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Cannabinoids for the Treatment of Chronic Headaches

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Abstract
Species of the Cannabis plant genus were among the earliest medicinal plants cultivated by man, with historical accounts of their medicinal uses dating back before the Common Era. Despite its current legal status, Cannabis has garnered nationwide attention as a therapeutic agent for various disease states, including chronic headaches, due to its medical indications as an antispastic, analgesic, antiemetic, neuroprotective and anti-inflammatory agent. Since headaches have a high prevalence in the American population and greatly impair simple daily aspects of living, chronic headaches have become a particular point of interest in regard to the therapeutic potential of Cannabis. Clinical trials and case reports have shown that Cannabis administration for headaches has greatly improved the quality of life and decreased the use of adjuvant medications for some patients. Studies are limited and conflicting, mostly due to the legal issues associated with Cannabis. Pharmacists play a major role in managing patients who are treating their chronic headaches and need to be able to educate patients about Cannabis. Patients may consider trying to treat their headaches with Cannabis even though it has legal restrictions regarding its use and is not U.S. Food and Drug Administration (FDA) approved. Pharmacists should understand federal and state restrictions, drug interactions, potential health risks, psychoactive effects and types of delivery systems for Cannabis use.

Key Terms
Analgesics; Antiemetics; Cannabinoids; Cannabis; Food and Drug Administration (U.S.); Headache; Headache Disorders; Humans; Marijuana Smoking; Pharmacists; Plants, Medicinal; Quality of Life; Review Literature

Introduction and Background

Species of the Cannabis plant genus (e.g., *Cannabis* sativa, *Cannabis* indica) were among the earliest medicinal plants cultivated by humans, with historical accounts of their medicinal and entheogenic uses dating back before the Common Era, primarily in Ancient India and other Asiatic regions.[1] In 1860, the Ohio State Medical Society organized the first conference examining the clinical benefits of Cannabis (also known as marijuana), and by 1870 the United States Pharmacopoeia recognized Cannabis Americana in a separate monograph as a legitimate medical compound with analgesic, sedative and hypnotic potential. Despite revision of the Cannabis monograph in 1880, the United States Pharmacopoeia removed Cannabis, USP in 1941, largely due to various legal restrictions on its agricultural production. Although efforts to elucidate the pharmacologic action and further therapeutic potential of Cannabis were published in the 1950s and 1960s, Cannabis was eventually classified as a schedule I substance under the Controlled Substances Act of 1970, claiming Cannabis as a drug with no accepted medical use and a high potential for abuse.

