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Review Article

Cannabis for migraine treatment: the once and future prescription? An historical and scientific review

Ethan Russo*

Department of Neurology, Western Montana Clinic, 515 West Front Street, Missoula, MT 58907-7609, USA

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Abstract

Cannabis, or marijuana, has been used for centuries for both symptomatic and prophylactic treatment of migraine. It was highly esteemed as a headache remedy by the most prominent physicians of the age between 1874 and 1942, remaining part of the Western pharmacopoeia for this indication even into the mid-twentieth century. Current ethnobotanical and anecdotal references continue to refer to its efficacy for this malady, while biochemical studies of THC and anandamide have provided a scientific basis for such treatment. The author believes that controlled clinical trials of *Cannabis* in acute migraine treatment are warranted. © 1998 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Migraine; Headache; *Cannabis*; Marijuana; Dronabinol; Ethnobotany

1. Introduction

One of the basic tenets of medical history is that remedies fall in and out of favor. Once supplanted, most pharmaceuticals fail to re-attain a position of prominence. Very few are popular for many decades.

Not many physicians today are aware of the prominence that *Cannabis* drugs once held in medical practice. Problems with quality control and an association with perceived dangerous effects sounded the death knell for *Cannabis* as a recognized Western therapy. Other medicines that are far more potentially damaging than *Cannabis* remain in our pharmocopeias because of recognized medical indications: opiates for pain control, amphetamines for narcolepsy and attention deficit hyperactivity disorder, etc. Thalidomide, which was banned due to its role in birth defects, may be effecting a therapeutic revival. Even the lowly leech is once again the object of serious medical investigation.

This study will examine the history of *Cannabis* use for one indication, that of headache treatment, its scientific rationale, and possible future as an alternative therapeutic agent.

2. Historical and ethnobotanical usage of Cannabis in migraine treatment

Headaches have likely afflicted man throughout history. Archeological records substantiate an ancient association between man and the plant genus *Cannabis*, plant family, Cannabaceae. Its botanical origin has been debated to be as far east as China, but most experts suspect it to be in Central Asia, possibly in the Pamir Plains (Camp, 1936). Some botanists have maintained *Cannabis* as monotypic genus, while others (Schultes et al., 1974) have provided convincing documentation of three *Cannabis* species: *sativa*, *indica*, and *ruderalis*. All contain the psychoactive chemical delta-9-tetrahydrocannabinol (THC) in varying degree.

Use of *Cannabis* fibers to make hemp has been documented as early as 4000 BC by Carbon-14 dating (Li, 1974), and that use has been maintained continuously up to the present day. Its seed grain was an ancient human foodstuff, which may have lead to an early recognition of its medicinal use. The first records of the latter seem to be in the *Pên-tsao*

* Tel.: +1 406 3297238; fax: +1 406 3297453;
e-mail: ptm5739@montana.com

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Ching, a traditional herbal written down in the first two centuries AD, but said to be based on the oral traditions passed down from the Emperor Shên-nung in the third millenium BC. The text noted that the plant fruits 'if taken in excess will produce hallucinations' (literally 'seeing devils') (Li, 1974).

The *Zend-Avesta*, the holy book of Zoroastrianism, which survives only in fragments, dating from around 600 BC in Persia, alludes to the use of *Banga* in a medical context, and it is identified as hemp by the translator (Darmsteter, 1895).

The classical Greek literature also documents knowledge of the inebriating actions of *Cannabis*. Herodotus, circa 450 BC, described how the Scythians set up tents, heated stones and threw *Cannabis* seeds or flowering tops upon them to create a vapor, and 'the Scythians, delighted, shout for joy'. The Greek physicians Dioscorides and Galen expounded on medical indications, mainly gastrointestinal (Brunner, 1977).

The *Atharva Veda* of India, dated to between 1400 and 2000 BC referred to a sacred grass, *bhang*, and medicinal references to *Cannabis* were cited by Susrata in the sixth to seventh centuries AD (Chopra and Chopra, 1957) and included indication for its use for headache (Dwarakanath, 1965).

O'Shaughnessy introduced the medical use of *Cannabis indica*, or 'Indian hemp', to the West in 1839 (Walton, 1938; Mikuriya, 1973). His treatise on the subject supported the utility of an extract in patients suffering from rabies, cholera, tetanus, and infantile convulsions.

