day; dihydrocodeine: 30–240 mg/day). Pain intensity measured using the VAS scale. Patients could not be under use of other cannabinoids, antipsychotics, benzodiazepines, or monoamine oxidase inhibitors. Dihydrocodeine provided statistically superior analgesia compared to nabilone (p=0.01), despite both treatments showing substantial and similar overall effect sizes (0.76 vs. 0.72, respectively). Nabilone was associated with a significantly higher frequency of adverse effects, though no serious adverse events were reported. There was no statistical difference between treatments concerning quality of life according to the SF-36 questionnaire results.

Nabilone was also compared to gabapentin on the treatment of diabetic, idiopathic and immune-mediated NP (BESTARD and TOTH, 2011). The open-label, non-randomized study included 249 patients (average age 61, average baseline VAS pain 45.8/100) distributed in five groups: nabilone monotherapy (average dose 3.05 mg/day), gabapentin monotherapy (average dose 2,372 mg/day), nabilone adjuvant therapy (3.02 mg/day), gabapentin adjuvant therapy (2,253 mg/day), or a non-pharmacological control group. The treatment lasted six months, with assessments every three months. Pain intensity was measured using VAS scale. All four active treatment groups achieved significant reduction in pain after six months compared to the control group. Nabilone and gabapentin demonstrated comparable overall efficacy and tolerability. Sleep quality, anxiety symptoms, and quality of life also improved with both medications. The most common adverse effects for both drugs were sedation and dizziness.

Another study investigated the efficacy of nabilone and gabapentin for patients with NP caused by multiple sclerosis (TURCOTTE et al., 2015). The study evaluated 15 patients aged between 18 and 65 years of both sexes, with persistent symptoms for at least three months. All participants were already receiving gabapentin (≥1,800 mg/day) with inadequate pain relief. Patients were distributed into two groups: nabilone as an adjuvant therapy to gabapentin, and placebo in combination with gabapentin. The treatment lasted nine weeks, with nabilone (or placebo) administered in escalating doses for four weeks, followed by five weeks of maintenance therapy (1 mg twice daily). Pain was assessed daily using VAS scale, in addition to the evaluation of its impact on daily activities. The combination of nabilone and gabapentin resulted in a significant reduction in pain intensity compared with the placebo plus gabapentin group ($P < 0.01$). However, the reduction in pain impact was greater in the placebo group during the initial titration phase. At the end of the study, 100% of patients receiving nabilone in

combination with gabapentin reported improvement, whereas only 43% of patients in the placebo/gabapentin group reported some degree of improvement. The high rate of perceived improvement in the nabilone group was possibly due to psychosomatic effect.

The efficacy of dronabinol (also known as synthetic THC) in providing pain relief was investigated in a randomized, double-blind, placebo-controlled crossover clinical trial involving patients with multiple sclerosis (SVENDSEN et al., 2004). The sample consisted of 24 patients (42% men) aged between 23 and 55 years, with central pain of average duration of 4.5 years and an average intensity of 5.5 on the NRS (0–10). Patients had no history of substance abuse, severe psychiatric disorders, or recent cannabinoid use. The treatment consisted of 2.5 mg/day and gradually increased up to 10 mg/day, for three weeks. In the event of adverse effects, the maintenance dose was reduced to 2.5 mg/day, followed by a three-week washout period and then three weeks using placebo. Pain intensity during the final week of treatment was significantly lower with dronabinol (average NRS=4) compared with placebo (average NRS=5). The number needed to treat (NNT) for one patient to achieve 50% pain relief was 3.5. Improvements in quality of life were observed in the "bodily pain" and "mental health" domains of the SF-36. Adverse events, primarily dizziness, were significantly more frequent during dronabinol treatment, particularly in the first week.

Similarly, Schimrigk et al. (2017) also investigated the efficacy of dronabinol in the treatment of NP in 240 patients diagnosed with multiple sclerosis (72.9% women). The study design included a randomized, double-blind, placebo-controlled phase lasting 16 weeks, followed by an open-label extension of 32 additional weeks and a long-term follow-up of up to 96 weeks. The patients age ranged between 21 and 68 years, with pain duration ranging from 54 to 59.5 months, and pain intensity average of 6.4 on the NRS (0-10). The treatment initiated at 2.5 mg/day following titration over four weeks to reach a daily dose between 7.5 mg and 15 mg, with an average dose of 12.7 mg/day during the study. There was an average reduction of 1.92 points on the NRS in the dronabinol group, compared with a reduction of 1.81 points in the placebo group ($p = 0.676$). Improvements in quality of life were observed, particularly in sleep and daily activities, in both groups. Although adverse effects were more frequent at the beginning of treatment, their incidence decreased over time.

