Review

Efficiency of cannabis and cannabidiol in managing chronic pain syndromes: A comprehensive narrative review

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2024;61(5):765–782

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Funding sources
This review was funded by Wroclaw Medical University (grant No. SUBK.B160.24.038 – M. Bort), according to records in the Simple system.

Conflict of interest
None declared

Acknowledgements
None declared

Received on July 16, 2024
Reviewed on August 28, 2024
Accepted on September 6, 2024

Published online on October 31, 2024

Abstract

Chronic pain affects up to 40% of adults, contributing to high medical expenses, the loss of productivity, reduced quality of life (QoL), and disability. Chronic pain requires detailed diagnostic assessment, treatment and rehabilitation, yet approx. 80% of patients report inadequate pain management. As new treatment options are needed, we aimed to explore the effectiveness of medical cannabis-based products in managing chronic pain, with a particular focus on treatment patterns.

We searched the PubMed, Scopus and Web of Science databases using keywords related to cannabinoids and chronic pain syndromes. In total, 3,954 articles were identified, and 74 studies involving 12,562 patients were included. The effectiveness of cannabis-based products varied across studies. Cannabinoids were most effective in treating chronic secondary headache and orofacial pain, chronic secondary musculoskeletal pain, chronic secondary visceral pain, and chronic neuropathic pain. Properly qualifying patients is the first crucial step in managing chronic pain, considering pain characteristics, comorbidities and other treatment options. Treatment should start with low doses of cannabinoids, which are then increased to achieve the desired therapeutic effect while minimizing adverse effects.

This narrative review revealed significant gaps in the evidence regarding precise treatment patterns, particularly for the long-term maintenance treatment needed by patients with chronic pain. Medical cannabis can be considered an option for carefully selected patients with chronic pain syndromes when other treatment options fail to achieve an adequate response, and when the potential benefits outweigh the risks. However, there is still a need for well-designed clinical research to establish the long-term efficacy and safety of cannabinoids.

Keywords: cannabis, cannabinoids, THC, cannabidiol, chronic pain syndrome

Cite as
Bort M, Olchowy C, Olchowy A, Nawrot-Hadzik I, Smardz J, Wieckiewicz M. Efficiency of cannabis and cannabidiol in managing chronic pain syndromes: A comprehensive narrative review. *Dent Med Probl.* 2024;61(5):765–782. doi:10.17219/dmp/193020

DOI
10.17219/dmp/193020

Introduction

The current definition of pain, describing it as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage", was proposed by the Task Force of the International Association for the Study of Pain (IASP) and published in 2020.[1] Pain is recognized as a subjective sensation. However, although it is often connected to a pathological process, it can occur without any tissue damage or clear physiological cause. Furthermore, patients with similar conditions may perceive pain differently. Pain intensity is assessed using patient-reported outcome measures, either as a stand-alone experience or in association with an underlying condition. Pain is categorized into acute and chronic types. Acute pain arises suddenly and typically resolves quickly, whereas chronic pain persists for more than 3 months and often recurs.[2] Chronic pain that lasts or recurs for over 3 months can become the main clinical concern for some individuals, necessitating specific diagnostic evaluation, therapy and rehabilitation. Such a condition is associated with significant distress, contributing to reduced quality of life (QoL), impaired daily functioning and lower productivity at work.[3] It is estimated that in the USA, chronic pain affects 11–40% of adults, contributing to an estimated annual cost of $560 billion in direct medical expenses, the lost productivity and disability support programs.[4] The understanding of pain is expanding due to the categorization based on its origin, such as nociceptive (resulting from a tissue injury), neuropathic (stemming from a nerve injury) or nociplastic (arising from the sensitized nervous system). Differentiating between chronic primary and chronic secondary pain syndromes enables more personalized antipain treatment for patients.[5,6] Guidelines commonly advocate a personalized, multimodal, interdisciplinary treatment strategy encompassing pharmacotherapy, psychotherapy, integrative therapies, and invasive procedures.[5,7] Yet, the percentage of patients not responding to treatment or those who benefit from the proposed strategies only for a limited period is high.[8–10] Nearly 80% of patients report inadequate pain management.[11]

The high burden of chronic pain and the lack of universal treatment prompt researchers to seek new treatment modalities. One of these are cannabis-based medicines. They embrace primarily cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), which interact with the endocannabinoid system (ECS) of the body. This reaction may help reduce pain and inflammation, offering relief to some chronic pain patients. It is also worth mentioning that there are many ways of administering cannabis, like inhalation, oral ingestion and sublingual application, which can be individually selected for particular patients. Recent systematic reviews have analyzed various aspects of cannabis-based medicines, including their efficacy, real-world effectiveness, comparison with other analgesics, and potential for reducing the use of other analgesics. These reviews have led to diverse conclusions.[12–16]

There is a lack of comprehensive analyses of studies specifically assessing the efficacy of cannabis in chronic primary and secondary pain syndromes. Hence, this narrative review aimed to explore the effectiveness of medical cannabis in managing chronic pain, with a particular focus on treatment patterns.

Methods

The search was conducted on April 28, 2024, using the PubMed, Scopus and Web of Science databases. Keywords and synonyms for cannabinoids were considered, including "*Cannabis sativa*", "cannabinoid", "cannabidiol", "CBD", "nabiximols", "marijuana", and "hemp". Regarding chronic pain syndromes, the classification of IASP was used.[6] Referring to pain, the keywords was "chronic pain" and all its types according to the IASP classification, i.e., "chronic primary pain", "chronic cancer-related pain", "chronic postsurgical or post-traumatic pain", "chronic secondary musculoskeletal pain", "chronic secondary visceral pain", "chronic neuropathic pain", and "chronic secondary headache or orofacial pain". Primary original articles reporting results on the efficacy of cannabis and cannabidiol in patients with chronic pain syndromes were considered. The selection of these articles was limited to studies on adult patients. For studies on treatment patterns, additional sources included treatment guidelines and consensus papers. The selection of studies on the mechanism of action aimed to include articles that best explained the pharmacokinetics and mechanism of action of cannabis and cannabidiol, including review papers and animal studies. Additionally, the bibliographies of review papers were screened for the papers potentially omitted in the search. Case reports were excluded due to the low quality of evidence (in connection with evidence-based medicine (EBM)).[17] All the included articles were in the English language. Studies only investigating illegal sources of hemp were not selected for this review. The collection and/or assembly of data, but also data analysis and interpretation were done by 3 authors (M.B., C.O. and A.O.). Information about the study selection and the characteristics of the included studies (including pain syndromes) are presented on Fig. 1 and 2.

Results

Description of the included studies

In total, 3,954 articles were identified, of which 74 were included for qualitative analysis. These studies

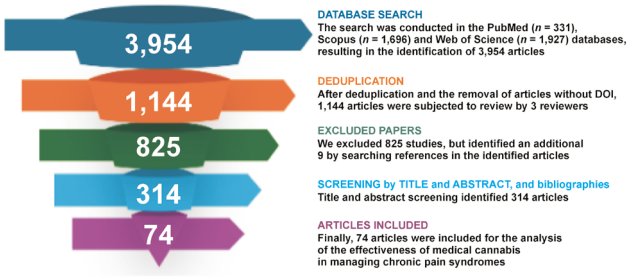

Fig. 1. Flowchart of the study selection process

included 12,562 patients with different chronic pain syndromes. Studies that were not focused on chronic pain syndromes were excluded. Additionally, studies involving pediatric populations, animal studies, laboratory studies, and experimental research were excluded. Regarding the study design, review papers, letters to the editors, book chapters, guidelines, conference proceedings, abstracts, and interviews were not included. Finally, papers in which cannabis and cannabidiol were used only as part of a multi-ingredient preparation were also excluded. The flowchart of the study selection process is shown in Fig. 1.

First, the studies were divided by chronic pain syndrome. Many of the studies included a mixed patient sample, followed by those focusing on chronic secondary musculoskeletal pain and chronic neuropathic pain. However, when considering the number of patients in each chronic pain syndrome, over half of the patients were in the mixed population studies. The distribution of studies and of patients across the included studies is illustrated in Fig. 2A and 2B, respectively.

To assess the effectiveness of medical cannabis in pain reduction, the studies were categorized into 3 groups: those showing the lack of significant improvement in pain indices (⊗); those reporting significant improvement (☑); and those with mixed results leading to inconclusive efficacy conclusions (**?**). Most studies reported significant improvement, followed by those reporting partial improvement. Fewer studies reported negative results. When examining the reported improvement, it is evident that medical cannabis is most effective in managing chronic secondary headache and orofacial pain, chronic secondary visceral pain, chronic secondary musculoskeletal pain, and chronic neuropathic pain. The distribution of studies by their effectiveness is shown in Fig. 3.