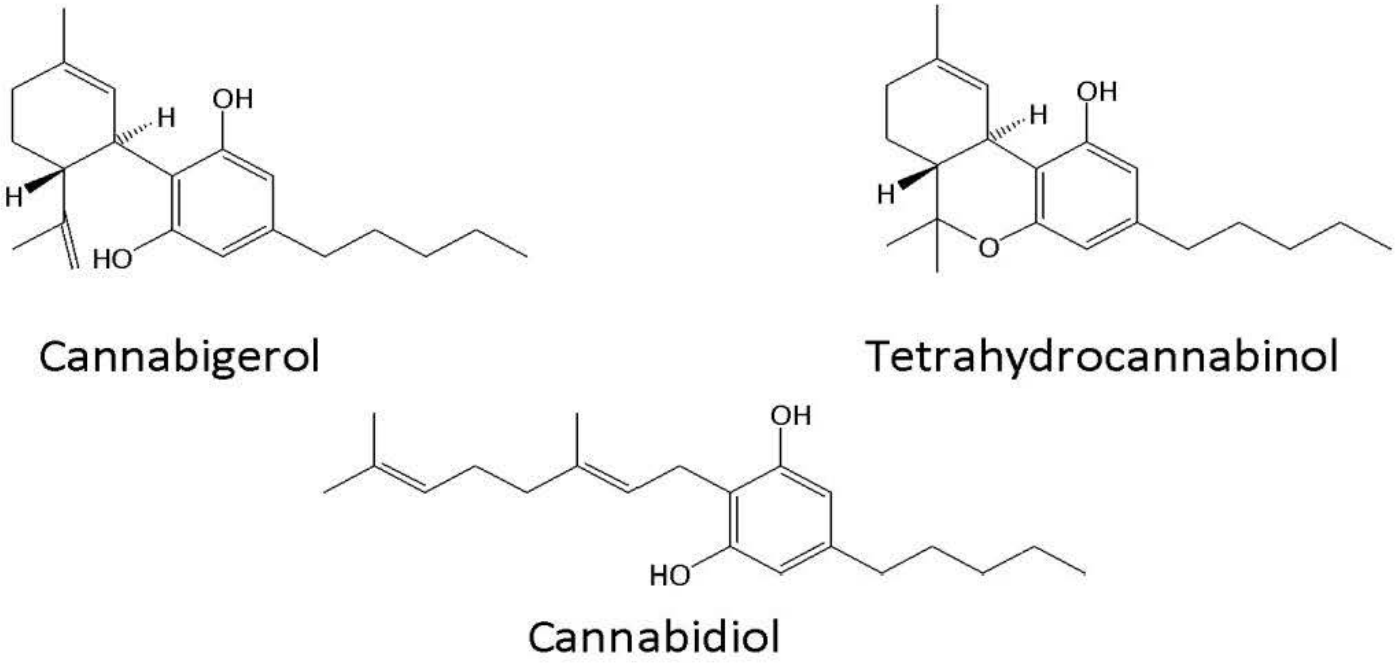
Despite its current legal status, Cannabis has garnered nationwide attention as a potential therapeutic agent. Due to its medical properties as an antispastic, analgesic, antiemetic, neuroprotective and anti-inflammatory agent, it has demonstrated positive effects toward the therapy of various disease states such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), various forms of cancer, multiple sclerosis (MS), chronic neuropathic pain, Parkinson's disease, Tourette's syndrome and certain psychiatric diseases.[2] Currently 20 states and the District of Columbia have enacted laws that allow medical Cannabis use with the recommendation of a physician.[3] Among the various disease states that Cannabis may treat, chronic headaches—headaches lasting more than 15 days a month for three months or longer—have become a particular point of interest with respect to Cannabis therapy.[4] This is primarily due to the high prevalence of chronic headaches in the American population and impairment of simple aspects of daily physical, social and occupational living. In the 21st century, efforts to examine the therapeutic potential of Cannabis in chronic headaches have largely focused on cannabinoids, the pharmacological compounds unique to both the Cannabis genus and endogenous compounds in animal species.

Pharmacology and Medicinal Chemistry of Cannabinoids

The term cannabinoid describes the group of terpenophenolic compounds present both in Cannabis and in the nervous and immune systems of a variety of animal species.[5,6] Cannabinoids are further classified as (a) phytocannabinoids, those which occur uniquely in the Cannabis plant; (b) endocannabinoids, those which are endogenously produced in animal species; and (c) synthetic cannabinoids, those which are chemically synthesized typically in a laboratory setting for the purpose of additional pharmacological studies or eventual marketing as a pharmaceutical preparation. At least 66 cannabinoids have been identified and isolated from the Cannabis plant, most of which differ in cyclization patterns from the terpenophenolic precursor molecule cannabigerol (Figure 1).

Efforts to examine the pharmacologic activity and therapeutic potential of cannabinoids, though limited due to federal legal restrictions, have largely focused on phytocannabinoids, particularly Δ^9-tetrahydrocannabinol (THC) and (-)-cannabidiol (CBD) (Figure 1).[7] Along with other cannabinoids, THC and CBD exert their pharmacologic effects on the endogenous cannabinoid system, or endocannabinoid system, located in human neural tissue and immune cells. The receptors comprising the endocannabinoid system include the cannabinoid receptor type 1 (CB_1 receptor) and the

Figure 1. Cannabigerol, Tetrahydrocannabinol, Cannabidiol.



cannabinoid receptor type 2 (CB_2 receptor). Specifically, CB_1 receptors are densely located in neuron terminals of the basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus and limbic cortex, whereas CB_2 receptors are located chiefly in immune cells. The extensive distribution of CB_1 receptors in the central nervous system renders the CB_1 receptor an attractive target for potential treatment of the neurological symptoms associated with chronic headaches.

