Chronic headache and cannabinoids use: myths and truths

Cefaleia crônica e uso de canabinoides: mitos e verdades

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ABSTRACT

BACKGROUND AND OBJECTIVES: The use of cannabis for medical purposes is known since ancient times. The endocannabinoid system is present throughout central and peripheral nervous system and plays a role in many important regulatory physiological processes like immune function, synaptic plasticity, pain and regulation of stress and emotion, among others. Due to its wide distribution and according to researches, cannabis can be indicated for symptoms management in different disorders such as chronic pain, headache, epilepsy, anxiety and other psychiatric disorders. The primary cannabinoids studied to date include delta-9-tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV). The active ingredients in cannabis include flavonoids, terpenes, delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and they are able to act within the endocannabinoid system and decrease nociception and also the frequency of the symptoms. The purpose of the article is to document the validity of how medical cannabis can be utilized as an alternative therapy for chronic headache management and enlighten about false beliefs regarding its use.

CONTENTS: Sixty-four relevant articles were selected after a thorough screening process using PubMed and Google Scholar databases. The following keywords were used: "Cannabis", "Medical Marijuana", "Headache", "Migraine", "Cannabis and Migraine", "Cannabis and Headache". This literature study demonstrates that medical cannabis use decreases migraine duration and frequency and headaches of unknown origin.

CONCLUSION: Patients suffering from migraines and related conditions may benefit from medical cannabis therapy due to its convenience and efficacy.

Keywords: Cannabis, Endocannabinoids, Headache, Medical marijuana, Migraine disorders.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso da cannabis medicinal é conhecido desde a antiguidadee. O sistema endocanabinoide está distribuído no sistema nervoso central e periférico e atua como importante regulador em processos fisiológicos como função imune, plasticidade sináptica, regulação da dor e das emoções/estresse, entre outros. Devido à sua ampla distribuição e, de acordo com pesquisas, a cannabis pode ser indicada no manejo de sintomas em diferentes condições, como dor crônica, cefaleias, epilepsia, ansiedade e outras doenças psiquiátricas. Os canabinoides primários estudados são o 9-tetrahydrocannabinol (THC), *cannabinol* (CBN), canabigeral (CBG), e a *tetrahidrocannabivarina* (THCV). Os ingredientes ativos da cannabis incluem flavonoides, terpenos, delta-9- *tetrahydrocannabinol* (THC), canabidiol (CBD), e eles são capazes de agir dentro do sistema endocanabinoide e diminuir a nocicepção e a frequência dos sintomas. O objetivo deste estudo foi documentar a validade de como a cannabis medicinal pode ser utilizada como terapia alternativa para o manejo da cefaleia crônica, além de esclarecer sobre falsas crenças ligadas a seu uso.

CONTEÚDO: Sessenta e quatro artigos foram selecionados por meio de pesquisa nas bases de dados Pubmed e *Google Scholar*. As seguintes palavras-chave foram usadas: "Cannabis", "Maconha Medicinal", "Cefaleia", "Enxaqueca", "Cannabis e Enxaqueca", "Cannabis e Cefaleia". A literatura mostra que o uso da cannabis medicinal reduz a duração e a frequência da enxaqueca e das cefaleias de origens não conhecidas.

CONCLUSÃO: Pacientes sofrendo com enxaqueca e condições relacionadas podem se beneficiar da terapia com cannabis devido à sua conveniência e eficácia.

Descritores: Cefaleia, Cannabis, Enxaqueca com aura, Enxaqueca sem aura, Maconha medicinal.

INTRODUCTION

The use of medical cannabis, both for adult recreational and medicinal use, is historical. Cannabis has been used since ancient

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times in China, Egypt, India and the West, for the treatment of different conditions such as glaucoma, colic, anxiety, chronic pain and headache[1]. The therapeutic effects result from a complex interaction of the approximately 500 compounds present in the plant. The main phytocannabinoids present in the plant are Δ9- tetrahydrocannabinol (THC) and cannabidiol (CBD)[2]. The active ingredients include flavonoids, terpenes, Δ9- tetrahydrocannabinol (THC), cannabidiol (CBD) and they are able to act on the endocannabinoid system and decrease nociception and also the frequency of symptoms[3,4].

