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Medical Cannabis: A Review of its Therapeutic Potential in the Treatment of Migraine

Carlos HL*

National University of La Rioja, Argentina

***Corresponding author:** Carlos H Laino, Biotechnology Institute, National University of La Rioja, La Rioja, Argentina, Tel: +54 9 380 439-1553; Email: carloslaino25@gmail.com

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Abstract

Migraine is a common episodic headache disorder. Currently, available medications are effective with moderate to severe adverse effects. Therefore, there is still a need to explore new therapeutic strategies to identify effective and safer drugs with minimal adverse effects.

This review explores the biochemical evidence of changes in the endocannabinoid system in migraine and examines cannabis treatments in both preclinical and clinical studies. However, further studies are still needed to determine the potential use of medical cannabis in the treatment of migraines.

Keywords: Cannabis; Cannabinoids; Medical Cannabis; Medical cannabis

Abbreviations

ICHD: International Classification of Headache Disorders; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; OnaB-A: Onabotulinumtoxin A; CGRP: Calcitonin Gene-Related Peptide; Δ9- THC: Delta-9-Tetrahydrocannabinol; CBD: Cannabidiol; CBR: Cannabinoid Receptors; ECS: Endocannabinoid System; 2-AG: 2-Arachidonoylglycerol; PEA: Palmitoylethanolamide; GABA: Gamma-Aminobutyric Acid; AEA: N-Arachidonoylethanolamide; MOH: Medication Overuse Headaches; AITC: Agonist Allyl Isothiocyanate; TRPA1: Transient Receptor Potential Cation Channel Subfamily A Member 1; FDA: Food and Drug Administration; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome.

Introduction

Migraine is just one of over 200 types of headache disorders, but it stands out as a significant cause of poor health in the population [1].

Each year, around 47% of the global population experiences some form of headache, including migraine (10%), tension-type headache (38%), and chronic daily headache (3%) [2]. According to the International Classification of Headache Disorders (ICHD), migraines are one of the primary headache disorders [3].

There is a difference in the prevalence of headache disorders between genders, with women being 2 to 3 times more likely

to experience migraine [4] and 1.25 times more likely to experience tension-type headaches than men [5].

Treatment for Migraines

The pharmacological therapy for migraine is typically categorized into acute and preventive treatments.
The most frequently used medications for acute migraine include analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, antiemetics, and triptans [6,7].

Unfortunately, the effectiveness is low, with 25% of patients not responding to triptans [8]. Furthermore, only one-third of patients taking one triptan are pain-free within 2 hours, and only 17% to 25% remain pain-free over the next 24 hours [9-11]. These pharmacological treatments can be complemented with non-pharmacological interventions such as cognitive-behavioral therapy or relaxation training [12].

Drugs that have demonstrated proven efficacy in the preventive treatment of migraine are mainly antiepileptics, antidepressants, and antihypertensives. However, many of these drugs are not well tolerated, resulting in poor compliance. The current treatment option for chronic migraine is OnabotulinumtoxinA (OnaB-A) [13], and CGRP antagonists [14] and neuromodulation devices [15] are also available or in late-stage development as both abortive and preventative migraine therapies.

The pharmacological efficacy of these medications indicates a significant unmet clinical need for new, more effective drugs for treating both acute migraine episodes and preventing them.

Migraine and Cannabinoids

Cannabis, also known as marijuana and referred to by many other names, has a long-standing history for both medical and recreational purposes.

Cannabis has been used since ancient times to alleviate a wide range of conditions, such as anxiety, depression, acute pain, cancer pain, chronic pain, headaches, and migraines [16].

There are three varieties of cannabis: Cannabis indica, Cannabis ruderalis, and Cannabis sativa, which contain 400 compounds [17].

Currently, the compounds of highest interest include delta-9-tetrahydrocannabinol (Δ9-tetrahydrocannabinol, THC), cannabidiol (CBD), flavonoids, and terpenes [17]. THC and CBD form the primary components of various pharmaceutical formulations of medical cannabis [17]. Currently, there are natural cannabinoid pharmaceuticals that are produced under strict and sterile conditions. This process helps to improve the growth of cannabis strains and standardize them with specific compositions of main cannabinoids like THC and CBD, as well as minor cannabinoids and other important phytochemicals such as terpenes and flavonoids.