Throughout the latter half of the nineteenth century, many prominent physicians in Europe and North America advocated the use of extracts of *Cannabis indica* for the symptomatic and preventive treatment of headache. Proponents included Weir Mitchell in 1874, E.J. Waring in 1874, Hobart Hare in 1887, Sir William Gowers in 1888, J.R. Reynolds in 1890, J.B. Mattison in 1891, and others (Walton, 1938; Mikuriya, 1973). *Cannabis* was included in the mainstream pharmacopeias in Britain and America for this indication.

As late as 1915, Sir William Osler, the acknowledged father of modern medicine, stated of migraine treatment (Osler and McCrae, 1915), '*Cannabis indica* is probably the most satisfactory remedy. Seguin recommends a prolonged course'. This statement supports its use for both acute and prophylactic treatment of migraine.

In 1916, in a quotation attributed to Dr. Dixon, Professor of Pharmacology, Kings' College, and the University of Cambridge (Ratnam, 1916), reference is specifically made to the therapeutic effects of smoked *Cannabis* for headache treatment. He stated, 'In cases where immediate effect is desired, the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, feelings of fatigue disappear and the subject is able to continue his work refreshed and soothed'.

In the years that followed, *Cannabis* came to be perceived as a drug of abuse, smoked by certain classes of people as 'marijuana' or 'marihuana'. Nevertheless, it retained adherents for a variety of medical indications, throughout the early decades of the twentieth century. In 1938 Robert Walton published a comprehensive review of *Cannabis*, with botanical, historical, chemical and political discussions (Walton, 1938). After discussing the abuse issue, he stated his belief that the political action that had rendered marijuana illegal in the USA in 1937 (and which the American Medical Association vigorously opposed), should not serve to prohibit further medical use and scientific investigation of *Cannabis*' possible applications. Walton referred to 12 major authorities on its efficacy for migraine, and only one detractor.

In 1941, *Cannabis* preparations were dropped from the United States Pharmacopeia (U.S.P.), but the following year, the editor of the *Journal of the American Medical Association* still advocated oral preparations of *Cannabis* in treatment of menstrual (catamenial) migraine (Fishbein, 1942). This practitioner seemed to prefer *Cannabis* to ergotamine tartrate, which remains in the migraine armamentarium, some 55 years later.

Thus, *Cannabis* was touted in eight consecutive decades in the mainstream Western medical literature as a, or the, primary treatment for migraine.

As late as 1957, despite governmental controls in that country, *Cannabis* drugs retained a role in the indigenous medicine of India (Chopra and Chopra, 1957), and other countries.

In the 1960s marijuana moved to center stage of Western consciousness, and attained a degree of notoriety sufficient to render medical usage inconceivable to most. Medical research has resumed only recently, spurred on by anecdotal reports of patients who serendipitously discovered its benefits on their maladies.

3. Modern research developments on Cannabis

In 1974, the first of several studies appeared examining issues of pain relief with Cannabis (Noyes and Baram, 1974). This article examined five case studies of patients who volitionally experimented with the substance to treat painful conditions. Three had chronic headaches, and found relief by smoking *Cannabis* that was comparable, or superior to ergotamine tartrate and aspirin.

One subsequent study of *Cannabis* pertained to pain tolerance in an experimental protocol (Milstein et al., 1975). A statistically significant increase in pain threshold was observed after smoking *Cannabis* in both naive (8% increase) and experienced subjects (16% increase).

Another trial involved oral THC in cancer patients (Noyes et al., 1975a). They observed a trend toward pain relief with escalating doses significant to the $P < 0.001$ level. The peak effect occurred at three hours with doses of 10 and 15 mg, but not until 5 h after ingestion of 20 mg.

Subsequently, the analgesic effect of THC was compared to codeine (Noyes et al., 1975b). In essence, 10 mg of oral THC vs. 60 mg of codeine, and 20 mg of THC vs. 120 mg of codeine relieved the subjective pain burden of patients by similar decrements. The effects of 10 mg of THC were well tolerated, but at 20 mg, sedation and psychic disturbances bothered many of the elderly *Cannabis*-naive subjects.