Evidence suggests a synergistic behavior between these components, especially between cannabinoids and terpenes. The "entourage effect" corresponds to the synergistic effect and interaction between them[5-7].

CBD was isolated in 1963, and THC in 1964. However, it was not until 1990 that cannabinoid receptors and endogenous cannabinoids were discovered. Evidence of cannabinoid activity through non-cannabinoid receptors was found in the early 20th century[8].

The distribution of the endocannabinoid system in the peripheral and central nervous system is wide. Among its many different functions, the endocannabinoid system is virtually important in all physiological regulatory activities such as inflammation, immune function, metabolism, sleep/wake cycle, appetite regulation, thermogenesis, neural development, cardiovascular function, synaptic plasticity, nociception/pain, stress regulation, and emotion[9,10].

The endocannabinoid system consists of receptors - cannabinoid 1 (CB1) and 2 (CBD2); ligands - the endogenous cannabinoid receptor ligands; endogenous cannabinoids such as N- arachidonoiletanolamine (anandamide, or AEA) and 2-arachidonoilglycerol (2-AG); and also synthesis and catabolism enzymes[11].

The cannabinoid receptors CB1 and CB2 are presynaptic G-protein-coupled types, which are essential to the activities of the endocannabinoid system. CB1 receptors are the most abundant G-protein-coupled receptors in the brain. They are prominent in anatomical pathways, including periaqueductal gray matter (PAG), rostral ventrolateral medulla (RVM) and abundant in the central and peripheral nervous system, including the primary dorsal afferent regions and spinal jelly substance, spinal interneurons and peripheral nerves. CB2 receptors are primarily concentrated in peripheral tissues, however they are present, but in lower concentrations, in the brain in regions such as the PAG[12-15].

The endocannabinoid system does not only act through receptors. It also appears to work synergistically by combining with other molecular targets within larger endogenous pain circuits, such as endorphin/encephalin, vanilloid/transient V (TRPV) cation channel receptor subfamily, and the inflammatory system.

Migraine affects approximately 10% of the world's population and is considered the second leading cause of disability worldwide[16]. Migraine is prevalent, female-dominated, and a complex disease. Pain attacks result from painful activation of the trigemino-vascular system[17,18].

There is evidence suggesting the low level of N-arachidonoiletanolamine (anandamide or AEA) in the cerebrospinal fluid when compared to the non-migraine population. In addition, the chronic migraine population has low levels of AEA reuptake and metabolism enzymes[19,20].

In migraine, current theory suggests that the cannabinoid system mitigates migraine through several pathways (glutamine, inflammatory, opioid, and serotoninergic), both centrally and peripherally[21].

There are no relevant data available to suggest that a deficiency in the endocannabinoid system is related to migraine. Migraine treatment is divided into acute and preventive therapy. Since the disease is highly disabling, it is important to begin prevention when indicated.

The most used drugs in acute migraine are nonsteroidal anti-inflammatory (NSAIDs) and triptans. Most of the available preventive therapies are based on antiepileptic, antidepressant, and antihypertensive drugs. Other modalities that are currently advocated are botulinum toxin - onabotulinum toxin A and calcitonin gene-related antagonists (anti-CGRP), available for the treatment of chronic migraine[22,23].

Regarding neuromodulation, one can currently count on devices that are available or are already in advanced stages of development, for the treatment of both acute and chronic headache. Despite the many alternatives, one still has to deal with patients who do not benefit from or tolerate the drugs on a routine basis. These non-responders correspond to a high number of patients who have their suffering and disability maintained with the symptoms of chronic headache.

CONTENTS

Chronic headache and the use of cannabinoids

Despite the use of cannabis for migraine between 1842 and 1942, much of the knowledge surrounding the treatment has been discovered recently, such as cannabinoid activity through non-cannabinoid receptors[8]. Activation of CB1 and CB2 receptors opens potassium channels with consequent presynaptic hyperpolarization, closing sodium channels that inhibit the release of stored inhibitory and excitatory neurotransmitters[24]. CB1 activation in the central nervous system inhibits the release of inhibitory and excitatory neurotransmitters (GABA, glutamate, serotonin, dopamine, norepinephrine, D-aspartate, and acetylcholine)[25].