Both CBD and THC stimulate cannabinoid receptors (CBR) throughout the human body as part of the endocannabinoid system [17].

The endocannabinoid system (ECS) consists of CBR1 predominantly in the brain and nervous system, as well as in peripheral organs and tissues. Also, CBR2 are particularly abundant in immune tissues. Additionally, there are three endogenous lipid ligands known as endocannabinoids: N-arachidonoylethanolamide (anandamide or AEA), 2-arachidonoylglycerol (2-AG), and palmitoylethanolamide (PEA), as well as the metabolic pathways they regulate [18].

Activation of CBR1 leads to reduced neurotransmission of dopamine, γ-aminobutyric acid (GABA), and glutamate, while activation of CBR2 results in analgesia and decreased immune system function [17,19,20]. CBR1 receptors decrease pain through a serotonin-mediated pathway, while CBR2 receptors relieve pain without developing tolerance or side effects [20].

Cannabis science is a quickly advancing field with growing evidence supporting its various therapeutic uses. The approach to clinical problem-solving in pharmaceutical science has traditionally centered on a single-compound, single-target strategy.

This is quite different from medicinal cannabis treatment, which often involves a multi-compound approach using the entire plant. While THC and CBD are well-known phytocannabinoids, others may also have biological activity [21,22].

Different combinations of phytocannabinoids may have varying levels of effectiveness in treating migraines. This multi-compound effect of cannabis is known as the “entourage effect” [23].

Studies suggest that research on individual cannabinoids may not capture the synergistic effects of medical cannabis treatment involving multiple compounds [23].

To add to the complexity of treating medical cannabis with multiple compounds, there are hundreds of different cannabis cultivars, each with its own particular chemical composition [24].

Data has shown that cannabinoids appear to act uniquely and synergistically within the inherent pathways of migraine and pain, including the mechanism of action of triptans (5-hydroxytryptamine, 5-HT1B/D receptor) [25-31].

In migraines, one theory suggests that the ECS alleviates migraines through multiple pathways (glutamate, anti-inflammatory, opioid, and serotonin) both centrally and peripherally [20].

AEA is an endogenous neurotransmitter analog of THC [32]. AEA potentiates serotonin 5-HT1A receptors and inhibits 5-HT2A receptors, supporting therapeutic efficacy in the acute and preventive treatment of migraine, and is also active in the periaqueductal gray matter, a migraine generator [33]. Cannabinoids also exhibit dopamine-blocking and anti-inflammatory effects [33].

Use of Cannabis for Headache

Changes in biochemical mechanisms were observed in the ECS, which may reflect an adaptive response to chronic headache and/or drug overuse.

In patients with chronic migraine, significantly lower concentrations of AEA and higher concentrations of PEA were found in the cerebrospinal fluid compared with control subjects [34].

Furthermore, patients with chronic migraine or medication overuse headaches (MOH) showed reduced levels of AEA-degrading enzymes in platelets [35].

Endocannabinoids may have a specific prophylactic effect on migraines because they can inhibit platelet serotonin release and have a peripheral vasoconstrictor effect [36].

Greco R, et al. [37] investigated the analgesic effect of AEA using a well-established animal model for persistent somatic pain, such as the formalin test in male rats [37].

In animal models of migraine, AEA administration decreased hyperalgesic behavior (36), and plant-derived THC showed antimigraine effects in rats [38].

However, it was investigated whether THC administration produces anti-migraine effects in female rats. Microinjection of the transient receptor potential cation channel subfamily A member 1 (TRPA1) agonist allyl isothiocyanate (AITC) onto the dura mater produced migraine-like pain. In this study, the researchers demonstrate that THC, when administered at the appropriate dose and time, can prevent migraine-like pain mediated by the CBR1 [38].

Research to date suggests that the endocannabinoid system plays a role in migraine relief, but further research is needed [39,40].

Despite conflicting evidence on the effectiveness of pharmaceutical medical cannabis for headaches and migraines, there is consensus on its use when first- and second-line treatments fail. Based on current ethnobotanical and anecdotal references, there is evidence of efficacy. Biochemical studies of THC and AEA have provided a scientific basis for both symptomatic and prophylactic clinical treatment of migraine [25].