Dronabinol was also investigated as an adjuvant to long-term opioid therapy in patients with NP due to reasons including chronic low back pain and diabetic neuropathy (NARANG et al., 2008). The randomized, double-blind, crossover study involved 30 patients with

moderate-to-severe chronic pain (NRS >5/10) and consisted of two phases. Phase I was a single-dose laboratory trial where all patients received, in separate sessions, placebo, 10 mg dronabinol, and 20 mg dronabinol. Both active doses provided significantly greater acute pain relief and treatment satisfaction compared to placebo ($p<0.01$). Phase II was a four-week, open-label extension where 28 patients underwent dose titration from 5 mg up to a maximum of 60 mg/day. The primary efficacy outcome was pain intensity. In phase II, the use of dronabinol resulted in continuous and significant reduction in pain ($p<0.001$), with clinically meaningful improvements evident after the third week. Pain interference with sleep decreased, sleep quality improved, and quality of life showed specific gains in the energy/fatigue and social functioning domains ($p<0.05$). Furthermore, scores for anxiety and improved, alongside increased overall treatment satisfaction.

More recently, dronabinol was investigated in an intervention to relieve pain and reduce opioid use in young adults with acute NP following traumatic injury (SCHNEIDER-SMITH et al., 2020). The study included a total of 66 patients (average age of 27 years, 73% men) with average injury severity score of 12 (range 9–18) and average length of hospital stay of 8 days (range 5–14 days). Dronabinol was administered at 5 mg or 10 mg twice daily, resulting in a median daily dose of 11 mg (range 8–16 mg), for a median duration of 3 days (ranging from 3 to 6 days). The control group received standard opioid analgesics without addition of dronabinol. A significant reduction of 79 morphine milligram equivalents in opioid consumption was observed in the dronabinol group ($p < 0.001$), whereas the control group showed no significant change ($p = 0.63$). Despite the reduction in opioid consumption, no significant difference was observed in NRS scores between the groups ($p = 0.78$).

Topical use of CBD for NP treatment

The interest in the topical and transdermal use of cannabinoids to treat pain, regardless of the pathophysiological mechanism, is very recent. Up to the moment of preparation of this manuscript, only 200 papers could be retrieved from PubMed using the keywords “topical cannabidiol”. Although the high lipophilicity of CBD benefits its absorption, it presents low oral bioavailability due to first-pass metabolism and poor gastrointestinal stability (LEFEBVRE et al., 2024). Considering the exposed and that some drugs can be used in transdermal formulations for the treatment of pain, it is reasonable to consider the external administration of cannabinoids, using also nanotechnology (DEMISLI et al., 2023). Studies

using animal models have provided positive results. Transdermal CBD (5%) decreased alcohol-induced neurodegeneration in mice and achieving target plasma concentrations of around 100 ng/mL, an effectiveness comparable to intraperitoneal CBD (LIPUT et al., 2013). CBD gel formulations at daily doses ranging from 0.6 to 62.3 mg reduced joint swelling, spontaneous pain scores, immune cell invasion and synovial thickening in a dose-dependent manner in a rat model of adjuvant-induced monoarthritis (HAMMEL et al., 2016).

Clinical trials on the use of topical or transdermal cannabinoids are scarce, being even more limited for NP treatments. A parallel-group, double-blind, randomized clinical trial assessed the effects of topically applied CBD in patients suffering from myofascial pain associated with temporomandibular disorders (NITECKA-BUCHTA et al., 2019). A total of 60 patients were randomly allocated to receive either a CBD formulation (14 days of twice-daily application) or a placebo formulation, with masseter muscle activity measured by surface electromyography (sEMG) and pain intensity evaluated by VAS scale. Patients in the CBD group experienced a significant reduction in sEMG masseter activity (11% right, 12.6% left) compared with minimal changes in the placebo group (0.23% right, 3.3% left), and a markedly greater decrease in VAS pain intensity (70.2% in the CBD group versus 9.81% in the placebo group).