It is important to note that cannabinoids are activated by CB1 receptors in areas of the brain and brainstem involved in the pathophysiology of migraine. These areas include: PAG (which is part of the pain modulation system and may be a migraine generating area), rostral medulla, area postrema, caudal trigeminal nucleus, and trigeminal ganglion[26-28].

When CB1 receptors are activated in the periaqueductal gray matter in the medulla, they can inhibit GABAergic and glutamatergic transmission by preventing the release of neurotransmitters. They also regulate nociception from multiple branches of the trigeminal ganglion[29]. The facial pain and headache that accompany migraine result from activation of the trigeminovascular system[30].

Studies show that platelet activation is increased in migraine patients. Oxidative stress is an important determinant of erythrocyte membrane changes. Migrainous patients may exhibit a

genetic susceptibility to a pro-inflammatory state. Cannabinoids have been shown to inhibit 5HT release from platelets during migraine[31]. Anandamide (AEA) is an endogenous cannabinoid that usually inhibits calcitonin gene-related peptide (CGRP) and nitric oxide (NO). In individuals with migraine, AEA levels are decreased compared to normal controls, and CGRP and NO levels are higher than in normal controls[20].

Cluster headache is classified as trigemino-autonomic and can be a chronic condition that causes intense suffering. The ipsilateral hypothalamus is believed to be a site of activation in cluster headache. CB1 receptors are highly concentrated in the hypothalamus. The hypothalamic region is part of the clinical panel of other autonomic headaches, such as short neuralgiform attacks, including unilateral short duration attacks with conjunctival hyperemia and lacrimation (SUNCT) and short duration attacks with autonomic symptoms (SUNA), paraoxysmal hemicranias, and continuous hemicrania[32].

Clinical studies on cannabis for chronic headache

Despite the growing interest in the medicinal use of cannabis and its health risks and benefits, medical research is still scarce. There is a lack of randomized, placebo-controlled, double-blind, multicenter trials evaluating the use of cannabis in chronic headache, which would be gold standard studies. Most of the current literature is limited to retrospective and observational studies (data collected by surveys with reports and self-assessments, such as telephone surveys), case reports, and case series.

Many of the currently available studies suggest benefits of cannabis in the treatment of chronic headache, highlighting migraine, which is the most commonly evaluated in the studies. The literature also shows evidence supporting the use of cannabinoids in the treatment of cluster headache, idiopathic intracranial hypertension, and multiple sclerosis (MS) associated with trigeminal neuralgia. In addition, patients and physicians should be aware of the limitations of cannabis and its adverse effects.

A randomized, double-blind, active-controlled, cross-sectional study[33] was conducted with 30 patients (10 eligible men and 20 women who were not pregnant) attending the University of Modena at the Interdepartmental Center for Research on Headache and Drug Abuse (Italy). All participants had suffered with chronic headache for at least 3 years and had a history of analgesic or antimigraine drug abuse. Patients were randomized to receive both treatments at home: one period with nabilone and another period with ibuprofen, in a blinded sequence. Each period lasted 8 weeks. Nabilone, a cannabinoid receptor 1 agonist, in daily doses, was more effective than ibuprofen for patients suffering with migraine from analgesic abuse[33].

In another retrospective, observational study of cannabis use in migraine, researchers reviewed histories of 121 adults from two medical marijuana specialist clinics in Colorado. The primary outcome was the number of migraine attacks per month at the start of visits and at follow-up. Eighty-five percent of patients reported decreased frequency of monthly migraine attacks[34]. A cross-sectional study[35] with a self-report survey of 145 migraine patients showed a reduction in migraine frequency with medical cannabis use over an average of 3 years. An online data questionnaire was collected. The sample consisted of a majority of women (n=97, 67%), with a mean age of 45 years. This study classified patients with ≥ 50% reduction in average monthly migraine-free days as responders. Sixty-one percent of patients were considered responders. Forty-five percent of patients used conventional pharmaceutical analgesics concomitantly.