The Food and Drug Administration (FDA) approved two synthetic THC medications for the first time in 1985. Dronabinol has been approved by the FDA for the treatment of anorexia induced by HIV/AIDS and for nausea and vomiting induced by chemotherapy in patients who have not responded to conventional antiemetics [41]. Also, nabilone has been approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments [42].

Later, on July 25, 2018, the FDA approved the first plant-derived, purified pharmaceutical-grade CBD known as Epidiolex® [43].

Medical Cannabis for the Treatment of Migraine or Headaches

Recent clinical studies have demonstrated that CBD can effectively alleviate symptoms and decrease the reliance on medication for patients with arthritis, chronic pain following kidney transplants, fibromyalgia, epilepsy and long-term chronic non-cancer pain. Additionally, CBD has been proven to be a safe treatment option for these conditions [44].

A growing body of clinical research suggests that CBD may help relieve pain related to several conditions [45]. Recent results of clinical studies have indicated the benefits of CBD in improving symptoms and reducing medications in patients with arthritis, in chronic pain in patients with kidney transplants, in fibromyalgia pain, and chronic non-cancer pain in long-term treatment with CBD, which also proved to be safe.

Clinical studies have shown that the topical application of CBD oil in the lower limbs can be beneficial in patients with peripheral neuropathy [46].

Also, several studies have reported both the benefits and effectiveness of medical cannabis use for headaches.

A study with 128 cannabis users in Germany, Austria, and Switzerland has self-reported cannabis use for migraines (10.2%) [47]. They mentioned that one of the indications for medicinal cannabis was for migraine (6.6%). The majority of patients used natural cannabis products such as marijuana, hashish, and an alcoholic tincture, and only five cases used dronabinol (Marinol). Cannabis users reported about the doses that 84.1% have not felt any need for dose escalation during the last 3 months, 11.0% had to increase their cannabis dose moderately, and 4.8% strongly in order to maintain the therapeutic effects.

A study was conducted in 2018 to examine the epidemiology of medical cannabis use in the USA and Canada through online surveys. The study included 27,169 participants aged 16-65, and 35% of them reported using medical cannabis for headaches or migraines [48].

Cluster headaches are a type of headache that is known for its intense pain. It is estimated that approximately 0.1% of the population is affected by this condition [49].

A case report was present of a patient with cluster headaches who was refractory to multiple acute and preventive medications. Acute attacks remained consistently responsive only to dronabinol 5 mg [50].

Later, Leroux E, et al. [51] conducted a prospective observational study over four months, using questionnaires to examine the frequency and potential benefits of cannabis use. Out of the 139 (45.3%) patients with cluster headaches, only 63 reported a history of cannabis use. Less than one-third of self-reported users reported experiencing relief of their attacks after using cannabis inhalation [51].

Rhyne DN, et al. [52] conducted a retrospective study using reviews of medical records with 121 patients diagnosed with migraine headaches [52]. The patients received treatment with medical cannabis vaporized (42 patients), edible (66 patients), topical (15 patients), and smoked (65 patients) forms for migraine treatment or prophylaxis. The mean monthly doses of each type of marijuana were 2.64 oz, 2.59 oz, 2.73 oz, and 1.59 oz for vaporized, edible, topical, and smoked forms, respectively. The study found that 103 patients (85.1%) who inhaled medical cannabis experienced a significant decrease in migraine frequency.

In 2018, Baron EP, et al. [53] conducted a retrospective via electronic survey study to investigate the clinical usefulness of medical cannabis treatment for migraine, headache, arthritis, and chronic pain syndromes. The study shows the significant advantage of medical cannabis in improving nausea and vomiting associated with migraines. Also, this study identified better patterns of medical treatment for migraine. Hybrid strains with high THC/THCA (tetrahydrocannabinolic acid) and low CBD/CBDA (cannabidiolic acid), with predominant terpenes β-caryophyllene and β-myrcene, were preferred in migraine and headache.