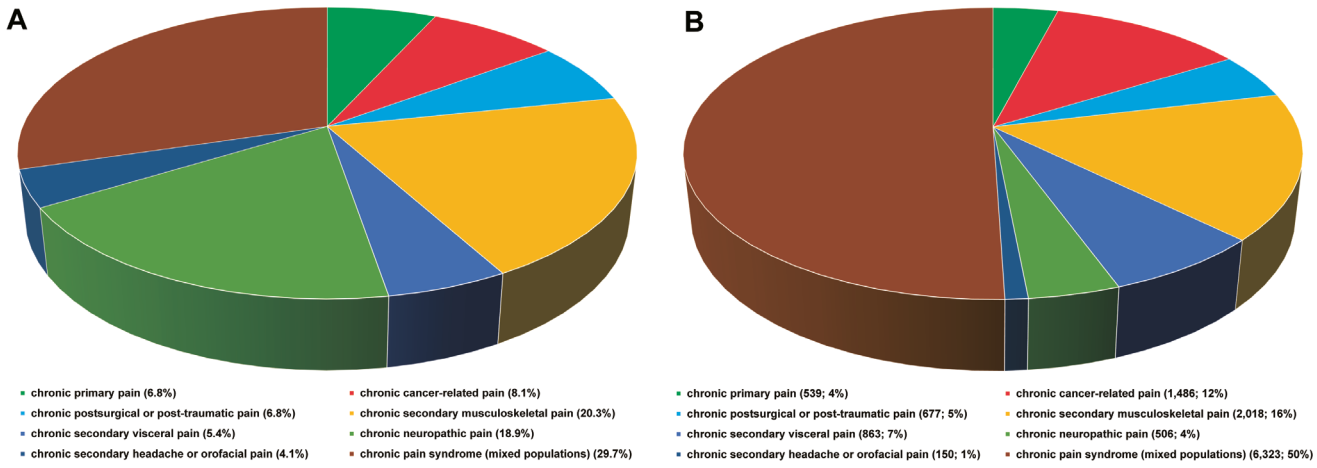

Fig. 2. Distribution of studies (A) and of patients across the included studies (B)

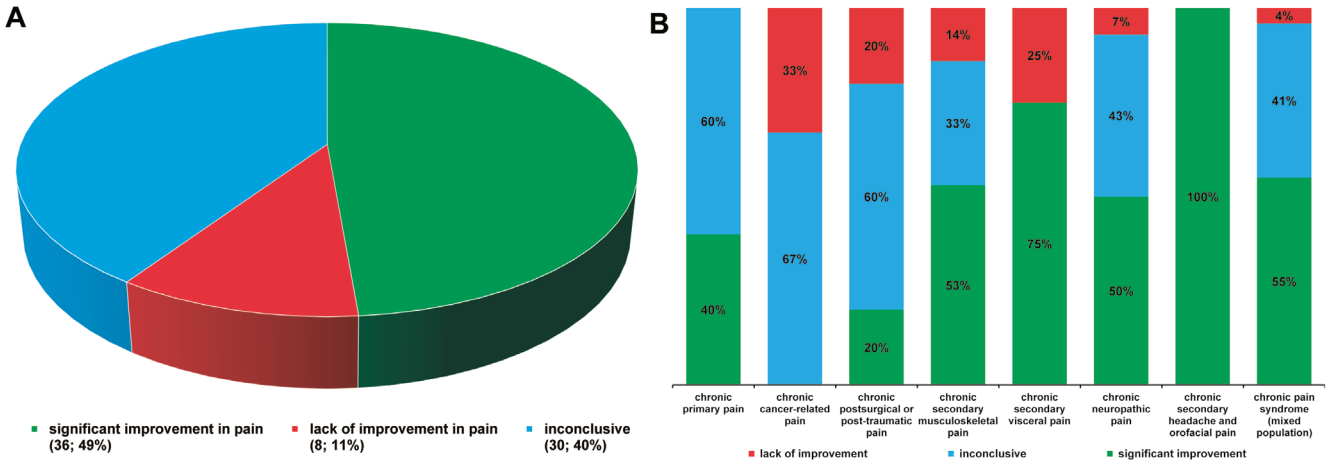

Fig. 3. Distribution of studies by their effectiveness – generally (A) and with regard to the type of chronic pain (B)

Mechanism of action of cannabinoids

Medical cannabis refers to the use of the cannabis plant or its components, such as cannabinoids, like THC and CBD, which interact with the ECS of the body, for medicinal purposes. It is prescribed by healthcare professionals to treat a variety of symptoms and conditions.[18] The terms "medical cannabis" and "medical marijuana"(MM) are often used interchangeably, but they technically refer to different substances they contain and their form. "Cannabis" is the scientific name for a plant species that includes both marijuana and hemp. "Marijuana" specifically refers to strains of cannabis that contain high levels of the psychoactive compound delta-9-tetrahydrocannabinol (THC), which is responsible for the intoxicating effects of the plant. "Hemp", on the other hand, is a strain of cannabis that contains very low levels of THC, and is mostly used for industrial and medical purposes.[19]

Canabis sativa, known for its medicinal properties, contains over 60 unique cannabinoids, each with distinct health benefits. These cannabinoids interact with the ECS of the human body. The most notable cannabinoids are THC, responsible for the psychoactive effects of cannabis, and CBD, recognized for its therapeutic potential and lack of psychoactivity.[20] The mechanism of action of CBD involves interaction with various receptors and signaling pathways in the body, as it interacts with the ECS through multiple pathways.[21]

Unlike THC, CBD does not directly bind to cannabinoid receptors CB1 and CB2, but can inhibit enzymes responsible for breaking down endocannabinoids, leading to increased endocannabinoid levels in the body.[22] Cannabidiol has a low affinity for the orthosteric binding sites of CB1 and CB2 receptors, and exhibits allosteric activity on both receptors. CB1 receptors, primarily found in the central nervous system (CNS), including regions responsible for pain perception, are affected by CBD. Additionally, the antagonistic effects of CBD on CB2 receptors contribute to the anti-inflammatory response by suppressing mast cell degranulation and neutrophil propagation near pain centers.[21] Furthermore, CBD activates transient receptor potential vanilloid type 1 (TRPV1) receptors involved in pain perception, influencing pain sensation and inflammation. Finally, CBD can modulate the levels of neurotransmitters, like serotonin (via serotonin 5-HT1A receptor) and anandamide (via the activation of CB1, CB2 and TRPV1 receptors), indirectly impacting the regulatory functions of ECS.[22] Cannabidiol may also target G-protein-coupled receptor 2 (GPR2), expressed in the brain and spinal cord, which is involved in pain reception.[21] Another pathway explored in experimental research involves the upregulation of matrix metalloproteases (MMP) in spinal cord injuries. Research shows that the inhibition of MMP through TRPV1 and cannabinoid receptors may reduce chronic neuropathic pain.[23]

Efficacy of cannabis in pain syndromes

Chronic primary pain

The features of chronic primary pain include emotional distress caused by pain, impaired daily life activities and reduced social participation.[24] This type of pain was identified in 5 studies: 2 included patients with migraines,[25,26] 2 included patients with fibromyalgia[27,28] and 1 included patients with pain originating in different anatomical regions.[29] In total, the studies included 539 patients. Three studies reported significant pain reduction after treatment with medical cannabis,[26–28] while 2 studies reported high percentages of responders to treatment – 61%[25] and 82%.[29] Only 2 studies utilized a unified treatment protocol. The details of the studies reporting results for chronic primary pain are listed in Table 1.

Chronic cancer-related pain

Patients with chronic cancer-related pain experience this type of pain due to either their active tumor (including metastases) or the oncology treatment they undergo to manage cancer, which may involve surgery, chemotherapy and radiotherapy.[30] We identified 6 studies that involved patients with cancer-related pain.[31–36] These studies included a total of 1,486 patients. None of the studies reported significant improvement in pain across all the conducted comparisons. Two studies revealed that MM was not effective for chronic cancer-related pain.[32,33] All studies, except one, utilized standardized dosing in the treatment schedule. The studies reporting results for chronic cancer-related pain are listed in Table 2.