In the 1980s more comprehensive data on pharmacological effects of *Cannabis* and its derivative, THC became available. In 1983, research with varying potencies of smoked *Cannabis* demonstrated some correlation between serum THC levels and subjective 'high' (Chiang and Barnett, 1984). Additionally, experimental subjects were able to distinguish the potency of the various samples with accuracy.

In a forensic review (Mason et al., 1985), the issue of marijuana's effect on driving was addressed, and it was indicated that isolated reports of adverse outcomes secondary to impairment by *Cannabis* as a sole inebriant were rare. The authors concluded that there was no suitable correlation between plasma or blood levels of THC and the degree of apparent impairment a human might exhibit.

In 1986 the journal *Pharmacological Reviews* devoted an entire issue to *Cannabis* and cannabinoids. In ''Cellular Effects of Cannabinoids'' (Martin, 1986), the author noted their analgesic properties, but reported that the mode of action was not blocked by naloxone, and seemed to work independently of opioid mechanisms.

Another article examined pharmacokinetics (Agurell et al., 1986). Many facets were presented, including their findings that smoking a standard marijuana cigarette destroyed 30% of available THC.

The final article of the issue was entitled ''Health Aspects of Cannabis'' (Hollister, 1986). Pertinent points made included dose delivery efficiency of THC by inhalation of 10% in marijuana-naive vs. 23% in experience smokers. Oral bioavailability for THC was only about 6%, and onset of effects was not seen for 30–120 min.

Smoking of massive *Cannabis* doses daily for a prolonged period produced lower intraocular pressure, serum testosterone levels, and airway narrowing, but no chromosomal aberrations, or impairment of immune responses were noted (Cohen, 1976).

Other 'marijuana myths' were unsupported by careful review of the literature. While aggravation of pre-existing psychotic conditions by marijuana use was documented, no cause and effect relationship was noted. Similarly, chronic use studies in Jamaica (Comitas, 1976), revealed no deficits in worker motivation or production. Two studies of brain computerized tomography (CT scan) refuted prior claims of heavy use producing cerebral atrophy (Co et al., 1977; Kuehnle et al., 1977).

With respect to behavior, Hollister refuted the tenet that depicted *Cannabis* as a contributor to violent and aggressive behavior. Concerning addiction, he noted minimal withdrawal symptoms of nausea, vomiting, diarrhea, and tremors in some experimental subjects after very heavy chronic usage. Such effects were brief and self-limited.

The next year, an article entitled 'Marijuana and Migraine' (El-Mallakh, 1987), presented three cases in which abrupt cessation of frequent, prolonged, daily marijuana smoking were followed by migraine attacks. One patient noted subsequent remission of headaches with episodic marijuana use, while conventional drugs successfully treated the others. The author hypothesized that THC's peripheral vasoconstrictive actions in rats, or its action to minimize serotonin release from the platelets of human migraineurs (Volfe et al., 1985), might explain its actions.

In 1988 action was initiated through the DEA to reclassify marijuana to Schedule 2, potentially making it available for prescription to patients. The DEA administrative law judge, Francis Young, reviewed a tremendous amount of testimony from patients, scientists, and politicians in rendering his ruling (Young, 1988). Although a medical indication of marijuana for migraine was not considered, its use was approved as an anti-emetic, an anti-spasticity drug in multiple sclerosis and paraplegia, while its utilization in glaucoma was considered reasonable. He stated, 'By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care'.

In 1992, a study examined subjective preferences of experimental subjects smoking *Cannabis*, or ingesting oral THC (Chait and Zacny, 1992). Ten subjects in two trials preferred smoking active *Cannabis* over placebo, while 10 of 11 preferred oral THC to placebo. These results call into serious question the plausibility of true blinding with placebo preparations in prospective therapeutic drug studies of marijuana, especially when smoked.

A more profound understanding of *Cannabis*, THC, and their actions in the brain has occurred with the discovery of an endogenous cannabinoid in the human brain, arachidonylethanolamide, named anandamide, from the Sanskrit word *ananda*, or 'bliss' (Devane et al., 1992). This ligand inhibits cyclic AMP in its target cells, which are widespread throughout the brain, but demonstrate a predilection for areas involved with nociception (Herkenham, 1993). The exact physiological role of anandamide is unclear, but preliminary tests of its behavioral effects reveal actions similar to those of THC (Fride and Mechoulam, 1993).