Chronic headaches consist of a variety of disorders including cluster headaches, hemicranias continua, idiopathic intracranial hypotension, migraines, tension type headaches and a mixture of various types; however, the exact mechanism of action of chronic headaches is not completely known, and the onset of a chronic headache event may be completely unpredictable by the patient.[8] In the United States, 70 to 80 percent of patients admitted to specialized headache clinics are diagnosed with chronic headaches and report a diminished quality of life due to impaired physical, social and occupational function. Furthermore, over half of chronic headache patients report sleep disturbances, depression and anxiety, which may worsen their symptoms.[4] Research suggests that the physical and neurological symptoms associated with chronic headaches may stem from the inflammation of cranial nerves and blood vessels, changes in cranial blood vessel sizes, cranial muscle tension and irregular changes in the release of neurotransmitters (e.g., serotonin, norepinephrine, dopamine) that regulate pain pathways.[9]

The principal psychoactive component in Cannabis, THC, has demonstrated therapeutic potential to treat and manage mild to moderate pain associated with chronic headaches, primarily due to its action as a partial agonist of the CB_1 receptor.[6,7] According to several small pharmacologic studies, the analgesic effects of THC may stem from its neuroprotective potential. Specifically, THC has demonstrated an ability to modulate rostral ventromedial medulla (RVM) activity, disrupt descending pain pathways and inhibit synthesis of prostaglandin, an endogenous regulator of inflammation associated with chronic headaches.[7] In neural tissue, the action of THC on CB_1 receptors reduces the contractile output and neurotransmitter release in smooth muscle, ultimately producing characteristic analgesic effects.[6] In contrast to the established therapeutic indications of THC, the pharmacologic activity of CBD, a nonpsychotropic component of Cannabis, is not well understood, and there are conflicting views regarding the mechanism of CBD in the endocannabinoid system.[7] Though CBD has no direct affinity for either the CB_1 or CB_2 receptors, several studies have indicated that it may serve as an allosteric antagonist on either cannabinoid receptor, therein reducing the psychoactive effects of THC on CB_1 and CB_2 receptors.[5] By reducing the affinity of THC for CB_1 and CB_2 receptors, CBD may modulate the analgesic effects of THC in neural and immune tissue. Although one of the primary medical delivery systems of phytocannabinoids in humans is by smoking herbs of the Cannabis flower, THC and CBD can also be administered by noncombustive vaporization of Cannabis herbs and oral ingestion of edible products containing Cannabis-infused oils.[7] Upon smoking, THC has an estimated bioavailability of 10 to 25 percent, a distribution phase half-life of 0.5 hours and a terminal phase half-life of 30 hours, primarily due to its extensive lipophilicity. On the other hand, CBD has a similar lipophilic profile but a shorter terminal phase half-life of nine hours. Following pulmonary administration, whether by combustive smoking or vaporization, the analgesic effects useful to providing relief associated with chronic headaches may occur as quickly as 30 seconds to three minutes and typically last for two to three hours.[5]

Current pharmacologic medications indicated for the treatment of chronic headaches include those that mimic serotonin effects (e.g., triptans and dihydroergotamine-45), modulate serotonin levels (e.g., selective serotonin reuptake inhibitors (SSRIs)), reduce inflammation (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids), stabilize blood vessels (e.g., calcium channel blockers and beta blockers) and decrease muscle tension (e.g., muscle relaxants).[9] Despite the historical success of these medications as a maintenance therapy in relieving symptoms associated with chronic headaches, these drugs fail to provide the immediate relief that fits the almost instantaneous and unprecedented onset of a chronic headache event. For example, some drugs, such as beta blockers and SSRIs, may take four to six weeks for any prolonged effect to occur, and other analgesic drugs, such as NSAIDs and corticosteroids, may induce rebound headache events. Furthermore, as single active pharmaceutical compounds, these drugs typically only target one of the many neuropathic features associated with chronic headaches, limiting the possibility of a collective therapeutic approach to all symptoms. Cannabinoids, which provide a relatively fast onset of action, extensive half-life and pharmacologic potential to act on numerous signaling pathways by way of CB_1 receptors, serve as an attractive therapeutic option in treating chronic headaches.