Chronic postsurgical or post-traumatic pain

Pain that develops or intensifies after a surgical procedure or a tissue injury, such as trauma or a burn, is categorized as chronic postsurgical or post-traumatic pain. This type of pain is characterized by several features – it begins or worsens after surgery, or trauma persists or recurs for more than 3 months, is localized in the affected area, and cannot be attributed to other conditions, including infection, cancer, or the pre-existing pain conditions.[37] The use of MM for pain was investigated in 5 studies.[38–42] These studies included a total of 677 patients. Of the 5 studies included in this category, only one reported significant improvement in response to treatment with CBD.[42] The studies on chronic postsurgical or post-traumatic pain are shown in Table 3.

Chronic secondary musculoskeletal pain

Chronic pain originating in joints, bones, tendons, muscles, the vertebral column, or soft tissue, either spontaneously or due to movement, is classified as chronic secondary

Table 1. Studies reporting results for chronic primary pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Aviram et al.[25] 2020 **?**	NA	cross-sectional study	145 treated patients with comorbid migraine (56 non-responders, 89 responders)	medical cannabis, not standardized	89 (61%) responded to treatment; responders were more likely to consume high doses (7.9–109.5 mg/month) of phytocannabinoid ms_373_15c (n = 27; 60%) and low doses (0–9.9 mg/month) of phytocannabinoid ms_331_18d (n = 28; 62%) as compared to non-responders ($p < 0.05$ and $p < 0.01$, respectively)
Baraldi et al.[26] 2022 **?**	oral route; bedrocan – flos form, bediol – granular form, FM2 – powder form	retrospective study 3 and 6 months	32 patients with chronic migraine	bedrocan, bediol, FM2	after 3 and 6 months, no reduction in the number of migraine days ($p = 0.1182$), but reduced pain intensity ($p = 0.0004$) and acute medication consumption ($p = 0.0006$)
Chaves et al.[27] 2020 ☑	oral route; cannabis oil	double-blind RCT 10 days	17 women with fibromyalgia	THC-rich cannabis oil (24.44 mg/mL of THC and 0.51 mg/mL of CBD	the FIQ pain score improved significantly: cannabis vs. control post-intervention (3.75 vs. 7.67; $p = 0.006$)
Habib and Artul[28] 2018 ☑	NA	retrospective study	26 patients with fibromyalgia	medical cannabis, not standardized	the level of pain before and after treatment (9.21 vs. 3.35; $p < 0.001$)
Habib et al.[29] 2021 **?**	NA	cross-sectional study	319 patients, mainly with fibromyalgia	THC/CBD (18.38 ±4.96% and 2.62 ±4.87%)	in 260 (82%) fibromyalgia patients, the mean pain reduction was 77% with a monthly dose of 31 g

RCT – randomized clinical trial; THC – tetrahydrocannabinol; CBD – cannabidiol; FIQ – Fibromyalgia Impact Questionnaire; ⊗ – all results non-significant; ☑ – all results significant; **?** – some results significant or no statistical comparison conducted; NA – data not available.

Table 2. Studies reporting results for chronic cancer-related pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Aviram et al.[31] 2020 **?**	sublingual and inhalational routes; medical cannabis oil extract, inflorescence inhalation	multicenter, prospective study 3 and 6 months	108 patients with treatment for metastatic cancer pain, and for chemotherapy-related nausea, vomiting, and/or pain	3 types of medication (THC dominant, CBD dominant, THC/CBD)	the weekly least and worst pain intensity improved not significantly ($p = 0.27$ and $p = 0.10$), significant improvement in the weekly average pain intensity ($p < 0.05$), affective pain intensity ($p < 0.01$), sensory pain intensity ($p < 0.05$), and the PCS score ($p = 0.47$)
Fallon et al.[32] 2017 ⊗	sublingual and buccal routes; aerosol for use in the oral cavity	2 phase 3, double-blind RCTs	399 advanced cancer patients with chronic pain unalleviated by optimized opioid therapy	adjunctive sativex; part A (sativex, 10.1%) and part B (sativex, 27.2%; placebo, 10.7%)	the mean average pain scores increased from 3.2 to 3.7 in the sativex group and from 3.1 to 3.6 in the placebo group, no differences in the worst pain NRS scores between the study groups
Fehniger et al.[33] 2021 ⊗	NA	retrospective study, median: 5.2 months	45 gynecologic cancer patients	MM	36% of patients using MM for pain relief
Johnson et al.[34] 2010 **?**	sublingual and buccal routes; oromucosal spray	multicenter, double-blind RCT 2 weeks	177 patients with moderate to severe cancer-related pain	THC, THC:CBD, placebo	the median changes from baseline for THC, THC:CBD and placebo were −1.00, −1.36 and −0.60, respectively, the adjusted mean treatment difference from placebo was significant for a reduction in pain with the THC:CBD extract (0.67 points, $p = 0.014$), but not the THC extract (0.32 points, $p = 0.245$)
Lichtman et al.[35] 2018 **?**	sublingual and buccal routes; aerosol for use in the oral cavity	phase 3, double-blind RCT 5 weeks	397 advanced cancer patients	sativex	the median percent improvement in the NRS pain score between baseline and the end of treatment in the nabiximols and placebo groups was 10.7% vs. 4.5% ($p = 0.0854$) in the intention-to-treat population (primary variable) and 15.5% vs. 6.3% ($p = 0.0378$) in the per-protocol population, nabiximols were statistically superior to placebo in week 3, as measured with 2 of 3 quality-of-life instruments, and in week 5, as measured with all 3 instruments
Portenoy et al.[36] 2012 **?**	sublingual and buccal routes; aerosol for use in the oral cavity	graded-dose RCT	360 advanced cancer patients	sativex	the 30% responder rate primary analysis was not significant for nabiximols vs. placebo ($p = 0.59$), a secondary continuous responder analysis of the average daily pain from baseline to the end of the study: The proportion of patients reporting analgesia was greater for nabiximols than placebo – overall ($p = 0.035$), and specifically in the low-dose ($p = 0.008$) and medium-dose ($p = 0.039$) groups

MM – medical marijuana; PCS – Pain Catastrophizing Scale; NRS – numeric rating scale; ⊗ – all results non-significant; ☑ – all results significant; **?** – some results significant or no statistical comparison conducted; NA – data not available.

Table 3. Studies reporting results for chronic postsurgical or post-traumatic pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Cardenas and Jensen[38] 2006 ?	NA	postal survey	117 patients with SCI	mixed	MM provided greater pain relief by 6.62 ±2.54 (scores rated from 0 to 10)
Cuñetti et al.[39] 2018 ?	oral route; oral solution	study design not provided 3 weeks	7 patients after kidney transplantation	CBD	2 patients had total pain improvement, 4 had a partial response in the first 15 days and in 1 there was no change
de Vries et al.[40] 2017 ⊗	oral route; tablets	phase 2 RTC 50–52 days	65 patients with chronic abdominal pain after surgery or due to chronic pancreatitis	THC	the VAS mean scores did not differ significantly between the THC and placebo groups ($p = 0.901$), between the start and the end of the study, the VAS mean scores decreased by 1.6 points (40%) in the THC group as compared to 1.9 points (37%) in the placebo group
Greis et al.[41] 2022 ?	NA	prospective, observational study 12 months	468 orthopedic pain patients	medical cannabis	the VAS pain score was significantly reduced at 3, 6 and 12 months (6.7 vs. 5.2 at the first follow-up; $n = 385$, $p < 0.001$), there were no significant differences in the VAS pain scores between follow-ups at 3, 6 and 12 months
Hall et al.[42] 2023 ☑	transdermal route; cream for lower extremities	retrospective study 6 weeks	20 patients with chronic pain resulting from acute lower extremity injuries	topical CBD	there was significant improvement in the self-reported pain levels (intake mean: 3.5 ±0.29, exit mean: 1.7 ±0.23; $p < 0.001$) and pain-related disability ($p < 0.001$)

SCI – spinal cord injury; VAS – visual analog scale; ⊗ – all results non-significant; ☑ – all results significant; ? – some results significant or no statistical comparison conducted; NA – data not available.

musculoskeletal pain.[43] This type of pain can develop due to a musculoskeletal disease with inflammation caused by infection, autoimmunity, autoinflammation, or metabolic disorders, a musculoskeletal disease with structural or biomechanical factors, or a neurological disease that alters the biomechanical function.[43] The use of MM for chronic secondary musculoskeletal pain was investigated in 15 studies.[44–58] These studies included a total of 2,018 patients. More than half of the studies ($n = 8$) reported significant improvement in pain.[46–49,53,55–57] The studies on chronic secondary musculoskeletal pain are shown in Table 4.

