Chapter 235

Phytocannabinoids and migraine: An integrative review

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Gabriela Ilias Bechara
Medical Student, Faculty of Medical Sciences, PUCSP
PUCSP FCMS, Joubert Wey Square, 290,
Boa Vista, Sorocaba, SP
18030-070, Brazil
E-mail: gabiiliasbe@gmail.com

Sandro Blasi Esposito
Head of the Department of Human Reproduction and Childhood, Faculty of Medical Sciences, PUCSP

ABSTRACT
The latest years have shown a relationship between the famous endocannabinoid system and pain processing, bringing the possibility of its exogenous form, phytocannabinoids, for treatment of epilepsy, neuropathic pain, and now migraine. This review seeks to evaluate the present literature and analyze the possibility of phytocannabinoids in migraine treatment. Based on the literature of the latest 20 years, the research terms were: "endocannabinoids and migrânea", "phytocannabinoids and migrânea" and "migrânea juvenile and cannabidiol", with 128 results total, of which only 19 have fitted the criteria for analysis. Though is a very pertinent theme, there is no literature enough for clinical analysis of the use of phytocannabinoid in migraine, even when the results in an animal model and reviews have shown a positive effect, it is not possible to speculate the dose, safety, and efficacy in clinical use for now. More randomized human trials are necessary.

1 INTRODUCTION

Migraine is a condition that affects 1-2% of the world's population and is the second leading cause of disability. Usually, migraine is treated using triptans, non-steroidal anti-inflammatory drugs, paracetamol, ergots, opioids, and antiemetics, yet with a high failure rate.

Several studies show a relationship between the endocannabinoid system and pain processing, generally related to pain inhibition. Its exogenous form, phytocannabinoids are currently being used for the control of epileptic seizures, and neuropathic pain, and is recently being analyzed for the aforementioned headache.

With its benefits and risks little evaluated, it becomes unknown what the child's reaction to such use is. Therefore, this integrative review aims to consider the risks and benefits of medical marijuana in children as a treatment for primary headaches.

What is the therapeutic application of phytocannabinoids in headaches?

Currently, most patients using phytocannabinoids as a treatment report chronic pain, and this has been one of the main complaints for the medicinal use of the drug.

Although very promising, it should be remembered that there are thousands of variations between the species of Cannabis, and in them, different concentrations of THC, cannabidiol, etc.

Like any herbal medicine, it is difficult to specify whether the reactions presented are due to only one compound or a complex interaction of several compounds present in the plant, and their concentrations. (1)

Studies in the treatment of epilepsy suggest high safety and tolerability, however, of these, few children under five years of age participated.

The endocrine system in the bio id is a physiological, neuro-modulatory system. Its effects are consequences of the action of Gi and Gq proteins.

The CB1 receptors of this system, mainly responsible for the effects of marijuana, are present mainly in the olfactory bulb, hippocampus, lateral striatum, striatal nuclei, and cerebellum. Moderate density in the forebrain, frontal lobe, parietal and cingulate, septum, amygdala, ventromedial hypothalamus, lateral subnucleus of the interpeduncular nucleus, parabrachial nucleus, nucleus of the solitary tract (caudal and commissural portion) and dorsal horn of the medulla. Low density in the thalamus and other brainstem nuclei, as well as in the ventral horn of the medulla.

These receptors act mainly presynaptically their action inhibits the enzyme adenylatociclase and consequently the reduction of the conversion of ATP in cAMP and consequent decrease of PKA with a decrease in phosphorylation of K+ channels and increase of K+ output from presynaptic terminals. Regardless of adenylcyclase, it inhibits N- and P/Q type Voltage-sensitive Ca2+ (CCV) channels and D-type D and M K+ channels; activates G-protein-gated inwardly-rectifying K+ channels (GIRK) and type A7 K+ channels. Thus, CB1 activation generates neuronal hyperpolarization and decreased neurotransmitter release. Hence its potential action as a pain reducer.

CB2 receptors are related to the immune system. Its action activates Gi proteins, inhibiting adenylatocyclase and activating the MAPC cascade. These receptors are in some areas of the CNS especially in the microglia and in postsynaptic locations. There was an increase in the expression of CB2 in certain pathological states of the CNS, namely chronic pain.

Several studies have suggested that the ECS (endocannabinoid system) is centrally and peripherally involved in the processing of pain signals. This finding is corroborated by the evidence that endocannabinoids inhibit, through a retrograde mechanism dependent on the cannabinoid receptor type 1 (CB1R), the release of neurotransmitters controlling nociceptive inputs and that the levels of these lipids are elevated in these regions (such as sensory receptors in the skin, dorsal root ganglia) known to be involved in the transmission and modulation of pain signals (2).