Recently, a prospective observational study, as a cross-sectional survey for three years, investigated the associations between medical cannabis treatment and migraine frequency [54]. In this study, 145 patients were divided into two groups: responders and non-responders. Responders were defined as those who experienced a decrease of ≥50% in monthly migraine attack frequency before starting medical cannabis treatment, while non-responders experienced a decrease of <50%. The study focused on 68 patients who smoked or vaped medical cannabis inflorescences, and aimed to compare the total monthly dose of medical cannabis between responders and non-responders. The results showed that responders consumed higher doses (ranging from 7.9 to 109.5 mg per month) of the phytocannabinoid ms_373_15c, or lower doses (ranging from 0 to 9.9 mg per month) of the phytocannabinoid ms_331_18d. The study reported a significant reduction in migraine frequency by those who consumed higher doses of ms_373_15c or lower doses of ms_331_18d.

MOH is one of the most common secondary headache disorders. MOH is a chronic daily headache and a secondary disorder in which acute medications used excessively cause headaches [55].

Pini LA, et al. [56] performed the first randomized, double-blind, active-controlled, crossover study comparing nabilone 0.5 mg/day and ibuprofen 400 mg in patients with MOH for 8 weeks [56]. In this design, 30 patients with MOH were randomly (1:1 ratio) assigned before nabilone and then ibuprofen or vice versa, using a two-period design and one-week wash-out between them. The results showed that nabilone was more effective than ibuprofen in reducing pain intensity and daily analgesic intake [56].

In recent years, some clinical studies demonstrated that medical cannabis can alleviate headaches and migraines, yet research on its effectiveness remains sparse.

Cuttler C, et al. [57] investigated the effects of inhalation and type of cannabis (concentrate vs. flower), THC, CBD, doses, and tolerance on patients with migraines and headaches [58]. A prospective survey study of 653 patients with migraine and 1,306 with headaches. The results indicated a significant reduction in headache and migraine ratings after cannabis use. Men experienced a greater decrease in headaches than women, and the concentrates were more effective than flowers. Finally, the study demonstrated tolerance to these effects [57].

Cannabis and cannabinoid compounds have been used to treat pain and possibly headache for centuries [58]. However, medical research for medical cannabis use is limited, given the lack of randomized control studies. Current literature is sparse to cell phone survey applications, case reports, case series and retrospective analyses.

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At this time, there are only a few randomized clinical trials ongoing on the treatment of CBD in headaches or migraines.

The first in a sample of 110 participants in Israel, a randomized, multicenter double-blind study studying the effect of CBD 133 mg + Cannabigerol (CBG) 66 mg + THC 4 mg/day as adjuvant therapy in the treatment of chronic migraine [59].

The second, in a sample of 20 participants in Canada, was a multicenter study studying the safety (tolerability) of CBD-enriched cannabis oil (50 mg/ml of CBD + 2 mg/ml of THC) in adolescents (14 to 17 years) with chronic headaches [60].

The third has a sample of 30 participants in the USA, studying the efficacy of a sublingual tablet (with 30 mg of CBD, 1 mg of THC, 97 mg of palmitoylethanolamide (PEA), and a combination of 0.2 mg of myrcene, beta-caryophyllene, humulene, linalool, limonene, and peppermint oil) for the treatment of dysmenorrhea with painful symptoms in women over 21 years of age [61].

Conclusions

While the available evidence suggests the involvement of the endocannabinoid system and the possibility that medical cannabis treatment may be therapeutic in migraine, further research is required to demonstrate the efficacy parameters of medical cannabis treatment for migraine.

References

1. Steiner TJ, Stovner LJ (2023) Global epidemiology of migraine and its implications for public health and health policy. Nat Rev Neurol 19: 109-117.

2. Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton RB, et al. (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27(3): 193-210.

3. Cephalalgia (2018) International Headache Society 38(1): 1-211.

4. Bille B (1996) Migraine and tension-type headache in children and adolescents. Cephalalgia 16: 80.

5. Robbins MS, Lipton RB (2010) The epidemiology of primary headache disorders. Semin Neurol 30(2): 107-119.

6. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, et al. (2009) EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol 16(9): 968-981.

7. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, et al. (2012) Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78(17): 1346-1353.

8. Diener HC, Limmroth V (2001) Advances in pharmacological treatment of migraine. Expert Opin Investig Drugs 10(10): 1831-1845.

9. Jensen R, Bendtsen L (2015) Tension-type headache. In: Siva A, Lampl C (Eds.), Case-based diagnosis and management of headache disorders Headache, Springer International Publishing, pp: 147-155.

10. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB (2002) Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 22(8): 633-658.

11. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 358(9294): 1668-1675.