Chronic secondary visceral pain

Patients classified with chronic secondary visceral pain exhibited specific characteristics: the pain arose from particular internal organs; their medical history indicated dysfunction or a disease in one or more internal organs; and the pain could not be explained by any other diagnosis of chronic pain.[59] Four studies included patients who met the criteria for suffering from chronic secondary visceral pain.[60–63] These studies included a total of 863 patients. Of the 4 studies included in this category, only 2 reported significant improvement in response to treatment with CBD,[61,63] whereas 1 study reported preliminary evidence with regard to the in efficacy of treatment. The last one showed no significant reduction of pain.[60] The studies reporting results for secondary visceral pain are shown in Table 5.

Chronic neuropathic pain

This category comprised studies involving patients who experienced chronic pain resulting from conditions that damage the somatosensory nervous system. Chronic neuropathic pain is characterized by a history of neurological lesions or disease, the consistent neuroanatomical distribution of pain sensation, and the presence of sensory signs in the affected area.[64] This pain may be caused by, among other things, diabetic neuropathy, a neurodegenerative, vascular or autoimmune condition, a tumor, trauma, infection, exposure to toxins, or a hereditary disease.[64] In our review, we identified 14 studies investigating chronic neuropathic pain in a total of 506 patients.[65–78] Seven studies reported satisfactory results,[65–71] 1 study showed unfavorable results,[72] and the remaining 6 studies reported inconsistent results after treatment with THC and CBD.[73–78] Table 6 presents the list of studies on chronic neuropathic pain.

Chronic secondary headache and orofacial pain

Chronic secondary headache and orofacial pain encompass all headache and orofacial pain conditions with underlying causes occurring on at least half of the days for a minimum of 3 months, with each episode lasting at least 2 h.[79] This type of headache may be diagnosed when another disorder known to cause headache or orofacial pain has been identified, supported by evidence demonstrating causation. This means that headache or orofacial pain correlates with the progression or regression of the presumed causative disorder.[79] Three studies were included in this group, with a total of 150 patients.[80–82] In 1 study, significant improvement in pain and better results as compared to ibuprofen were reported.[80] The remaining 2 studies reported significant improvement in pain after the topical use of CBD in patients with temporomandibular disorders (TMD).[81,82] Table 7 shows the

Table 4. Studies reporting results for chronic secondary musculoskeletal pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Bakewell et al.[44] 2022 ?	oral route; CBD gel caps	observational study, 6 visits	48 patients with LBP caused by lumbar spinal stenosis	CBD	the usual pain levels and the worst pain levels demonstrated significant improvement ($p < 0.001$ and $p < 0.0015$, respectively), while the pain right now and the best pain level did not improve significantly ($p > 0.05$)
Campbell et al.[45] 2023 ⊗	oral route; oral capsules	double-blind RCT 4 weeks	37 patients with knee osteoarthritis	hydromorphone, dronabinol, placebo	no significant analgesic effects were observed for clinical pain severity or physical functioning across all drug conditions
Corey-Bloom et al.[46] 2012 ☑	inhalational route; smoked cannabis	RCT 2 weeks	37 patients with multiple sclerosis and pain due to spasticity	THC, placebo	the VAS pain score improved after THC (16.61 vs. 8.34), the mean difference as compared to placebo was significant (8.27 vs. 2.90; $p = 0.008$)
Fari et al.[47] 2023 ☑	oral route; hemp seed oil in soft-gel capsules	double-blind, prospective case–control study 45 days	38 patients with knee osteoarthritis	hemp vs. hemp with caryophyllene, myrcene, ginger extract	the NRS pain score in the hemp group dropped from 7.6 ±1.4 to 5.7 ±1.2 ($p < 0.0001$)
Frane et al.[48] 2022 ☑	NA	cross-sectional study	428 with arthritis and joint pain	CBD	CBD users reported that their average daily pain was much better (37.9%) and a little better (45.1%), patients reported a 44% (2.58-point) reduction in the NRS pain score after CBD use ($p < 0.001$), improvement in pain was related to greater frequency of CBD use and longer treatment ($p < 0.001$)
Glare et al.[49] 2023 ☑	oral route; oil	single-arm, open-label study 35 days	40 patients with chronic back or neck pain	cybis	there was dose-dependent improvement in the NRS pain score ($p < 0.001$), with a clinically significant reduction in pain at 1.0 mL bd and 1.5 mL bd doses (a reduction by 28.8% and 34.1%, respectively; $p < 0.001$)
Greis et al.[50] 2022 ?	sublingual and transdermal routes; sublingual tincture and/or topical cannabinoids on legs/lower back	retrospective database study 9 months	186 patients with chronic back pain	medical cannabis	as compared to baseline, the VAS pain score decreased from 73.1 to 58.1, 53.2 and 51.9 at 3, 6 and 9 months, respectively ($p < 0.01$), pain intensity decreased from 7.5 to 6.0, 5.8 and 5.7, respectively ($p < 0.01$), pain frequency decreased from 7.8 to 6.4, 6.2 and 5.6, respectively ($p < 0.01$), insignificant pain drops included: radiating right leg pain; radiating left leg pain; leg pain intensity; and leg pain frequency
Gustavsen et al.[51] 2021 ?	oral route; cannabis oil	prospective, observational safety study 4 weeks	32 multiple sclerosis patients	THC, CBD, THC+CBD	for THC, pain decreased from a median NRS score of 7 to 4 ($p = 0.01$), for CBD, pain decreased from a median NRS score of 7 to 5 ($p = 0.10$)
Pramhas et al.[52] 2023 ⊗	oral route; capsules	double-blind RTC 8 weeks	83 patients with knee osteoarthritis	CBD	the mean reduction in the WOMAC pain subscale scores was 2.5 (95% *CI*: 1.8–3.3) in the CBD group and 2.4 (95% *CI*: 1.7–3.2) in the placebo group, with no significant difference between the groups ($p = 0.80$), the mean reduction in the weekly VAS pain score was 1.9 (95% *CI*: 1.1–2.7) in the CBD group and 2.4 (95% *CI*: 1.6–3.2) in the placebo group, with a mean group difference of −0.51 (95% *CI*: −1.5–0.5) ($p = 0.30$)
Renslo et al.[53] 2022 ☑	sublingual and transdermal routes; sublingual tincture and/or topical cannabinoids	prospective, cohort study 6 months	40 patients with osteoarthritis	medical cannabis	the VAS pain score decreased significantly from 6.6 at baseline to 5.0 at 3 months ($p < 0.01$) and 5.4 at 6 months ($p < 0.05$)
Robinson et al.[54] 2022 ?	sublingual and inhalational routes; sublingual extract, smoked inflorescence	observational, open-label study 2 × 12 months	24 patients with LBP	THC and CBD	the VAS pain score decreased for all participants overall during the study from 83.3 ±15.4 at baseline to 39.1 ±18.5 at 24 months ($p < 0.001$), during the extract therapy phase, this decrease was not significant and averaged 12.3% (*SE*: 5.8, 95% *CI*: −5.3–29.8); changes in VAS were significant at 12–24 months and 12–18 months, which was attributed to the superiority of the inhalation of cannabis as compared to cannabis extract

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Rog et al.[55] 2005 ☑	sublingual and buccal routes; oromucosal spray	double-blind RCT 4 weeks	66 patients with central pain in multiple sclerosis	CBM, placebo	CBM was superior to placebo in reducing the mean pain intensity (CBM: mean change: –2.7, 95% *CI*: –3.4 to –2.0; placebo: mean change: –1.4, 95% *CI*: –2.0 to –0.8; $p < 0.005$)
Wissel et al.[56] 2006 ☑	oral route; capsules	placebo-controlled, double-blind crossover study 4 weeks each	13 patients with spasticity-related pain in multiple sclerosis	nabilone, placebo	the score in the 11-point-Box Scale test (a measure of spasticity-related pain) decreased by a median of 2 points with nabilone as compared to placebo treatment ($p < 0.05$), whereas placebo treatment showed no change ($p = 0.8$)
Zajicek et al.[57] 2003 ☑	oral route; cannabis extract	RCT 15 weeks	667 patients with stable multiple sclerosis	cannabis extract, THC, placebo	improvement in pain: cannabis extract (46%); THC (50%); and placebo (30%), no change: cannabis extract (32%); THC (33%); and placebo (41%), deterioration: cannabis extract (22%); THC (17%); and placebo (30%); a significant difference ($p = 0.002$)
Zajicek et al.[58] 2012 ?	oral route; capsules	RCT 12 weeks	279 patients with stable multiple sclerosis	cannabis extract, placebo	responders with regard to body pain at 4 weeks (28.0% vs. 17.2%; $p < 0.005$), at 8 weeks (30.1% vs. 19.4%; $p < 0.003$) and at 12 weeks (28.0% vs. 18.7%; not significant)

LBP – low back pain; CBM – whole-plant cannabis-based medicine; WOMAC – Western Ontario and McMaster Universities Index of Osteoarthritis; *CI* – confidence interval; *SE* – standard error; ⊗ – all results non-significant; ☑ – all results significant; ? – some results significant or no statistical comparison conducted; NA – data not available.

characteristics of studies on chronic secondary headache and orofacial pain.