Similarly to exogenous vanilloid compounds, endovanilloids are potential activators of TRPV1 meningeal receptors and, consequently, activators of the trigeminovascular nociceptive complex resulting in CGRP release and increasing meningeal blood flow, which may play a significant role in the pathophysiology of headaches. The results also suggest that prejunctional CB1 receptors may modulate vascular responses (3).

With this, it became necessary to specify and define the cannabinoids in phytocannabinoids, endocannabinoids and synthetic cannabinoids. Thus, phytocannabinoids are those produced by plants of the genus Cannabis, being the main delta-9-THC and CBD, among about 60 cannabinoids found in the resin of the plant. The endocannabinoids are the constituents of the endocannabinoid system, the first discovered were anandamide (arachdonoyl-ethanolamine) and 2AG, with others under study. Among the synthetics, we have nabilone, dronabidol and dexanabinol as agonists and o, rimonabant (Acomplia® suspended in 2008) an antagonist, being the dexanabinol a great promise under study for neuroprotection (4).

Although headaches are a very broad concept, it is necessary to differentiate primary headache, which will be the subject treated here, from neuropathic pain.

Neuropathic pain (ND) is a pain caused by injury or disease in the afferent somatosensory system, which can be caused by infection, diabetes, HIV, phantom limb pain, etc. .. Approximately seven percent of the population has this disease, which can be chronic, and is often disabling.

ND manifests itself through several symptoms, the most common being continuous burning pain, shock sensation and mechanical allodinea. Neurophysiological studies and skin biopsy suggest that burning pain is a reflection of spontaneous activity in afferent nociceptive fibers, while the sensation of shock presumably originated from high-frequency ectopic stimuli, generated indemyelined A β fibers. Já the mechanisms involved in the genesis of mechanical allodynea are not yet fully understood, knowing, however, that innocuous stimuli can cause pain by stimulating sensitized afferent fibers.

Headache is a very prevalent symptom, being considered the second most frequent type of pain in epidemiological studies worldwide. It is also a symptom that has a high cost for patients, families, society and for health services in general, compromising the quality of life of those who suffer from this problem. Primary headaches, including migraine and tension-type headaches, are classified as dysfunctional headaches. It is important to understand why these two disorders cannot be seen as somatic, neuropathic, or visceral pain.

The type of pain of primary headaches could not be classified as NocP or NeuP. Migraine headache is provoked by stimulation of peripheral nociceptors of the trigeminal endings of the meninges innervated by the first branch of the trigeminal at this level. Is it then a nociceptive pain? The great difference between this headache and the classic nociceptive one is that in the latter the stimulation of the nociceptors is made by direct aggression of these by tissue injury and release of local neurotransmitters. In migraine the stimulation of nociceptors is carried out by a neurogenic inflammation provoked by central dysfunction – cortex or specific nuclei of the brainstem. Neurogenic inflammation is provoked by endovascular factors released by local vasodilation, with activation of nociceptors. Vasodilation in the meninges is mainly caused by CGRG, neurokinins and substance P released retrogradely by the trigeminal endings. The great difference between classic nociceptive pain and migraine pain is that in the latter the stimulation of peripheral nociceptors is done by processes initiated in the NS and not in the periphery. Therefore, migraine

pain has been considered dysmodulatory pain, because the processes that originate neurogenic inflammation in the meninges begin in the CNS. Nor could they be classified as neuropathic due to the absence of lesion or specific disease in the CNS or SNP (5)

Experimental and clinical data do suggest a link between dysregulation of this signaling complex and migraine headache. Clinical observations, in particular, show that levels of anandamide (AEA) – one of the two primary endocannabinoid lipids – are reduced in the cerebrospinal fluid and plasma of patients with chronic migraine (CM), and that this reduction is associated with facilitating the conduction of pain in the spinal cord. AEA is produced on demand during inflammatory conditions and exerts most of its effects by acting on the cannabinoid receptor (CB). AEA is rapidly degraded by the enzyme fatty acid amide hydrolase (FAAH) and its levels can be modulated in the peripheral and central nervous system (CNS) by FAAH inhibitors. Inhibition of AEA degradation via FAAH is a promising therapeutic target for migraine pain since it is presumably associated with greater availability of the endocannabinoid, specifically at the site where its formation is stimulated (e.g., trigeminal ganglion and/or meninges), thereby prolonging its action (6)

