

Cannabinoids for Headache

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Headache. 2013;53(3):447-458.

Cannabis

Historical Aspects

Cannabis was probably the first crop grown for reasons other than food and is found in the ancient writings of Galen and Hippocrates, who both prescribed cannabis.^[1,2] Chinese writings from the first 2 centuries AD refer to Emperor Shen Nuang in the third millennium BC using cannabis medicinally, the first medical use of cannabis.^[3] In India in the fourth and third centuries BC, Ayurvedic mixtures called *Rasachandrika vati* and *Mahalakshmvilasa rasa*, which contained cannabis, were used for neuralgic headaches and hemicranias.^[4] The cannabis family of plants has long been known for industrial uses, notably hemp, which has an ultralow amount of cannabinoids and no psychoactive effects compared with marijuana. East Asian and European societies used cannabis mostly for its strong fibers and the nutrient value of the seeds. Hemp fabrics were routinely used for clothing, canvas, rope, and even high-quality paper. South and South-East Asian cultures along with Middle Eastern and African cultures used cannabis primarily for its psychoactive effects and less so for manufacture and food. Legal issues with the psychoactive cannabinoids along with efforts by industrial competitors have retarded the growth of hemp industrial products in the United States.

The 12th century German mystic, abbess, philosopher, and herbalist Hildegard von Bingen, known for her vivid visual perceptions (interpreted as religious experience but were highly likely migraine aura) also wrote about cannabis. She stated in *Physica* "Whoever has an empty brain and head pains may eat it and the head pains will be reduced. Though he who is healthy and full of brains shall not be harmed by it." An Arabian physician, Abu Mansur Muwaffak (950 AD), writing in Persia noted that hemp used for rope making could produce headache, although this translation is disputed.^[5]

The introduction of medical marijuana into Western medicine is credited to the Irish-born physician and scientist W.B. O'Shaughnessy, who graduated from the University of Edinburgh and was a professor of chemistry at the Medical College of Calcutta. His 1839 paper reviewed Indian hemp (marijuana), which he found to be an effective analgesic and a muscle relaxant among other actions. He shared these observations with physicians on a return trip to England in 1842.^[6] This treatise did not however refer to the treatment of headache with hemp but instead discussed the treatment of tetanus, rabies, and cholera in particular, including analgesic effects. O'Shaughnessy made many contributions to science and was knighted by Queen Victoria for the introduction of the telegraph to India. Dr. Clendinning, a physician at St. Marylebone Infirmary in London, was one of the first Western physicians to treat migraine with cannabis (1840s).^[7] By 1854, cannabis was listed in the United States Dispensatory as a powerful "narcotic." Dr. Greene espoused daily doses of cannabis for the prophylactic treatment of migraine.^[8] Interestingly, he wrote of an incomplete response on a patient who would not give up daily tea and coffee ingestion, referring to those beverages as "these

wretched stimulants." This represents a very early recognition of possible caffeine overuse and daily headache.

Another influential physician of the time was Sir John Russell Reynolds, president of the British Medical Association and physician to the royal household. His 1890 *Lancet* paper reviewed 30 years of personal experience, advocating for a legitimate medical use for marijuana stating "Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess."^[9] He treated migraine, neuralgia, cramps, and dysmenorrhea with marijuana. Reynolds said of migraine "Very many victims of this malady have for years kept their suffering in abeyance by taking hemp at the moment of threatening, or onset of the attack." He acknowledged that it was not useful for all afflictions and described Indian hemp as "worse than useless" in the treatment of mania. Of particular note, in 1890, there was a commercial product in Germany for migraine called *Migranin*, containing 1% cannabis, as described by Fankhauser.^[10] Around the same time, Mackenzie published an article in the *British Medical Journal* on the treatment of "a certain type of headache" (which by description was chronic daily headache or chronic migraine) with gradually increasing doses of marijuana twice daily, one of the first descriptions of daily headache treated with marijuana.^[11] Apart from oral administration, marijuana was also given by suppository, described by Farlow as having "few equals in its power over nervous headaches."^[12] There was recognition that failure of treatment was often due to inferior preparations, likely reflecting extremely variable amounts of active cannabinoids, and in addition, popularity suffered from unreliable sources of supply as it does to this day.