Chronic pain investigated in mixed patient groups

Overall, 22 studies with 6,323 patients reported results for patients with more than one type of chronic pain syndrome.[7,83–103] This group was summarized separately. Twelve studies reported that medical cannabis relieved pain successfully,[83–94] 1 study reported negative results[95] and the remaining 9 studies reported inconclusive results.[7,96–103] The studies reporting results for chronic pain investigated in mixed patient groups are listed in Table 8.

Cannabis treatment patterns for chronic pain

Overall, 36 studies showed a significant reduction in pain, and were further reviewed to identify the most effective treatment patterns. However, after excluding studies using mixed treatment, those shorter than 4 weeks and those involving fewer than 20 patients, only 17 studies were available.[42,49,53,55,57,68,70,80,84,86–89,91–94] The analysis of treatment approaches identified distinct phases in the treatment pathway for reducing pain in patients with chronic pain syndromes, which is illustrated in Fig. 4.

Table 5. Studies reporting results for chronic secondary visceral pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Abrams et al.[60] 2020 ⊗	inhalational route; inhaled vaporized cannabis	RCT 5 days	23 with SCD with chronic pain	THC and CBD, placebo	the mean difference in pain rating assessment between the cannabis and placebo groups was –5.3 ±8.1 for day 1, –10.9 ±7.0 for day 2, –16.5 ±9.2 for day 3, –8.9 ±6.7 for day 4, and –8.2 ±8.1 for day 5; however, none was significant, the mean difference in pain interference rating was not significant
Armour et al.[61] 2019 ☑	oral route; oil	cross-sectional online survey	484 women with endometriosis	medical cannabis	among the self-management modalities, cannabis was rated to bring the highest self-reported pain relief on an 11-item pain relief scale (0–10) with a score of 7.6 ±2.0
Tripp et al.[62] 2014 ☑	sublingual and buccal routes, inhalational, transdermal and rectal routes; smoked, sublingual spray, a vaporizer, an inhaler, rectal suppositories, skin patches, hashish	cross-sectional online survey	342 men with chronic prostatitis/ chronic pelvic pain syndrome	medical cannabis	the effectiveness of cannabis was rated "somewhat/ very effective" by 57% of patients recruited in the urology clinic and by 63% of patients recruited online
Yacyshyn et al.[63] 2020 ☑	oral route; tablets	phase 2a study 8 weeks	14 patients with chronic abdominal pain associated with Crohn's disease	olorinab (25 mg or 100 mg)	at week 8, the mean change from baseline in AAPS at peak olorinab plasma concentrations was –4.61 ±1.77 in the 25-mg group ($p = 0.0043$) and –4.57 ±2.17 in the 100-mg group ($p = 0.0036$), the change from baseline at week 8 in the mean number of pain-free days per week was 1.60 ±2.61 in the 25-mg group and 2.33 ±3.62 in the 100-mg group

SCD – sickle cell disease; AAPS – average abdominal pain score; ⊗ – all results non-significant; ☑ – all results significant; ? – some results significant or no statistical comparison conducted.

Table 6. Studies reporting results for chronic neuropathic pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Abrams et al.[65] 2007 ☑	inhalational route; smoked, pre-rolled cannabis	RCT 5 days	50 patients with HIV-associated sensory neuropathy	cannabis (3.56% THC)	smoked cannabis reduced daily pain by 34% (*Me*) (*IQR*: −71 to −16) vs. 17% (*IQR*: −29–8) with placebo ($p = 0.03$), a greater than 30% reduction in pain was reported by 52% in the cannabis group and 24% in the placebo group ($p = 0.04$), the first cannabis cigarette reduced chronic pain by a median of 72% vs. 15% with placebo ($p < 0.001$)
Eisenberg et al.[66] 2014 ☑	inhalational route; an inhaler	single-dose, open-label phase 1a study 2 h	8 patients with chronic neuropathic pain	Syqe® inhaler device with THC	a significant 45% reduction in pain intensity was noted 20 min post inhalation ($p = 0.001$), turning back to baseline within 90 min
Ellis et al.[67] 2009 ☑	inhalational route; smoked active cannabis	phase 2, single-group, double-blind, placebo-controlled crossover trial 2 × 5 days	28 patients with HIV-associated neuropathic pain	THC, placebo	pain reduction was significantly greater with cannabis as compared to placebo (median difference in pain reduction: −3.3 DDS points; $p = 0.016$)
Kluwe et al.[68] 2023 ☑	inhalational route; dried flowers	retrospective study 6 weeks	99 patients with neuropathic pain, a high severity of symptoms and exhausted treatment options	dried flowers (<12–22% of THC)	the median of the pain scores decreased from 7.5 to 4.0 ($p < 0.001$), the proportion of patients with severe pain (score >6) decreased from 96% to 16% ($p < 0.001$)
Mondello et al.[69] 2018	oral route; oleic suspension	retrospective study 12 months	11 patients with failed back surgery syndrome refractory pain diagnosed with neuropathic pain	THC/CBD combination	the mean pain score decreased from 8.18 ±1.07 to 4.72 ±0.9 ($p < 0.001$)
Toth et al.[70] 2012 ☑	oral route; capsules	double-blind RTC 4 weeks	26 patients with diabetic peripheral neuropathic pain	adjuvant nabilone, placebo	85% of patients on nabilone experienced ≤30% pain reduction as compared to 38% of patients on placebo ($p < 0.05$), for achieving ≤50% pain reduction, it was 31% vs. 8% ($p > 0.5$), at the end of the study, the NRS pain scores were 3.5 ±1.3 for nabilone and 5.4 ±1.7 for placebo, with a mean difference of 3.0 ±1.2 for nabilone and 1.1 ±1.5 for placebo ($p < 0.01$)
Turcotte et al.[71] 2015 ☑	oral route; capsules	RCT 9 weeks	14 patients with multiple sclerosis-induced neuropathic pain	adjuvant nabilone, placebo	a significant group × time interaction term was reported for both the VAS pain ($p < 0.01$) and VAS impact ($p < 0.01$) score, demonstrating that the adjusted rate of decrease for both outcomes was statistically greater in the nabilone group as compared to the placebo group
Rintala et al.[72] 2010 ⊗	oral route; capsules	randomized, controlled, double-blind, crossover pilot study 2 × 12 days	5 patients with central neuropathic pain after SCI	dronabinol, diphenhydramine	changes in pain from baseline to the end of the maintenance phase did not differ between the 2 medications (dronabinol: 0.20 ±0.837, diphenhydramine: −1.80 ±2.490; $p = 0.102$)
van Amerongen et al.[73] 2018 ?	oral route; tablets	crossover RCT 6 weeks	24 patients with progressive multiple sclerosis	THC, placebo	pain rating was significantly reduced overall during 4 weeks of treatment (2.74 for active treatment vs. 4.25 for placebo; $p = 0.0198$), when pain was measured with a daily diary at home, no significant treatment effect was observed (−0.47; 95% *CI*: −2.66–1.71; $p = 0.6581$)
Wade et al.[74] 2006 ?	sublingual and buccal routes; aerosol for use in the oral cavity	open-label, placebo-controlled study 12 months	137 patients with multiple sclerosis	sativex	pain on the VAS scale at baseline vs. 66 weeks in 47 responders (68.1 ±10.6 vs. 26.4 ±18.7), overall, 42.3% withdrew due to the lack of efficacy
Wallace et al.[75] 2015 ?	inhalational route; inhaled vaporized cannabis	crossover RCT 3 h	16 patients with painful diabetic peripheral neuropathy	placebo, doses of THC – low (1%), medium (4%) and high (7%)	the comparison of spontaneous pain over time showed significant differences in the pain scores between the doses ($p < 0.001$), specific significant comparisons were placebo vs. low ($p = 0.031$), medium ($p = 0.040$) and high ($p < 0.001$) dose, and high dose vs. low and medium doses (both $p < 0.001$), it was effective with medium and high doses for up to 2 h
Ware et al.[76] 2010 ?	inhalational route; inhaled through a pipe	crossover RCT 14 days	21 patients with chronic neuropathic pain	placebo, and 2.5%, 6.0% and 9.4% THC	the daily average pain intensity was significantly lower on 9.4% THC than on placebo (5.4 vs. 6.1; $p = 0.023$), the drop in pain for lower concentrations of THC was not significant