12. Lyngberg AC, Rasmussen BK, Jorgensen T, Jensen R (2005) Prognosis of migraine and tension-type headache: a population-based follow-up study. Neurology 65(4): 580-585.

13. Ray JC, Hutton EJ, Matharu M (2021) OnabotulinumtoxinA in Migraine: A Review of the Literature and Factors Associated with Efficacy. J Clin Med 10(13): 2898.

14. Mohanty D, Lippmann S (2020) CGRP Inhibitors for Migraine. Innov Clin Neurosci 17(4-6): 39-40.

15. Tiwari V, Agrawal S (2022) Migraine and

Neuromodulation: A Literature Review. Cureus 14(11): e31223.

16. Leinen ZJ, Mohan R, Premadasa LS, Acharya A, Mohan M, et al. (2023) Therapeutic Potential of Cannabis: A Comprehensive Review of Current and Future Applications. Biomedicines 11(10): 2630.

17. Baron EP (2018) Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: an update on current evidence and cannabis science. Headache 58(7): 1139-1186.

18. Rezende B, Alencar AKN, Bem GF, Fontes-Dantas FL, Montes GC (2023) Endocannabinoid System: Chemical Characteristics and Biological Activity. Pharmaceuticals 16(2): 148.

19. Giudice ED, Rinaldi L, Passarotto M, Facchinetti F, Arrigo AD, et al. (2007) Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells. J Leukoc Biol 81(6): 1512-1522.

20. Chayasirisobhon S (2019) Cannabis and neuropsychiatric disorders: an updated review. Acta Neurol Taiwan 28(2): 27-39.

21. ElSohly MA, Slade D (2005) Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sci 78(5): 539-548.

22. Russo EB (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 163(7): 1344-1364.

23. Christensen C, Rose M, Cornett C, Alleso M (2023) Decoding the Postulated Entourage Effect of Medicinal Cannabis: What It Is and What It Isn't. Biomedicines 11(8): 2323.

24. Baram L, Peled E, Berman P, Yellin B, Besser E, et al. (2019) The heterogeneity and complexity of Cannabis extracts as antitumor agents. Oncotarget 10(41): 4091-4106.

25. Okusanya BO, Lott BE, Ehiri J, McClelland J, Rosales C (2022) Medical Cannabis for the Treatment of Migraine in Adults: A Review of the Evidence. Front Neurol 13: 871187.

26. Baron EP (2015) Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: What a long strange trip it's been. Headache 55(6): 885-916.

27. Lochte BC, Beletsky A, Samuel NK, Grant I (2017) The use of cannabis for headache disorders. Cannabis Cannabinoid Res 2(1): 61-71.

28. Russo E (2001) Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. J Cannabis Ther 1: 21-92.

29. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ (2013) Endocannabinoids in the brainstem modulate dural trigemino vascular nociceptive traffic via CB1 and "triptan" receptors: implications in migraine. J Neurosci 33(37): 14869-14877.

30. Akerman S, Holland PR, Goadsby PJ (2007) Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. J Pharmacol Exp Ther 320(1): 64-71.

31. Akerman S, Kaube H, Goadsby PJ (2004) Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. J Pharmacol Exp Ther 309(1): 56-63.

32. Maccarrone M, Finazzi-Agro A (2003) The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis. Cell Death Differ 10(9): 946-955.

33. Russo EB (2004) Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions. Neuro Endocrinol Lett 25(1-2): 31-39.

34. Sarchielli P, Pini LA, Coppola F, Rossi C, Baldi A, et al. (2007) Endocannabinoids in Chronic Migraine: CSF Findings Suggest a System Failure. Neuropsychopharmacology 32(6): 1384-1390.

35. Cupini LM, Costa C, Sarchielli P, Bari M, Battista N, et al. (2008) Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiol Dis 30(2): 186-189.

36. Poudel S, Quinonez J, Choudhari J, Au ZT, Paesani S, et al. (2021) Medical Cannabis, Headaches, and Migraines: A Review of the Current Literature. Cureus 13(8): e17407.

37. Greco R, Mangione AS, Sandrini G, Maccarrone M, Nappi G, et al. (2011) Effects of anandamide in migraine: Data from an animal model. J. Headache Pain 12(2): 177-183.