Additional research sheds light on possible mechanisms of therapeutic action of the cannabinoids on migraine. An inhibitory effect of anandamide and other cannabinoid agonists on rat serotonin type 3 ($5\text{-}HT_3$) receptors was demonstrated (Fan, 1995). This receptor has been implicated as a mediator of emetic and pain responses. In 1996, a study in rats demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray matter (Lichtman et al., 1996). The PAG has been frequently cited as a likely anatomic area for migraine generation (Goadsby and Gundlach, 1991).

The understanding that *Cannabis* and THC effect their actions through natural cerebral biochemical processes has

intensified the public debate on medical benefits of marijuana. In 1993, a book entitled *Marihuana: The Forbidden Medicine* (Grinspoon and Bakalar, 1993) examined a variety of claims for ailments treated by marijuana, and included an entire section on migraine. One clinical vignette discussed at length the medical odyssey of a migraineur through failures with standard pharmaceuticals, and ultimate preference for small doses of smoked marijuana for symptom control.

The editor of the *British Medical Journal* (Smith, 1995) recently wrote an editorial espousing moderation in the drug war. The *Journal of the American Medical Association* published a supportive commentary in 1995 (Grinspoon and Bakalar, 1995). The author rated the respiratory risks potent medical marijuana as low, and pointed out the contradiction of the Schedule 2 status of synthetic THC, dronabinol, while its natural source, marijuana remained a Schedule 1 product, and thus unavailable for legal use to patients who might prefer its easier dose titration. Grinspoon raised as a theoretical possibility the synergistic effects of the whole plant and its components as compared to pure THC.

The *American Journal of Public Health* issued its plea (AJPH, 1996), to allow access to medical marijuana as an Investigational New Drug (IND).

The Australian government (Hall et al., 1995) recently compiled a recent exhaustive review of sequelae of *Cannabis* use. In the summary, it states the following acute effects:

> Anxiety, dysphoria, panic and paranoia, especially in naive users;
> Cognitive impairment, especially of attention and memory, for the duration of intoxication;
> Psychomotor impairment, and probably an increased risk of accident if an intoxicated person attempts to drive a motor vehicle, or operate machinery;
> An increased risk of experiencing psychotic symptoms among those who are vulnerable because of personal or family history of psychosis;
> An increased risk of low birth weight babies if cannabis is used during pregnancy.

In a current review of over 65 000 patient records in an HMO (Sidney et al., 1997), little effect of smoked *Cannabis* was seen on morbidity and mortality of non-AIDS patients.

Surely, not all in the medical establishment are convinced of the relative safety or benefit of *Cannabis* for medical usage. In a recent review (Voth and Schwartz, 1997) the authors concluded, 'The evidence does not support the reclassification of crude marijuana as a prescribable medicine'. However, their study was far from comprehensive, confining itself to the clinical issues of nausea, appetite stimulation, glaucoma, and spasticity. Methodologically, it was flawed in that only the medical literature from 1975 to 1996 was screened, an era during which it was quite difficult to initiate research seeking to support medical indications for *Cannabis*. These authors did not examine migraine as an indication for *Cannabis* usage, nor did they review the extensive literature of the past. The debate on the subject of 'medical marijuana' has extended to the World Wide Web, and includes myriad postings with anecdotal attestations of efficacy for a variety of indications.

Various investigators have examined the roles of different smoke delivery systems (Gieringer, 1996). From these studies, it is clear that vaporization of marijuana makes it possible to deliver even high doses of THC to the lungs of a prospective patient far below the flash point of the *Cannabis* leaf, eliminating a fair amount of smoke, containing tar and other possible carcinogens. However, the marijuana joint was about as effective as any examined smoking device, including waterpipes, in providing a favorable ratio of THC to tar and other by-products of smoking. A standardized smoking procedure for use of *Cannabis* in medical research has been developed (Foltin et al., 1988).

Suppository preparations of *Cannabis* have been used to advantage in the past, and may be an acceptable form of administration for the migraineur, although dose titration would be less available.