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Wilsey et al.[77] 2008 ?	inhalational route; smoked, cannabis cigarettes	crossover RCT three 6-hour experimental sessions	38 patients with central and peripheral neuropathic pain	placebo, and 3.5% and 7.0% cannabis	significant analgesia (a 0.0035 reduction in VAS pain intensity/min) was noted for 3.5% and 7.0% cannabis vs. placebo ($p = 0.016$), although a trend for the separation of the active agents from placebo is visible by the time of 120 min, significant separation for a specific time point occurred only after a cumulative dose of 9 puffs at 240 min ($p = 0.02$)
Xu et al.[78] 2020 ?	transdermal route; CBD cream applied to the symptomatic area	crossover RCT 4 weeks	29 patients with peripheral neuropathy	CBD, placebo	significant reductions in intense ($p = 0.009$), sharp ($p < 0.001$) and itchy ($p = 0.001$) sensations, and surface pain sensations ($p = 0.013$), no significant reduction in deep pain was observed ($p = 0.064$)

Me – median; *IQR* – interquartile range; DDS – Descriptor Differential Scale; ⊗ – all results non-significant; ☑ – all results significant; **?** – some results significant or no statistical comparison conducted.

Table 7. Studies reporting results for secondary headache and orofacial pain

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Pini et al.[80] 2012 ☑	oral route; capsules	crossover RCT, 8 weeks	30 patients with medication overuse headache	ibuprofen, nabilone	nabilone was more effective than ibuprofen in reducing pain intensity ($p < 0.05$), the VAS pain scores: 7.9 ±1.6 (baseline); 5.7 ±1.9 (nabilone); 6.6 ±2.2 (ibuprofen); and 6.2 ±2.4 (follow up)
Walczyńska-Dragon et al.[81] 2024 ☑	buccal route; CBD gel for both masticatory muscles intraorally	RCT 14 days	60 patients with TMD	placebo, and 5% and 10% CBD	pain reduction on the VAS scale was 40.8% ($p < 0.05$) in patients using a 5% CBD formulation and 57.4% ($p < 0.05$) in those using a 10% CBD formulation
Nitecka-Buchta et al.[82] 2019 ☑	transdermal route; topical application of CBD cream on the masseter muscle	RCT 14 days	60 patients TMD	CBD, placebo	pain intensity decreased significantly on the VAS scale by 70.2% in the CBD group and by 9.81% in the placebo group

TMD – temporomandibular disorders; ⊗ – all results non-significant; ☑ – all results significant; **?** – some results significant or no statistical comparison conducted.

The qualification of patients is the first key step for patients with chronic pain. Factors that should be considered include the type of the main diagnosis of pain syndrome, the co-occurrence of other conditions that could improve alongside pain,[55,57,88] and exhausted treatment options.[68] The initiation of treatment should be discussed with the patient and based on shared decision-making. Treatment goals can include not only the reduction of pain, but also the improvement of other symptoms and the reduction of opiate and other analgesic intake.[80,86]

A personalized approach to setting the dose, type and route of administration of cannabinoids is underscored in the included studies. Most studies identified a combination of THC and CBD as the most frequent type of effective treatment for chronic pain syndromes. Researchers recommend starting with low doses of cannabinoids and slowly adjusting the doses to reach the desired therapeutic effect.[86] Dose adjustment is made by patients based on the perceived level of pain. Self-titration did not lead to the use of maximal doses allowed in the trials, but varied across the studies. In an RCT by Rog et al., patients could increase the intake of cannabis-based medicine (CBM) to a maximum dose of THC 130 mg:CBD 120 mg; however, the mean final dose was 25.9 mg of THC and 24 mg of CBD.[55] Increasing doses were also used for patients who were prescribed synthetic CB1 receptor agonists (nabilone). In a study by Toth et al., nabilone was started at a dose of 0.5 mg twice daily for 1 week and increased to a maximum dose of 2.0 mg twice daily.[70]

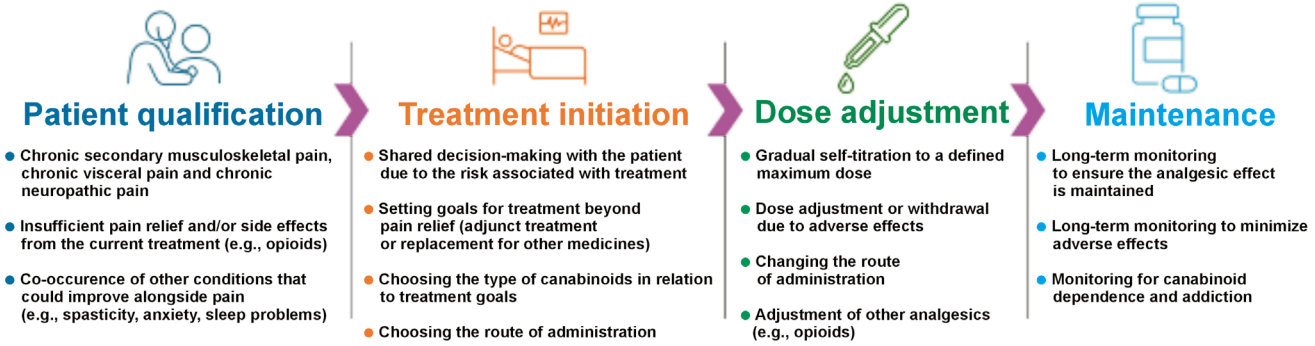

Fig. 4. Distinct phases in the treatment pathway for reducing pain in patients with chronic pain syndromes