It is well known that Sir William Osler advocated for the use of cannabis to treat migraine in his medical textbook *The Principles and Practice of Medicine* – "Cannabis indica is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug."^[13] His support for cannabis provided continued impetus for the use in both acute treatment and prophylaxis of migraine in the early 1900s. Osler was referring to E.C. Seguin, a well-known neurologist and president of the New York Neurological Society who was a vocal proponent of cannabis for migraine. As the tide turned against the use of cannabis, Bragman wrote "The weed of insanity" in 1925 and still conceded "It has some value in the relief of migraine."^[14] Walton in his 1938 book notes frequent mild headache after moderate doses of marijuana, likely a withdrawal headache.^[15]

In the early 1900s, marijuana use was heavily associated with the low income and minority community. There was a campaign by the Federal Bureau of Narcotics, under the direction of Harry Anslinger, attempting to attribute violent crimes, psychosis, mental deterioration, and addiction to marijuana use in the 1930s. The film "Reefer Madness" is a good example of this fear mongering (reefer refers to a marijuana cigarette). This movement resulted in the *Marihuana Tax Act of 1937*, forcing anyone using the cannabis plant for industrial or medical use to pay a heavy tax; those failing to comply were subject to large fines and prison.^[9] In effect, this law made the use of cannabis as a medication very difficult. The legal status and political biases dramatically inhibited clinical research into cannabinoids. These changes were strongly opposed by the American Medical Association.^[15] Cannabis preparations were taken out of the *United States Pharmacopoeia* and *National Formulary* in 1941 as marijuana became looked upon as a drug of abuse. In Britain, cannabis became prohibited in 1925 but remained available in pharmacies for psychiatric indications until 1971.^[16] Grinspoon

and Bakalar's 1993 book *Marihuana: The Forbidden Medicine* outlines the medical benefits of cannabis, including a section on migraine.^[17] Two years later, both authors published "Marihuana as Medicine: A Plea for Reconsideration" in the *Journal of the American Medical Association*.^[18]

Cannabinoid Biology

The endogenous cannabinoid signaling system in mammals is comprised of several components, including the cannabinoid receptors CB1 and CB2, endogenous ligands (naturally occurring cannabinoids) such as anandamide (AEA), and the enzymes involved with production and inactivation of these ligands.^[19] Cannabinoid receptors occur throughout the vertebrates – hence are evolutionarily extremely old. Genes for such a receptor are found in the deuterostomian invertebrate *Ciona intestinalis* (transparent sea squirt), but not in protostomian invertebrates (eg, *Drosophila*).^[20] Hence it is likely that cannabinoid receptors developed first in deuterostomian invertebrates roughly 500 million years ago. On the plant side, the ancestors of cannabis originated in Asia, in the Altai Mountains or possibly on the gentle slopes of the Himalayas only about 50,000 years ago. The evolutionary pressure may be as a protection against ultraviolet B radiation.^[21, 22]

The most important endocannabinoid is AEA, which acts as a modulator of both neurotransmitter release and synaptic transmission, acting mainly presynaptically. AEA was named after the Sanskrit word *ananda* meaning "supreme joy." In contrast to most neurotransmitters, AEA is synthesized when it is needed, by the enzymatic cleavage of a phospholipid precursor in the cell membrane and is not stored in vesicles. In addition, endocannabinoid duration of action is very short, being removed by a membrane transport mechanism that is poorly understood, contrasting with tetrahydrocannabinol (THC), which is metabolized over several hours.^[23] 2-arachidonoylglycerol (2-AG) is another identified endocannabinoid; both AEA and 2-AG are closely related to arachidonic acid. Endocannabinoids are able to influence many regulatory systems such as sleep/wake cycles, appetite, nociception, memory, thermogenesis, and movement.^[24] Cannabinoid receptors are divided into type-1 (CB1) and type-2 (CB2), CB1 predominating in the nervous system. Both CB1 and CB2 receptors are members of the family of G-protein-coupled receptors. Originally, CB1 receptors were thought to be found exclusively in the central nervous system, but now they have been identified in numerous other organs. Within the nervous system, CB1 receptors are found presynaptically, facilitating inhibition of neurotransmitter release. Formerly, CB2 receptors were only described on immune cells, but there is now evidence for their expression on primary sensory neurons.^[25] Activation of CB2 receptors alone does not cause psychoactive effects but has anti-inflammatory actions, contributing to local analgesic effects.