MYTHS AND ERRORS

The global movement toward the legalization of cannabis is resulting in a public perception, never before seen, that cannabis is safe. Cannabis is not the first drug available for non-medical use, nor is it the only drug to have a safe profile for use. Many exogenous cannabinoids have been shown to connect with the CB1 and/or CB2 receptor. These receptors are expressed almost everywhere in the human body. CB1 receptors are located primarily in the central nervous system[36], while CB2 receptors are found primarily in the hematopoietic and immune systems[37,38].

Adverse effects can be present with both its medicinal and recreational use. There are multiple variables that can influence the presence or severity of side effects with cannabis use, as well as its benefits[36-38]. The fear of the psychoactive effects of cannabis use and the existing prejudice still greatly limit its use. Although psychoactive effects are already a concern with the use of medical cannabis, the use of cannabidiol is safe. Delta-9-tetrahydrocannabinol is the phytocannabinoid connected to the psychoactive effects. Nevertheless, caution should be taken regarding the factors described and related risks should be avoided as much as possible.

Before prescribing CBD for the treatment of migraine, it is important to consider whether there is a contraindication on an individual basis. There are contraindications and/or precautions that require risk/benefit assessment of the use of cannabis and cannabinoids to which one should be alert[3,9,12,17,35-38,39-49], and which may even be prohibitive to its use. An example that requires caution is patients with a history of substance abuse such as alcohol, given the potential for abuse, as well as those taking sedative-hypnotics or other psychoactive substances due to the potential for synergistic effects.

It is important to always consider the patient's renal and hepatic function prior to starting treatment. Follow-up with periodic laboratory tests helps to safely follow the treatment with cannabidiol. In severe cases of kidney or liver disease, including chronic hepatitis C, daily use is not recommended because it worsens the potential for steatosis, so a more regular follow-up with short intervals is necessary in these patients, preventing avoidable complications.

Another important caveat is patients with lung disease, including asthma and chronic obstructive pulmonary disease, in whom treatment should be judiciously indicated and periodically followed up. Failure to consider a cardiologic evaluation in senior patients or those with a cardiologic history may result in serious complications. CBD has the potential for hypotension, hypertension, tachycardia, and syncope, which may be a risk for patients with a history of severe cardiopulmonary disease.

In patients with a psychiatric history, particularly schizophrenia, or a family history of schizophrenia, there should be great cau-

tion. Some authors even recommend avoiding the use if possible. Caution and care are also needed with use in those under 18 years old because of its greater potential for adverse mental health effects during adolescent development. There is no formal contraindication for patients who perform activities such as operating machinery or performing risky activities, but caution and observation of adverse effects should always be exercised. If possible, avoid use.

Women have no contraindication for the prescription of cannabidiol, but for those who are not on contraceptives or who plan to become pregnant it is recommended to avoid treatment with cannabidiol, which should also not be recommended for pregnant and lactating women.

DISCUSSION

Cannabis is the most widely used drug since ancient times for the treatment of different diseases such as glaucoma, colic, chronic pain and headache[1,2]. In the west, Dr. Clendinning was the first physician to treat migraine with cannabis in the mid 1840s in London, followed by Dr. Greene[3]. Migraine is the second most disabling disease, followed by low back pain[50,51]. Currently, there is abundant support for its medicinal use, as well as its potential benefits for headaches, including migraine and cluster headache, as well as for facial pain, such as trigeminal neuralgia related to multiple sclerosis. On the other hand, medicinal properties of cannabinoids, such as the activity of cannabinoids via non-cannabinoid receptors, have been discovered recently[8].

The endocannabinoid system is widely distributed in the brain and plays an important role in many physiological regulatory processes[9,10]. The endocannabinoid system consists of receptors (CB1 and CB2), endogenous endocannabinoid receptor ligands (endogenous cannabinoids) N-aracdonoiletanolamide (anandamide or AEA) and 2-araquidonoilglycerol (2-AG), and degradation enzymes[11].