Table 8. Studies reporting results for mixed patient groups

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Abelev et al.[7] 2022 ?	oral route; oil	prospective, observational, open-label study 3 months	71 patients with chronic refractory pain	THC, CBD (LGP Classic 10:10)	a significant decrease in the pain impact score was found, with the mean impact score reduced by 2.3 ±9.4 points ($p = 0.034$), the PROMIS-29 domains of pain score did not improve significantly (6.3 ±2.1 vs. 5.7 ±2.3; $p = 0.053$)
Almog et al.[83] 2020 ☑	inhalational route; an inhaler	RCT 150 min	21 patients with chronic focal or distal symmetric (diabetic) neuropathic pain, and 6 with complex regional pain syndrome	placebo, and THC 0.5 mg and 1 mg Syqe® inhaler	the reduction in the VAS pain score was significantly greater for 1 mg THC as compared to placebo ($p = 0.0015$) and 0.5 mg THC ($p = 0.0058$), the number of patients whose VAS pain score was reduced by ≤30% reached the maximum 120 min post inhalation
Aviram et al.[84] 2021 ☑	sublingual and inhalational routes; inflorescence for smoking/inhaling or oil extract (sublingual use)	prospective study 12 months	551 patients with chronic pain continued the study at 12 months	medical cannabis	the weekly average pain intensity reduced by 20%, from 8 (7–9) to 6 (5–8) (*OR*: −1.97, 95% *CI*: −2.13 to −1.81; $p < 0.001$), the least pain intensity declined by 33%, from 6 (4–8) to 3 (2–6) (*OR*: −1.88, 95% *CI*: −2.08 to −1.67; $p < 0.001$) and the worst pain intensity by 21%, from 9 (8–10) to 8 (6–9) (*OR*: −1.36, 95% *CI*: −1.52 to −1.21; $p < 0.001$)
Balestra et al.[85] 2023 ☑	oral, sublingual and inhalational routes; capsules, aerosol for use in the oral cavity, cannabis flos, cannabinoid flowers	retrospective study	64 patients with chronic pain conditions lasting at least 6 months	medical cannabis	changes before vs. under treatment in the mean pain intensity (6.7 ±1.8 vs. 5.6 ±2.0; $p < 0.001$), pain-associated disability (6.9 ±2.2 vs. 5.8 ±2.4; $p < 0.001$) and pain tolerability (3.3 ±0.7 vs. 2.9 ±0.8; $p < 0.001$)
Crowley et al.[86] 2018 ☑	sublingual and buccal routes; cannabinoids via aerosol	observational study 12 weeks	49 patients with chronic non-cancer pain	Trokie® lozenges	a mean reduction in pain intensity on NRS of 4.9 ±2.0 points was observed (from 7.4 ±1.3 to 2.4 ±1.8; $p < 0.0001$)
Harris et al.[87] 2022 ☑	oral route, sublingual and buccal routes, inhalational route; tablets, a vaporizer, aerosol	database study 6 months	190 patients with chronic pain from the UK Medical Cannabis Registry	CBM	significant improvement was observed within BPI for pain severity and pain interference, in all domains of SF-MPQ-2, the EQ-5D-5L index for pain and discomfort, and VAS measures at all time points ($p < 0.050$)
Horsted et al.[88] 2023 ☑	oral route; oil or capsules	retrospective study *Me*: 126 days	826 patients with chronic refractory pain insufficiently controlled by conventional analgesics or experiencing intolerable adverse events from those	THC, CBD, THC:CBD	the reduction on NRS was significantly different at both follow-up consultations as compared to baseline ($p < 0.0001$), clinically relevant pain reduction (NRS ≥ 30%) was reported by 17% at follow-up 1 and by 10% of patients at follow-up 2 in intention-to-treat analysis, whereas the figures were 32% and 45%, respectively, in per-protocol analysis
Kawka et al.[89] 2021 ☑	oral route; oil	database study 6 months	110 patients from the UK Medical Cannabis Registry	Adven® oil preparation	significant improvement was demonstrated in the EQ-5D-5L pain and discomfort subscale score, the VAS pain score, and BPI at 1, 3 and 6 months ($p < 0.05$)
Narang et al.[90] 2008 ☑	oral route; capsules	crossover RCT: phase 1 – 8 h phase 2 – 1 week	30 patients taking opioids for chronic non-cancer pain	placebo, and adjuvant 10 mg and 20 mg dronabinol	phase 1: total pain relief for placebo (31.1), for 10 mg dronabinol (39.7; $p < 0.05$) and 20 mg dronabinol (41.7; $p < 0.001$), the pain intensity difference was −6.4 for placebo, −17.4 for 10 mg dronabinol ($p < 0.001$) and −19.7 for 20 mg dronabinol ($p < 0.001$) phase 2: a significant decrease in the average pain scores as compared to baseline ($p < 0.001$), there was also a significant change from baseline in the measures of pain and pain relief ($p < 0.01$), in BPI pain interference, a decrease by 1.48 points was found ($p < 0.05$)
Poli et al.[91] 2018 ☑	inhalational route; cannabis flos	prospective study 12 months	338 patients with different chronic pain conditions	cannabis flos, 19% decoction	the VAS pain intensity score dropped significantly between baseline and 12 months (*Me*: 9 vs. 5; $p < 0.001$), the median pain disability score at baseline was 6.28 and decreased to 5.93 ($p < 0.01$), the results improved over the first 3 months, and then remained stable
Pud et al.[92] 2024 ☑	oral route; cannabis oil	prospective study 6 months	218 patients with chronic pain	THC:CBD	52 (24%) patients reported a ≤30% reduction from baseline in their weekly average pain at least at 1 follow-up time point, significant differences in comparisons between baseline and 12 months: weekly pain (7.9 ±1.7 vs. 6.6 ±2.2); daily pain (7.6 ±1.89 vs. 6.2 ±2.5); the MPQ total score (23.5 ±10.7 vs. 21.0 ±10.5)

Study	Route and form of administration	Study design	Population	Medication	Effectiveness
Safakish et al.[93] 2020 ☑	oral and inhalational routes; smoked flower or oil	prospective study 12 months	751 chronic pain patients initiating medical cannabis treatment	THC, CBD, THC:CBD	improvement in pain severity and interference was observed at 1 month and maintained over the 12-month observation period, the comparison of variables between baseline and 12 months: BPI pain interference (6.23 ±1.63 vs. 3.54 ±2.84; $p = 0.001$); and BPI pain severity (5.58 ±1.53 vs. 3.49 ±2.17; $p < 0.001$)
Ueberall et al.[94] 2019 ☑	sublingual and buccal routes; aerosol for use in the oral cavity	database study 12 weeks	800 patients with different types of chronic pain	sativex	the lowest, average and highest 24-hour pain intensity (VAS score) dropped significantly between baseline and the end of the study ($p < 0.001$ for each intensity), with ASR-9, the highest ≥50% relief rates were observed for stress (78.8%) and pain intensity (67.5%)
Kliuk-Ben Bassat et al.[95] 2022 ⊗	sublingual route; oil	crossover RCT 2 × 8 weeks	15 patients undergoing hemodialysis with chronic pain	whole-plant extract, cannabinoid extraction, placebo	differences in the BPI scores between the treatment arms did not reach statistical significance, the baseline VAS scores did not allow for comparison
Bapir et al.[96] 2023 ?	NA	cohort study 6 months	1,254 patients with chronic pain patients, with and without comorbid anxiety	CBM	in the anxiety cohort, the results for pain were inconsistent, in the non-anxiety cohort, all domains of pain improved significantly ($p < 0.05$)
Berlach et al.[97] 2006 ?	oral route; capsules	prospective study 1.5 years	20 adult patients with chronic non-cancer pain	nabilone	no significant differences between the baseline and final scores were detected for current pain intensity, and for the average and lowest pain, 45% of patients subjectively reported pain relief described as temporal, partial or extensive
Bonomo et al.[98] 2022 ?	oral route; oral solution	open-label, non-controlled dose escalation study 36 days	9 patients with chronic non-cancer pain on long-term, high-dose opioid analgesia	THC:CBD	there was no significant change in the mean pain severity, from day 17, there was a consistent reduction in the mean pain interference scores until day 30, an increase in the mean pain interference scores was observed from day 31 (after the cessation of the medication)
Capano et al.[99] 2020 ?	oral route; capsules	prospective, single-arm, cohort study 8 weeks	97 patients with chronic pain who have been on opioids for at least 1 year	THC:CBD	the PEG scale showed significant differences between the follow-up time points (6.5 (95% *CI*: 6.16–6.81), 5.9 (95% *CI*: 5.55–6.25) and 5.7 (95% *CI*: 5.31–6.12) at baseline, week 4 and week 8, respectively, $p = 0.006$), PDI showed no significant changes starting from 38.02 (95% *CI*: 35.38–40.66) at baseline, and declining to 36.40 (95% *CI*: 34.15–38.73) and 34.10 (95% *CI*: 31.61–36.58) at weeks 4 and 8, respectively ($p = 0.090$)
Gruber et al.[100] 2021 ?	NA	observational study 6 months	37 patients with chronic pain	medical cannabis	changes from baseline through 6 months: VAS (47.94 ±27.59 vs. 39.85 ±26.31; $p = 0.10$); NRS (4.56 ±2.62 vs. 3.78 ±2.42; $p = 0.10$); PAD (3.74 ±2.23 vs. 2.74 ±1.97; $p = 0.04$); PDI (26.93 ±16.36 vs. 19.15 ±13.60; $p < 0.01$)
Lynch et al.[101] 2006 ?	oral and inhalational routes	mean follow-up: 23.6 months	30 patients with chronic severe pain not controlled by traditional medical approaches	MM	93% of patients reported moderate or greater pain relief (no p-values reported)
Schubert et al.[102] 2023 ?	oral route; oral liquids, capsules granulate, or flos	database study	718 patients with chronic refractory pain, including arthritis	THC, CBD, THC:CBD	for the overall cohort on THC:CBD, the pain interference ($p = 0.007$), pain intensity ($p = 0.025$), and pain impact scores ($p = 0.023$) improved, corresponding with clinically meaningful improvement in 49 (43%), 27 (24%) and 47 (42%) participants, patients taking a CBD-dominant or THC-dominant product did not report any statistically significant improvement in any PROMIS-29 domain
Weber et al.[103] 2009 ?	oral route; capsules	retrospective study	124 patients with chronic central neuropathic pain and fibromyalgia	THC	pain intensity on VRS decreased from median 8 to median 4 ($p < 0.001$), there were differences in treatment success depending on the diagnosis

LGP – Little Green Pharma (Perth, Australia); PROMISE-29 – Patient-Reported Outcomes Measurement Information System; OR – odds ratio; BPI – Brief Pain Inventory; MPQ – McGill Pain Questionnaire; SF-MPQ-2 – Short-form McGill Pain Questionnaire 2; ASR-9 – nine-factor aggregated symptom relief score; PEG – three-item scale assessing pain intensity and interference; PDI – pain disability index; PAD – Pain and Distress scale; VRS – verbal rating scale; ⊗ – all results non-significant; ☑ – all results significant; **?** – some results significant or no statistical comparison conducted; NA – data not available.