An industrialized manufactured CBD formulation (Theramu Relieve CBD® - 250 mg/3 fl oz) was used in the study of Xu et al. (2020) for relieving pain associated with symptomatic peripheral neuropathy. The study involved 29 participants (average age of 68 years, 62.1% men), which reported weakness, paresthesia, burning, and sharp pain, as well as sensory alterations confirmed by neurological examinations, which have been in course for at least 3 months. The treatment consisted of applying the product to symptomatic areas up to four times daily. The study was double-blind and placebo-controlled, with the control group receiving a placebo cream. Pain was assessed using the Neuropathic Pain Scale (NPS). There was a statistically significant reduction in intense pain ($p = 0.009$), sharp pain ($p < 0.001$), cold sensation ($p = 0.043$), and itching ($p = 0.001$) in the CBD group compared with placebo.

Preclinical studies have provided *in vivo* evidence of the modulatory effects of cannabinoids in pain mechanisms; however, their translation into clinical benefits remain challenging. Across the clinical trials analyzed, cannabinoids failed to demonstrate superiority over placebo in pain relief when used as monotherapy, nor in functional outcomes such as mood or sleep quality, even under escalating dosing regimens (EIBACH et al., 2021; AROUT et al.,

2022; ZUBCEVIC et al., 2023). These findings may be partially explained by methodological limitations, including small sample sizes, heterogeneity in pain etiology, cannabinoid formulations, dosing strategies, routes of administration, and outcome measures. Such heterogeneity complicates the interpretation of pain intensity and pain relief, both inherently subjective observations, and increases susceptibility to expectancy effects. Interestingly, the use of vaporized products resulted in good pain control compared to placebo (WILSEY et al., 2016; VAN DE DONKET al., 2019; ALMOG et al., 2020). Such studies are scarce and, in certain groups of patients, it might require overcoming varied social stigmas associated with recreational use.

The pharmacotherapy of pain should be multimodal, aiming to cover its multiple pathophysiological mechanisms. Both synthetic and phytocannabinoids exhibit mechanisms of action that are partially distinct from those of clinically relevant drugs, what open doors for combined therapies. Therefore, technically, combinations of clinically relevant drugs to cannabinoids therapy may improve pain control or patient-reported outcomes. However, these benefits were not uniformly observed in the analyzed studies (FRANK et al., 2008; LYNCH et al., 2014; DE VRIES et al., 2016). The addition of cannabinoids to ongoing therapies also raises considerations regarding drug interactions, a point that was not extensively studied in any of the trials. *In silico* studies are of interest to provide insights into possible interactions that are not desirable for the treatment of pain.

Despite the heterogeneity and methodological limitations identified across the available studies, cannabinoids still represent a therapeutic class for NP management. Their varied mechanisms of action make careful integration into multimodal analgesic treatments more plausible of presenting effective results in clinical practice rather than an isolated use. Part of the trials indicated that combined therapies resulted in meaningful benefits in selected patient subgroups, beyond improvements in sleep quality, reductions in opioid consumption, and acceptable safety profiles under controlled conditions (NARANG et al., 2008; LANGFORD et al., 2013; TURCOTTE et al., 2015; SCHNEIDER-SMITH et al., 2020).

CONCLUSION

The evidence derived from randomized clinical trials evaluating synthetic and phytocannabinoids for NP remains limited due to methodological heterogeneity. This lack of standardization makes cross-study comparisons, systematic reviews, and evidence-based

clinical decision-making difficult endeavors. Although selected trials suggest that cannabinoids might offer benefits when used as adjunctive therapy, particularly in terms of maintenance of analgesic effect, sleep quality, or opioid-sparing outcomes, these seem to be restricted to specific patient subgroups. The incorporation of cannabinoids as adjuvant therapy should be planned with caution if considered, with monitoring of safety and tolerability, and preventing drug interactions. The current evidence is not strong enough to support the use of cannabinoids as monotherapy for NP. Well-powered, rigorously designed, and standardized clinical trials are, therefore, essential to clarify the therapeutic role of cannabinoids and to support rational clinical recommendations in NP treatment.

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