Fatty acid amide hydrolase (FAAH) is an intracellular serine hydrolase that catalyzes the cleavage of endogenous fatty acid amides, including the anandamide endocannabinoid (AEA). The peripherally restricted FAAH inhibitor URB937, selectively increases AEA levels outside the central nervous system, reduces hyperalgesia and c-Fos expression in the trigeminal caudal nucleus (TNC) and locus coeruleus in an animal model of migraine based on nitroglycerin administration (NTG). (7)

Dietary interventions that increase the supply of omega-3 fatty acid by reducing omega 6 linoleic acid (H3-L6 intervention) reduced headache episodes in CCD carriers. It is admitted that clinical improvement results from changes in the endocannabinoid system, since both are precursors (8)

THC primarily acts as an agonist on the same receptor cell surface as the endocannabinoid anandamide (AEA), cannabinoid receptor 1 (CB1R). Activity after AEACB1R interaction controls many areas involved in migraine pathophysiology, including thalamic pain relays, basal ganglia activity and cerebellar regulation. Simply put, THC allows the correction of the mechanisms associated with migraine through endogenous G-protein coupled receptor (GPCR) signaling. CBD's interactions within the body are more complex than those of THC. Although the effects of THC are largely mediated by CB1R, CBD exhibits a non-appreciable active site affinity for cannabinoid receptors. The action of CBD involves both metabotropic and inotropic effects. CBD's metabotropic effects include balancing excitatory brain signaling by GPR inhibition. The ionotropic effects of CBD include reducing the sodium current by stabilizing the lipid membranes associated with Nav channels.

Chronic migraine (migraine) determines a significant personal, social and economic load and is characterized by headaches present on fifteen or more days per month for at least three months, with at least eight days of migraine headaches each month. It is often associated with excessive use of acute analgesic or anti-migrase medication and this should not be overlooked. Oral topiramate and onabotulin A toxin

injections are the only treatments that have received class A recommendation, while valproate, gabapentin, and tizanidine have received class B recommendation, along with acupuncture, biofeedback, and mindfulness. Anti-CGRP or anti-CGRPr monoclonal antibodies are promising new drugs, already approved in other countries for the prophylactic treatment of migraine, whose efficacy in chronic migraine is yet to be definitively proven (9)

2 METHOD

To conduct an Integrative Review of the articles published in the last 20 years with the use of Cannabinoids in the treatment of migraine headaches.

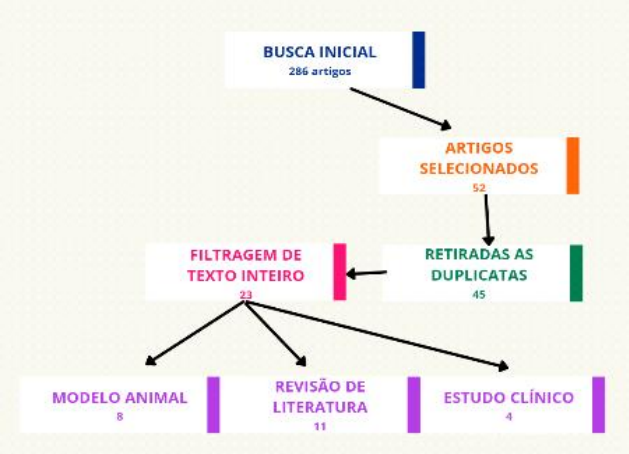
Its main focus is to evaluate the indications and risks for its use.

Bibliographic and cross-sectional research was performed through publications of scientific articles in English, between 2002 and 2022 obtained in electronic media in the database: PubMed (National Center for Biotechnology Information), Cochrane, Lilacs and Scielo. Searching for the following descriptions: "Cannabinoids AND Headache";" Phytocannabinoids AND Headache"; "Cannabidiol AND Headache"; "Cannabinoids AND Migraine"; "Cannabidiol AND Migraine".

In the first search on Pubmed with the terms "Cannabinoids AND headache"; " Cannabidiol AND Headache".

There were 286 results that in manual filtering were reduced to only 23 related to the proposed theme.

The exclusion criteria were:



- Have no relation to the proposed subject.
- Qualis from the journal (B2 or more) and citations.

3 FINDINGS

Of the 286 articles, only 23 were selected through full analysis. Of these, most are based on a literature review.

Of the selected articles, approximately 52% are literature reviews, including meta-analyses, and integrative and systematic reviews. Approximately 35% of experiments with animal models and finally,

17.5% of clinical trials, which makes it impossible to conclude clinically on the subject, requiring further tests.