Human Clinical Trials

Clinical data on Cannabis use among chronic headache patients is limited due to the fact that marijuana is classified as a schedule I substance in the United States.[10] Therefore, its use is strictly regulated and still illegal in many states; although some states have legalized the use of medicinal marijuana, it is still illegal on a national level. Another limiting factor is that the exact pathophysiology of headaches is not completely known, and it is likely that multiple different mechanisms can produce headaches. Despite marijuana's illegal status, some patients use it for relief of headache, which is made easier by the increasing number of states that are legalizing medical marijuana. There are no blinded studies on headache subjects from which true efficacy can be assessed. However, many observational case studies and case reports have demonstrated resolution of headache symptoms with administration of Cannabis or dronabinol, the pharmaceutical formulation of THC.

In 2012, Pini et al. published a randomized, double-blind, active-controlled, crossover study regarding medication overuse headache (MOH) in which they evaluated the efficacy and safety of nabilone (a synthetic THC analogue) in reducing pain and frequency of headache.[11] Medication overuse headache is a chronic headache lasting more than 15 days per month that develops from primary headaches (migraine, tension-type headaches) as a result of overuse of a pharmaceutical agent. The authors also evaluated quality of life and analgesic intake in patients with MOH. Thirty MOH patients were enrolled in a study at the University of Modena's Interdepartmental Centre for Research on Headache and Drug Abuse (Italy), which compared safety and efficacy between oral nabilone 0.5mg/day and oral ibuprofen 400mg/day. Patients were given eight weeks of nabilone followed by eight weeks of ibuprofen, or vice versa, with a one week washout period between regimens. At the end of the study, both treatments demonstrated improvements from baseline, but nabilone showed greater efficacy in reducing pain intensity, daily analgesic intake, and medication dependence. Adverse events due to nabilone were uncommon and mild, and included dizziness, decreased appetite, vomiting, nausea, epigastric discomfort and dry mouth. Overall this study demonstrated the potential benefit of nabilone in relieving headache, decreasing analgesic consumption and improving the quality of life while being relatively well tolerated. Due to the small sample size of this study, larger clinical trials are needed to determine the clinical relevance of these findings.

A case cohort report by Leroux et al. about the frequency of Cannabis use in cluster headache patients reported the effects Cannabis had on the headache attacks.[12] From July to October 2009, 139 patients with cluster headaches answered questionnaires in two French headache centers regarding Cannabis use and its effects on cluster headaches. It was reported that 27 patients (19.4%) had tried Cannabis to treat cluster headache attacks, of which 25.9 percent reported some efficacy, 22.3 percent negative (worsening) effects and 51.8 percent variable or uncertain effects. The authors concluded that Cannabis use is relatively frequent in patients with cluster headaches, but it has limited efficacy in treating attacks due to the variable effects observed by patients. Multiple factors may have affected the data collected in the study, such as the variations in amount of Cannabis inhaled and possible differences in the cannabinoids produced in the marijuana plants obtained by patients. Furthermore, the study had a small sample size of 27 patients who had tried Cannabis to treat their headaches, questioning if the power of the study was sufficient to make adequate conclusions. Additionally, collecting information by patient survey introduces many uncontrollable variables, and data that could affect marijuana efficacy was not collected (patient current medications, diet, exercise, genetics, etc.). The authors concluded that a recommendation for use of Cannabis to treat cluster headaches is not justified unless further controlled trials using synthetic cannabinoids demonstrate more convincing evidence for efficacy. This study, although very limited, shows that some patients are using marijuana to self-treat their cluster headaches and that it is beneficial for some patients.