When CB1 receptors are activated in the PAG or RVM, they can prevent GABAergic or glutamatergic transmission by preventing neurotransmitter release, an example of cannabinoid activity at non-cannabinoid receptors[8]. Migraine patients may exhibit genetic susceptibility to a pro-inflammatory state, and studies show that platelet activation is increased in migraine patients. Cannabinoids inhibit 5HT release from platelets during migraine[31].

In migraine patients, AEA levels are decreased in cerebrospinal fluid compared to controls without migraine, and CGRP and NO levels are higher than in normal controls[20]. The headaches and facial pain that accompany migraine are a result of activation of the trigemino-vascular system[30]. The hypothalamic region is related to part of the trigemino-autonomic headache scenario, such as cluster headaches[32]. CB1 receptors are highly concentrated in the hypothalamus.

Epidemiological studies from 2016 show that In Brazil the prevalence of migraine is approximately 15.2%; tension-type headache is 13%, and daily headaches, 6.9%[52]. A relevant observation is that other studies have shown a high number of probable migraine prevalence and an overall growth of migraine in Brazil[53,54]. Migraine is highly disabling and responsible for high direct and indirect economic costs. It is the second leading cause of disability globally[55] and affects more than 10% of the world's population[56].

The studies discussed above were conducted in different centers and with different methodologies[34,57] (retrospective observational studies, randomized control studies, cross-sectional studies with individual report surveys), and the results were similar when the reduction of migraine attack frequency with cannabinoid use was observed. The samples consisted of adults (men and women) and the results were statistically significant despite different outcomes analyzed.

Several studies indicated that inhaled cannabis use reduced the severity of headaches and migraine by approximately 50%[41,38]. Most patients who were treated with cannabis for headache were migraine sufferers (88%)[58]. Cannabinoid science is growing rapidly and a new sector in the industry is developing with use of different strains and cross breeding for composing cannabinoids, terpenes and other phytochemicals, focusing on diseases or symptoms, including migraine and headaches[41,58]. Repeated use of cannabis is associated with tolerance to its effects, making tolerance a risk factor for its use in the treatment of headaches[45].

Cannabinoids are considered analgesics for migraine, but their overuse with drugs containing delta-9-THC or other components of *marijuana*, remains uncertain. Caution should be exercised in patients with a history of substance abuse; patients taking sedatives or hypnotics or other drugs with psychoactive effects (potential synergistic effect); severe kidney or liver disease, severe cardiopulmonary disease; and psychiatric illness[37-39]. If possible, avoid use in persons under 18 years old and women at childbearing age at risk of pregnancy or lactating women.

Establishing the safety of the effects of long-term use is still necessary. A recent study showed low potential for CBD abuse with therapeutic doses of 750 mg in a sensitive population using polypharmacy[42]. Safe assessment of each step of the patient's journey in cannabis use is necessary. Prior to initiation, physicians should investigate a potential for contraindications and potential pharmacological interactions[3]. The safest patient-specific chemo-variant, route of administration, and initial dose should be evaluated[45].

CONCLUSION

The historical use of medical cannabis is described for various ailments. There is abundant support for its medicinal use as well as for potential benefits in different kinds of headache, including migraine and cluster headache.

The positive evidence base for cannabinoid medicine for pain is based on extensive scientific research and is best explained by comprehending the endocannabinoid system and its properties and mechanisms of action of phytocannabinoids in the central and peripheral nervous system.

Repeated use of cannabis is associated with tolerance to its effects, making tolerance a risk factor for its use in the treatment of migraine. There is fear currently that false beliefs about the safety of cannabis may be judged by future generations in the same way that tobacco is now criticized.

Double-blind, placebo-controlled, randomized studies are needed and will help evaluate the placebo effect and provide a more accurate assessment of dose, type of cannabis, THC, CBD, and interactions with THC and CBD. This review article shows encouraging results for the medicinal use of cannabis and its therapeutic effects on migraine relief. The short- and long-term benefits of medicinal cannabis have been reported, as well as its effectiveness in reducing daily analgesic intake, dependence, and pain intensity.

AUTHORS' CONTRIBUTIONS

Natally Marques Santiago
Conceptualization, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Validation
Yara Maria Lima
Writing - Preparation of original, Writing - Review and Editing, Visualization

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