Cannabinoid receptors are located widely throughout the brain, including multiple areas of the cortex (frontal lobe, somatosensory cortex, entorhinal cortex, and olfactory cortex), basal ganglia, hippocampus, amygdala, cerebellum, substantia nigra, periaqueductal gray matter, and in the substantia gelatinosa of the spinal cord. The cardiopulmonary centers in the brainstem are only sparsely populated with CB1 receptors, hence the lack of respiratory depression with cannabinoids. CB1 receptors are 10 times more frequent than mu-opioid receptors in the brain. Cannabinoid receptors also co-localize with opioid receptors and augment the analgesic effects of opioids,

likely by pharmacodynamic mechanisms. In clinical studies, levels of morphine and oxycodone were not affected by the addition of marijuana.^[26] Agonists at the CB1 receptor have been shown to cause dopamine release in the nucleus accumbens, which is likely helpful in painful disorders like headache.^[27] However, dopamine release in the mesolimbic dopamine system (as with cannabinoids) is also characteristically seen in drugs of abuse.^[28] Furthermore, CB1 activation is involved in the modulation of pain by inhibiting the release of the neurotransmitters gamma-aminobutyric acid (GABA), glutamate, acetylcholine, and noradrenaline.^[29]

Cannabinoids have also been demonstrated to act as neuroprotective anti-oxidants against glutamate toxicity and cell death. This may not all be a CB1-mediated effect. The neuroprotective anti-oxidant effect may be of benefit in situations of cerebral ischemia that might rarely occur with migraine.^[30] The anti-inflammatory effect of cannabinoids has been studied and is likely related to the inhibition of the conversion of arachidonic acid by cyclooxygenase.^[31] In addition, CB2 receptor activation induces immunosuppression and also reduces inflammation.^[32]

Marijuana, Cannabinoids, and Headache

Use of marijuana has long been known to cause an increase in relaxation and euphoria along with, at times, memory impairment. Marijuana can be associated paradoxically with anxiety and dysphoria in some people and this relates to a biphasic effect of cannabinoids.^[32] The reduction in anxiety is likely beneficial in the headache patient. The adverse effect on working memory is presumably due to a very high density of CB1 receptors in the hippocampus. Marijuana is known to contain over 60 cannabinoids, which made early isolation of THC, thought to be the only mood-altering constituent, more difficult.^[33] THC was isolated in 1964. Cannabidiol, another plant cannabinoid, has been shown to have potent anti-inflammatory effects among other actions and this could theoretically be important in reducing headache.^[34]

Three main species of cannabis have been documented, *sativa*, *indica*, and *ruderalis*, with *sativa* containing the most THC and *ruderalis* the least.^[35] It was Linnaeus who named Indian hemp *Cannabis sativa*. The cannabinoid content differs tremendously in the different varieties of the cannabis plant.^[32] The ratio of lethal dose to psychoactive dose is about 40,000 from early animal studies and this contrasts with a ratio for alcohol of about 10. Cannabinoids have been found to exert a mild to moderate analgesic effect in a variety of different pain conditions such as multiple sclerosis-related pain, HIV-associated neuropathy, and cancer pain, but clinical experimental evidence on headache is lacking.^[2]

The role of the endocannabinoid system in migraine, although not clear, has been explored. Reduced levels of AEA have been found in the cerebrospinal fluid of patients with chronic migraine.^[36] One may hypothesize that reduced inhibition from AEA leads to greater activation of the trigeminovascular system and greater propensity to migraine and longer term sensitization. It is not known whether other head pain conditions are associated also with lower AEA levels. Hence deficiency of endocannabinoids has been hypothesized to be critical in the pathophysiology of migraine and also other pain disorders.^[37] The human gene encoding for the CB1 receptor, *cnr1*, has been mapped to chromosome 6 in a region that shows linkage with migraine.^[38] Variations in the *cnr1* gene have recently been associated with a greater risk of migraine.^[39] Also, platelets of

female migraineurs, but not male, exhibit an increased activity of AEA hydrolase, suggesting accelerated endocannabinoid degradation.^[40] It has also recently been demonstrated with positron emission tomography radioligands (in vivo) that female migraine subjects exhibit increased CB1 receptor binding compared with those without migraine, although it is not clear whether this is due to migraine or medication use.^[41] Cannabinoids have also been shown to block release of serotonin from platelets of subjects during a migraine attack.^[42]