An observational case study by Robbins et al. involved a 19-year-old male patient reporting to the Montefiore Headache Center (New York City) for management of his cluster headaches.[13] When untreated, the patient's headache attacks occurred for about four hours every other day for a two week period followed by a headache-free period of four to six weeks. Prophylactic medications (verapamil, lithium, sodium valproate, melatonin, topiramate, nifedipine, indomethacin, zonisamide, venlafaxine, ergotamine tartrate and clonazepam) were administered with either minimal success or intolerable adverse effects. Treatment for the patient's headaches with sumatriptan tablets, zolmitriptan nasal spray, ergotamine/caffeine, oxycodone, aspirin/butalbital/caffeine, acetamino-

phen/dichlorphenazone/isometheptene and indomethacin were all ineffective as well. However, the patient stated that administration of marijuana by inhalation at the onset of the headache consistently led to complete relief within five minutes. Due to the lack of response to multiple other medications, the patient was given dronabinol 5mg as a replacement for marijuana for acute treatment of the headaches. Dronabinol was found to consistently and dramatically relieve the patient's cluster headaches within five to 15 minutes of administration. The authors noted that the relief from headaches was probably not due to a placebo effect due to the large number of agents used that failed to prevent or treat the patient's headaches. However, other patients suffering from cluster headaches have reported that marijuana use can trigger cluster headaches or worsen a current headache. This case study shows that marijuana may have chemical components that could be effective in the treatment of headaches, especially those refractive to other medications, but it must be used with caution because it has also been shown to trigger headache attacks in some patients.

Role of the Pharmacist

Due to the prevalence of chronic headaches in the United States and the growing interest in Cannabis as a viable medicinal agent, patients suffering from chronic headaches may be interested in cannabinoids as agents for improving their headaches. Important features of cannabinoids include the ability of phytocannabinoids to be administered through rapidly-acting delivery systems, such as inhalation, and to provide a steady, collective relief from many of the neuropathic features of chronic headaches. These benefits may lead patients to consider the use of cannabinoids as a replacement to their current pharmacologic therapies. However, due to the controversial legality of Cannabis, as well as its concerning psychoactive effects, many patients may consult health care providers such as pharmacists for guidance. Pharmacists should have a good understanding of the potential benefits of cannabinoid treatment for chronic headaches as demonstrated through clinical studies and case reports, and they should also be mindful of federal and state restrictions on Cannabis use. As Cannabis remains a schedule I substance in the United States and has no federally-recognized accepted medical uses, it is important that the pharmacist not actually recommend use of Cannabis, but rather explain that several studies have demonstrated potential therapeutic benefits associated with the treatment of chronic headaches for some patients. Not recommending these agents avoids any legal consequences, but more importantly educates the public that compounds in Cannabis may be beneficial to treating treatment-resistant headaches and can greatly impact the quality of life of some patients. Some cannabinoids may also be useful for treating chemotherapy-related nausea and vomiting that has not been alleviated by conventional treatments.

Additional counseling points about cannabinoids should include cautioning patients about the possible health risks. These include lung or respiratory infections, chronic cough, heart attack, psychosis and depression relating to certain delivery systems for administering Cannabis (e.g., smoking); potentially unwanted psychoactive effects that may lead to cognitive impairment in daily social and occupational functioning, including hallucinations, paranoia, anhedonia, dizziness, driving impairment, decreased appetite, vomiting, nausea and asthenia; and legal and occupational consequences associated with drug use in the workplace.[14] Pharmacists should also be aware of drug interactions of Cannabis or its components in case patients admit that they are using Cannabis or are prescribed a cannabinoid. Major drug interactions include propoxyphene, buprenorphine, levomethadyl acetate, sodium oxybate, alcohol and drugs causing central nervous system depression.[15]

Conclusion

Many patients in the United States who suffer from chronic headaches seek treatment because of the debilitating effects of headaches in physical, social and occupational functioning. Headache relief has been documented with administration of Cannabis or its extracted ingredients in several case studies and case reports; therefore Cannabis and its respective cannabinoids are worth studying despite strict and conflicting legal restrictions in the United States. One major problem with Cannabis use in the treatment of headaches is that although activation of cannabinoid receptors may induce pharmacologic effects that provide headache relief in some patients, it may not provide relief in all patients, since the mechanisms of chronic headaches are highly complex and different among individual cases. Despite these challenges, cannabinoids may still provide a more desired immediate relief and an ability to treat multiple symptoms at once beyond the scope of conventional pharmaceutical treatments that may only exhibit a limited number of pharmacologic effects. Pharmacists play an important role in educating patients regarding the potential efficacy and safety of Cannabis use in treating chronic headaches; however, additional studies are required to establish long-term safety and efficacy.

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