As for animal studies, Arachidonylethanolamide (Andamine), an endogenous ligand of CB1 and CB2 receptors and with known effects similar to Delta(9)-tetrahydrocannabinol(THC), has been analyzed as having a modulating role in the trigeminovascular system, with blockade of electrical vasodilator action, via CGRP, capsaicin and nitric oxide (NO).(10)

One of the models of induced headache is through NO and Nitroglycerin (NTG), and the modulatory role of andamine in NGT has been analyzed in studies. (11)

In other research, AM1241, a CB2 receptor agonist, was able to reduce NTG-induced headaches in mice. (12,13)

Also in nitroglycerin-induced headache, it has been noted in rats that this is related to the increased activity of fatty acid amine hydrolase (FAAH)(which degrades endocannabinoid andamine), and monoacylglycerol lipase(which degrades the endocannabinoid 2-arachidonoylglycerol) and increased density of CB receptors in the midbrain. In the hypothalamus, it was observed that FAAH was increased as also the density of CB receptors, in the medulla only FAAH had increased activity and rats without FAAH activity had the effects of NTC-induced mechanical alodinea and completely reduced trigeminal activation. (14.15)

As for the administration of THC itself, in TRPA1-induced headache, the injection of 0.32mg/kg after 30 minutes proved to be effective in combating the effects of headache, however, the same dose injected after 90 minutes has already been shown to be ineffective and the dose of 0.1mg/kg at the same time also showed – if ineffective and, finally, administration of CB1 agonists, but not CB2, also appeared to reduce the effects of migraine in rats (10,16,2)

In the review studies, it is concluded that Cannabis has a complex interaction of agonists and antagonists, some of which are partial, and some total, which can thus result in the result obtained clinically, and this is a problem already widely known in herbal medicines because the plants present many compounds, it is very difficult to locate the exact substance and or combination of these that results in the therapeutic effect. In addition, different species or even different intentions have different concentrations of the substances present, making it even more difficult to isolate the effect. (1,17)

Only a minority of the compounds present in cannabis have ever been studied and are understood, but this one, based on case reports, animal model and literature seem to affect multiple diseases particularly chronic pain, such as migraine. This seems to have to interact and modulate migraine pathways, and opioid and triptan pathways and may suggest a similar effect. (6,7,18,19,20)

As the main hypotheses causing headaches we have the activation of the trigeminovascular system and the vasoactive release in the trigeminal extremes, near the meningeal vessels. Among several mechanisms present in these sites, the endocannabinoid system stands out. In clinical observation, a

reduction in andamine, one of the main binding substances to CB receptors, was found in plasma and cerebrospinal fluid in patients with chronic migraine.

Cannabinoids have also demonstrated anti-inflammatory effects, dopamine blockers, and blockage of spine, peripheral, and gastrointestinal pathways that promote pain. (15.16,18,19,20,21,22,23)

In one of the clinical studies, it was observed that: responsive patients (61% n=81) presented, in three years of medical cannabis use, a reduction >50% in the reduction of monthly attacks and their severity, as well as the use of opioids and triptan was also reduced. (24)

In another, the use of oral cannabidiol presented only mild adverse effects and was present in 43.3% of the patients, but although the drug reduced pain in these patients, the effects were modest (25).

In a tertiary clinic for migraine, up to one-third of patients used phytocannabidiol-derived medications, and 25% to 60% perceived significant improvement (26).

Cannabidiol derivatives also have their effect altered concerning sex, age, and symptom, for example, Women have a preference for oil and products with more CBD, while men prefer the form of smoking and prefer products with CBD: THC=1. Products with more THC were consumed by patients with symptoms of pain and sleep, while dominant CBD was more popular among patients younger or who had anxiety and depression. (27)

4 DISCUSSION

Although there are few randomized clinical trials, the four found in this study showed a positive response, with a reduction even of opioids and triptans in patients with promising results.

100% of the literature reviews and animal studies showed evidence that cannabis can, in theory, help in the picture of headaches.

However, the use of herbal medicines becomes complicated due to the great variability of the components present depending on the soil, humidity, sunlight, subspecies of the plant, the difficult location and isolation of the compost or the determination of the effective combination.

Even though there is theoretical speculation, in research on doses, the research in animals of Kasadamy (11), carried out in rats demonstrated a delicate balance between dose and time, with an interval of 60 minutes of difference for the effectiveness and ineffectiveness of the drug and 0.2mg more, so there is a great need for more research on the metabolism of these compounds in humans before speculating their effectiveness.

More tests are needed for this drug, so promising in theory, to serve its numerous patients, who have almost no treatment alternatives.

5 CONCLUSION

Although it is a very pertinent topic, there are not enough articles in the literature for the clinical evaluation of the use of medical cannabis, although the results in an animal model and the data from reviews show favorable evidence for the use, it is not possible to speculate the dose, safety or efficacy of clinical use, and more randomized clinical research in humans is needed.

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