4. Discussion

Despite the development of serotonin 1D-agonist medications, migraine remains a serious public health issue. An estimated 23 million Americans suffer severe migraine. Of these, 25% have four or more episodes per month, and 35% have one to three severe headaches each month (Stewart et al., 1992). In economic terms, the impact of migraine is enormous: an estimated 14% of females, and 8% of males missed a portion of, or an entire day of work or school in one month (Linet et al., 1989). Migraine has been estimated to account for an economic impact of US$1.2 to $17.2 billion annually in the USA in terms of lost productivity (Lipton and Stewart, 1993).

In 1990 studies were published outlining the biochemical basis of migraine treatment in serotonin receptor pharmacology (Peroutka, 1990). It was this research that led to the development of the first drugs active on serotonin receptor subtypes, sumatriptan, and ondansetron.

However, despite the justifiable success of sumatriptan in treating acute migraine, problems remain. Although rapidly active subcutaneously, its oral absorption is relatively slow, and often unreliable in the migraineur. Sumatriptan and its analogs are ineffective when administered in the 'aura phase' of classic migraine (Ferrari and Saxena, 1995). Additionally, headache recurrence after 'triptan' 5-HT_{1D} agonist agents is a not infrequent occurrence. Unfortunately, repetitive dosing, and development of agents with longer half-lives does not seem to avert the issue (Ferrari and Saxena, 1995).

Another curiosity in the development of sumatriptan is its relative inability to pass the blood–brain barrier. Once more, the development of newer agents with improved central nervous system penetration has not necessarily

improved efficacy, but does increase the likelihood of side effects, such as chest and throat tightness, numbness, tingling, anxiety, etc. (Ferrari and Saxena, 1995; Mathew, 1997). Ultimately disappointing, none of the triptan drugs seems to exert any benefit on the frequency of migraine incidence, unlike dihydroergotamine, which has degree of prophylactic benefit.

Thus, it is the author's contention that this group of agents, though impressive, may represent somewhat of a 'therapeutic dead end'. Especially considering the large percentages of migraineurs who either fail to respond to the triptans, or cannot tolerate them, there seems to be definite need for alternative treatment agents.

The author believes that the issue of medical marijuana, and its possible role in migraine treatment deserves proper scientific examination, both biochemically and clinically.

Results of controlled clinical trials may be valuable for migraineurs and professionals who treat them because there is a strong need for additional medications that will effectively this condition in its acute state. At this time, the best available medication, injected sumatriptan (Imitrex) has been ineffective in up to 30% of patients, or has produced undesirable side effects for up to 66% when administered subcutaneously (Mathew, 1997). The available evidence seems to suggest that smoked *Cannabis* would be a far safer alternative than butorphanol nasal spray (Stadol-NS), which, heretofore, has been an unscheduled drug approved in the USA for migraine treatment despite its addictive potential and unfavorable side effect profile (Fisher and Glass, 1997).

5. Conclusions

1. *Cannabis*, whether ingested or smoked, has a long history of reportedly safe and effective use in the treatment and prophylaxis of migraine.
2. *Cannabis* has a mild but definite analgesic effect in its own right.
3. *Cannabis* seems to affect nociceptive processes in the brain, and may interact with serotonergic and other pathways implicated in migraine.
4. *Cannabis* is reportedly an effective anti-emetic, a useful property in migraine treatment.
5. *Cannabis*, even when abused, has mild addiction potential, and seems to be safe in moderate doses, particularly under the supervision of a physician.
6. *Cannabis*' primary problem as a medicine lies in its possible pulmonary effects, which seem to be minimal in occasional, intermittent use.
7. *Cannabis*, when inhaled, is rapidly active, obviates the need for gastrointestinal absorption (impaired markedly in migraine), and may be titrated to the medical requirement of the patient for symptomatic relief.
8. *Cannabis* delivered by pyrolysis in the form a marijuana cigarette, or 'joint', presents the hypothetical potential for quick, effective parenteral treatment of acute migraine.

In closing, a quotation seems pertinent (Schultes, 1973):

> There can be no doubt that a plant that has been in partnership with man since the beginnings of agricultural efforts, that has served man in so many ways, and that, under the searchlight of modern chemical study, has yielded many new and interesting compounds will continue to be a part of man's economy. It would be a luxury that we could ill afford if we allowed prejudices, resulting from the abuse of *Cannabis*, to deter scientists from learning as much as possible about this ancient and mysterious plant.

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