The brainstem is heavily populated with CB1 receptors and descending modulation of trigeminovascular nociceptive transmission through midbrain nuclei (periaqueductal gray and rostroventral medulla) is likely responsible for the quick antinociceptive effect on headache, as is often voiced by marijuana users.^[43] That said, CB1 receptors are also located on trigeminal ganglia, so it is possible that the clinical effect is due in part at least, to a more peripheral action. Akerman and colleagues demonstrated that AEA was able to inhibit dural blood vessel dilation from electrical stimulation, administration of calcitonin gene-related peptide, nitrous oxide, and capsaicin. This effect was reversed by a cannabinoid antagonist.^[44] Cannabinoids have been shown experimentally to reduce nitroglycerin (NTG)-induced c-Fos expression (indirect marker of neuronal activity) in a wide variety of cerebral nuclei (in the rat), including the nucleus trigeminalis caudalis, an area involved in the generation of migraine pain.^[45] Cannabinoids have also been shown reduce NTG-induced c-Fos expression in the area postrema of the medulla, which is an important autonomic regulatory center for vomiting, hence important in migraine.^[45]

The study of cannabinoids for pain only started in the early 1970s and there are no blinded studies on the use of cannabinoids for headache.^[2] Patient self-report surveys on marijuana have been positive for a variety of symptoms including headache.^[46] El-Mallakh described 3 long-term daily marijuana users who developed headache after cessation of marijuana, matching clinical experience of headache being a symptom of withdrawal.^[47] Robbins and colleagues describe a man with cluster headache who was able to abort an attack in 5 minutes with marijuana inhalation.^[48] However, the author has spoken to many cluster headache sufferers who state that marijuana use can trigger cluster headache, making things worse. Surveys on 2480 patients of the Oakland Cannabis Buyer's Club by Mikuriya indicate 5% used cannabis for relief of migraine.^[49]

Daily use of marijuana has been reported to trigger the rare and potentially serious condition of reversible cerebral vasoconstriction syndrome (RCVS) which is prominently associated with headache.^[50] In such cases, it is not uncommon for an additional risk factor such as the daily use of selective serotonin re-uptake inhibitors. When a diagnosis of RCVS is made, all possible triggers should be stopped immediately.

Cannabinoid Preparations

While smoking marijuana is popular, it can also be taken orally, advisable with some first-time users. The slow and variable gastrointestinal absorption can make oral ingestion less desirable and this applies equally to dronabinol, the synthetic THC. Dronabinol (taken orally) is available on prescription and has US Food and Drug Administration (FDA)-approved indications for anorexia, with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in those who

have failed to respond to conventional anti-emetic treatments. Dronabinol preparation has more intoxicating metabolites and does not contain other cannabinoids such as cannabidol which has analgesic activity; hence dronabinol overall has not been a great choice for migraineurs. The use of medical marijuana necessitates adequate monitoring for adverse effects and the prevention of addiction. Nabiximols is another pharmacological option now available in the United Kingdom for spasticity in multiple sclerosis, sold under the trade name Sativex. This preparation is really a tincture of cannabis, being made from cannabis plants rather than purely a synthetic process. In doing so, it contains other cannabinoids besides THC and more typically reflects the cannabis plant. This product is undergoing clinical trials in the United States for cancer pain. When inhaling marijuana, using a vaporizer is also popular and avoids the potentially carcinogenic and toxic by-products of burning. Cannabis is heated to 180°-190°C (356–374 degrees Fahrenheit), where vapors form but below the point of combustion. In addition, vaporization delivers higher doses of THC to the lungs compared with smoking. In recent years, a variety of "herbal" preparations that are now illegal has been sold on the black market under the genericized names "K2" and "Spice." These products contain synthetic agents that have CB1 agonist activity, such as cannabicyclohexanol. This group of psychoactive designer drugs is also known as synthetic cannabis, the active ingredients of which have only been poorly studied and should not be used for headache relief.

Conclusions

Cannabinoids enjoyed considerable prominence in the early medical pharmacopeia, advocated by top physicians of the time, and continue to be used by patients for relief of headache generally without physician recommendation. There is much anecdotal support and experimental evidence for this use but no good clinical trials for headache. The actions of cannabinoids, including the analgesic activity on the trigeminal nucleus caudalis, presynaptic inhibition of glutamate release, an anti-inflammatory effect, anti-emetic effect, and vasoconstrictive effect appear to make cannabinoids a good migraine treatment, albeit with health concerns in connection with smoking and overuse. Progressive state legislature support for medical marijuana is making this option somewhat easier for health care professionals, but remains federally prohibited. The future may bring therapeutic options based on these treatments, with new research and clinical study.

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