38. Kandasamy R, Dawson CT, Craft RM, Morgan MM (2018) Anti-migraine effect of Δ9-tetrahydrocannabinol in the female rat. Eur J Pharmacol 818: 271-277.

39. Greco R, Demartini C, Zanaboni AM, Piomelli D, Tassorelli C (2018) Endocannabinoid system and migraine pain:

an update. Front Neurosci 12: 172.

40. Cogan PS (2020) Practical considerations of hypotheses and evidence in cannabis pharmacotherapy: refining expectations of clinical endocannabinoid deficiency. J Diet Suppl 17(5): 608-624.

41. Di Marzo V, Petrocellis LD (2006) Plant, synthetic, and endogenous cannabinoids in medicine. Annu Rev Med 57: 553-574.

42. (2006) Cesamet (Nabilone) Capsules. For Oral Administration, pp: 3-13.

43. Office of the Commissioner (2018) Press Announcements-FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Silver Spring, MD: US Food and Drug Administration.

44. Binkowska AA, Jakubowska N, Redel A, Laskowska S, Szlufik S, et al. (2024) Cannabidiol usage, efficacy, and side effects: analyzing the impact of health conditions, medications, and cannabis use in a cross-sectional online pilot study. Front Psychiatry 15: 1356009.

45. Fiani B, Sarhadi KJ, Soula M, Zafar A, Quadri SA, et al. (2020) Current application of cannabidiol (CBD) in the management and treatment of neurological disorders. Neurol Sci 41(11): 3085-3098.

46. Xu DH, Cullen BD, Tang M, Fang Y (2020) The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm Biotechnol 21(5): 390-402.

47. Schnelle M, Grotenhermen F, Reif M, Gorter RW (1999) Results of a standardized survey on the medical use of cannabis products in the German-speaking areas. Forsch Komplementarmed 6(3S): 28-36.

48. Leung J, Chan G, Stjepanovic D, Chung JYC, Hall W, et al. (2022) Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. Psychopharmacology (Berl) 239(5): 1509-1519.

49. San-Juan D, Velez-Jimenez K, Hoffmann J, Martínez-Mayorga AP, Melo-Carrillo A, et al. (2024) Cluster headache: an update on clinical features, epidemiology, pathophysiology, diagnosis, and treatment. Front Pain Res (Lausanne) 5: 1373528.

50. Robbins MS, Tarshish S, Solomon S, Grosberg BM, et al. (2009) Cluster attacks responsive to recreational cannabis and dronabinol. Headache 49(6): 914-916.

51. Leroux E, Taifas I, Valade D, Donnet A, Chagnon M, et al. (2013) Use of cannabis among 139 cluster headache sufferers. Cephalalgia 33(3): 208-213.

52. Rhyne DN, Anderson SL, Gedde M, Borgelt LM (2016) Effects of medical cannabis on migraine headache frequency in an adult population. Pharmacotherapy 36(5): 505-510.

53. Baron EP, Lucas P, Eades J, Hogue O (2018) Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain 19(1): 37.

54. Aviram J, Vysotski Y, Berman P, Lewitus GM, Eisenberg E, et al. (2020) Migraine Frequency Decrease Following Prolonged Medical Cannabis Treatment: A Cross-Sectional Study. Brain Sci 10(6): 360

55. Lipton RP (2015) Risk Factors for and Management of Medication-Overuse Headache. Continuum 21(4): 1118-1131.

56. Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, et al. (2012) Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain13(8): 677-684.

57. Cuttler C, Spradlin A, Cleveland MJ, Craft RM, et al. (2020) Short- and Long-Term Effects of Cannabis on Headache and Migraine. J Pain 21(5-6): 722-730.

58. Russo E (1998) Cannabis for migraine treatment: The once and future prescription. An historical and scientific review. Pain 76: 3-8.

59. Kaup A (2024) Cannabidiol 133mg + Cannabigerol 66mg + Tetrahydrocannabinol 4mg vs Placebo as Adjuvant Treatment in Chronic Migraine - (CAMTREA). ClinicalTrials.gov.

60. Kelly L (2024) Cannabis for Chronic Headaches in Adolescents: the CAN-CHA Trial (CAN-CHA). ClinicalTrials.gov.

61. Kimless D (2024) Sublingual Tablets with Cannabinoid Combinations for the Treatment of Dysmenorrhea. ClinicalTrials.gov.