Maintenance treatment remains being investigated. Most studies lasted only several weeks, which is insufficient for chronic pain management. Additionally, real-world evidence indicates low adherence and high treatment discontinuation rates. Horsted et al. reported that in long-term follow-up, 30% of patients discontinued treatment due to the lack of perceived analgesic effect and 7% due to the lack of funds.[88] However, the cause for treatment withdrawal remains unknown for most patients.

Discussion

The authors decided not to perform a systematic review, since they wanted to present the diversity of studies. Systematic reviews use specific types of studies and the authors wanted to present a broader approach to the topic. The studies presented in this article show a diversity of studies in terms of the composition of the substance, the route and time of its administration and, above all, the method of measuring the effect.

The goal of this review was to investigate the effectiveness of cannabis in chronic pain syndromes. The effectiveness of cannabis-based products varied across the studies. Cannabinoids were most effective in treating chronic secondary headache and orofacial pain, chronic secondary visceral pain, chronic secondary musculoskeletal pain, and chronic neuropathic pain. When qualifying a patient for cannabis treatment for pain reduction, factors including pain characteristics, comorbidities and the availability of other treatment options should be taken into account. Shared decision-making is essential to set additional treatment goals, such as reducing opiate use. Researchers recommend starting with low doses of cannabinoids and gradually adjusting them to achieve the desired therapeutic effect while minimizing adverse effects. This review revealed substantial gaps in the evidence regarding precise treatment patterns, particularly for the long-term maintenance treatment needed by patients with chronic pain.

In the present review, cannabis and CBD were found to be most effective in managing chronic secondary musculoskeletal pain, chronic secondary visceral pain and chronic neuropathic pain, which is consistent with recommendations from clinical research. However, guidelines and recommendations vary considerably across contexts due to the legal status of these medicines and the varying acceptance levels of low-quality evidence as a proof of effectiveness. The increasing popularity of cannabis and its derivatives has prompted researchers to summarize the evidence concerning their use in a recent systematic review and meta-analysis by Bell et al.,[104] and to develop clinical practice guidelines for managing chronic pain and co-occurring conditions by using these products. The authors reached several conclusions regarding the use of CBM in individuals with chronic pain. Cannabis-based medicines can be used for managing chronic pain as monotherapy, replacement therapy or adjunctive treatment, including central and peripheral neuropathic pain, to enhance pain outcomes (a strong recommendation, moderate-quality evidence). As adjunctive treatment, CBM can be used if other modalities fail to achieve an adequate response, for managing pain in individuals with multiple sclerosis (a strong recommendation, moderate-quality evidence), for fibromyalgia pain, and other chronic pain in individuals with fibromyalgia, arthritic conditions, chronic migraines, or chronic headaches (a strong recommendation, low-quality evidence).[104] The European Academy of Neurology (EAN) included medical cannabis for the management of pain in the guidelines on the palliative care of people with severe, progressive multiple sclerosis.[105] The guidelines recommend the use of any of the 3 different cannabinoid preparations (Δ9-THC, *Cannabis sativa* plant extract or nabiximols) to reduce pain in patients with severe multiple sclerosis (a weak recommendation, low-quality evidence).[105] In the clinical practice guideline from the American Society of Clinical Oncology (ASCO) on the management of chronic pain in survivors of adult cancers, medical cannabis is included in the chapter on pharmacological interventions/miscellaneous analgesics.[106] Medical cannabis or cannabinoids can be considered for use in cancer survivors experiencing chronic pain, following the careful consideration of the potential benefits and risks associated with the available formulations (a moderate recommendation, intermediate-quality evidence).[105] On the other hand, the National Institute for Health and Care Excellence (NICE) developed separate guidelines for the use of cannabis-based medicinal products, which advise against providing CBM for the management of chronic pain in adults.[107,108]

Despite the positive impact of cannabis on the treatment of pain of various origin, it is necessary to mention its side effects and risk. Evidence has suggested that cannabis may be harmful for mental, but also physical health. Side effects can be as minor as nausea, drowsiness, diarrhea, anxiety, and impaired memory and concentration. Yet, in the long run, it can lead to the deterioration of QoL, as well as mental disorders or strong addiction to cannabis.[109] Evidence suggests detrimental effects on cognition and an association with motor vehicle accidents, what can lead to injuries or death.[110] Marijuana smoke and tobacco smoke share common carcinogens, such as toxic gases, reactive oxygen species (ROS) and polycyclic aromatic hydrocarbons, which can lead to cancer.[111]

People using cannabis for chronic pain often experience a range of comorbid conditions, such as insomnia, obstructive sleep apnea (OSA) and depression. According to research, up to 54% may suffer from comorbid depression, and nearly half of patients prescribed MM (for any medical indication) report using it in order to cope with depression.[112] A study by O'Brien et al. showed that over 70% of the study sample reported at least one additional comorbid or secondary condition, and about 12.5% reported 5 or more comorbid or secondary conditions.[113] Cannabis is sometimes used as a self-medication strategy to manage these symptoms, given its potential to alleviate pain, improve sleep quality and reduce depressive symptoms.[114] However, the relationship between cannabis and comorbidities is complex, and highly dependent on the person and their specific physical and mental condition.

Availability and the legal environment determine patient access to cannabinoids, and impact both treatment patterns in patients with chronic pain and the conduct of clinical research.[115,116] The legal environment differs

between countries, affecting access to cannabis-based medicinal products, and their composition, labeling and online distribution.[117,118] In Israel, local legal regulations permit issuing a medical cannabis license to treat chronic non-cancer pain, preferably of neuropathic origin, only for patients who have unsuccessfully used conventional treatment for at least a year and have exhausted all other treatment options.[84] The approved initial monthly dose is 20 g, with concentrations of 0–24% for CBD and 0–20% for THC. Upon license renewal, the dose can be incrementally increased by 10 g per month. Cannabinoids can be administered via inhalation or as sublingual oil extracts.[84] Furthermore, using THC alone is not allowed.[92] In other countries, like Germany, medical cannabinoids were introduced for pain treatment in 2017, despite regulatory institutions not approving any of the available substances for this indication.[85] In the UK, the NICE guidelines issued in 2019 advised against the use of cannabis-based medicinal products.[108] Only patients who had already started using this treatment for pain before the guidelines were issued could continue; new patients cannot start treatment with cannabis-based medicinal products for the management of pain.[108]

The main limitation of evidence in this review is the absence of large, well-designed controlled trials. Many studies encompassed mixed patient populations, characterized not only by a high diversity of pain diagnoses and characteristics, but also by various treatment patterns and forms of CBM usage.[38,61,62] It is important to highlight that ⅓ of the studies and over half of the included patients represented diverse diagnoses. This emphasizes the necessity for more evidence from homogeneous patient groups to better inform clinicians and enable more precise recommendations. Another factor that could have potentially biased the results is the inclusion of studies that analyzed pain as a secondary outcome, focusing more on co-occurring conditions while also examining the impact of cannabinoids on pain. Such studies might be underpowered to properly determine the effectiveness of cannabinoids in pain management. Many conditions are closely linked to pain, such as spasticity in multiple sclerosis, anxiety and depression, and musculoskeletal disorders with impaired mobility. Improving co-occurring impairment may result in the alleviation of pain.[46,56,119]

In addition, the included studies show different routes of drug administration, including oils, dried herbs, gels, creams, tablets, capsules, inhalations, vaporizers, and simply smoking. Treatment regimens were not provided in relation to the route of administration. A visible gap in the studies is therefore the dependence of treatment effectiveness on the route of drug administration.

It should also be emphasized that the conducted review is a narrative review, which has its limitations. There are differences in the power of studies, heterogeneity of findings, and other factors compared to a systematic review that can be considered as limitations of the conducted review.

Conclusions

Medical cannabis can be considered an option in carefully selected patients with chronic pain syndrome for the management of chronic pain when other treatment options fail to achieve an adequate response, and when potential benefits outweigh the risks. Patients with chronic secondary headache and orofacial pain, chronic secondary visceral pain, chronic secondary musculoskeletal pain, and chronic neuropathic pain can benefit more than other groups of patients experiencing chronic pain. However, there is still a need for well-designed clinical research to establish the long-term efficacy and safety of cannabinoids.

Ethics approval and consent to participate

Not applicable.

Data availability

All the data generated and/or analyzed during this study is included in this published article.

Consent for publication

Not applicable.

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