Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State: CT	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Migraines, chronic migraines

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

See attached

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

I have been on almost every medication for migraine prevention and nothing has helped. I've been suffering for over 20 years. I am currently receiving the sphenopalatine ganglion block procedure every 3 months, which causes me to miss a day of work and can sometimes make the migraine worse the week following the procedure. The effectiveness also wearing off.

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Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

The chronic migraines cause severe pain and severe nausea, photosensitivity, tinnitus, and auras (my auras cause half of my body to go numb prior to migraine).

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Conventional therapies which are composed mostly of medications are really available, however they don't work for every migraine sufferer.

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

See attached

People who suffer from chronic migraines suffer from chronic pain. Chronic pain is already an approved diagnosis for medical marijuana

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

See attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

I am a nurse practitioner.

Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

I am a practitioner and I fully believe based on the provided evidence that medical marijuana will help chronic migraine sufferers to have an improved quality of life.

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Signature: [redacted]	Date Signed: 01/19/17

MAYO CLINIC

Section C

Migraine

Overview

By Mayo Clinic Staff

A migraine can cause severe throbbing pain or a pulsing sensation, usually on just one side of the head. It's often accompanied by nausea, vomiting, and extreme sensitivity to light and sound.

Migraine attacks can cause significant pain for hours to days and can be so severe that the pain is disabling.

Warning symptoms known as aura may occur before or with the headache. These can include flashes of light, blind spots, or tingling on one side of the face or in your arm or leg.

Medications can help prevent some migraines and make them less painful. Talk to your doctor about different migraine treatment options if you can't find relief. The right medicines, combined with self-help remedies and lifestyle changes, may help.

Migraine care at Mayo Clinic

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Section C

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Defining the Differences Between Episodic Migraine and Chronic Migraine

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Abstract

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Chronic migraine (CM) and episodic migraine (EM) are part of the spectrum of migraine disorders, but they are distinct clinical entities. Population-based studies have shown that those with CM demonstrate higher individual and societal burden because they are significantly more disabled than those with EM and have greater impaired quality of life both inside and outside the home. Proper diagnosis of both conditions requires clearly defined clinical criteria. Diagnosis enables the initiation of appropriate treatments and risk-factor modification, which ultimately improve functional status and quality of life for persons with migraine. Recognizing that both disorders are on the spectrum of migraine, this review serves as a guide to define the disease state of CM as distinct from EM in terms of clinical, epidemiological, sociodemographic, and comorbidity profiles.

Keywords: Chronic migraine, Episodic migraine, Epidemiological profiles, Sociodemographics, Risk factors, Treatment, Chronic daily headache, Chronification, Diagnosis

Introduction

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Migraine is a debilitating headache disorder. Including both episodic and chronic forms, it affects 14% of the population, and up to 18% of women [1, 2]. Migraine is currently ranked by the World Health Organization (WHO) as 19th among causes for years lived with disability [1]. Given the current barriers, improving diagnosis and optimizing treatment paradigms could substantially reduce this global burden.

Because there are no biological markers for migraine, diagnosis is based on clinical history and the exclusion of other headache disorders. Health care professionals apply clinical criteria to guide diagnoses and subsequent treatment. The definition of migraine without aura from the second edition of the International Classification of Headache Disorders (ICHD-2) requires all of the following symptoms: a) recurrent headaches (at least 5 lifetime attacks); b) untreated or unsuccessfully treated headache duration of 4 to 72 h; and c) at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are associated with at least one of nausea/vomiting, photophobia, or phonophobia. Finally, other causes of headache must be excluded [3].

Episodic migraine (EM) is characterized by those with migraine who have 0 to 14 headache days per month, while chronic migraine (CM) is characterized by 15 or more headache days per month. Specifically, revised ICHD-2 (ICHD-2R) criteria define CM as headache on 15 or more days per month for 3 or more months, of which 8 or

more days meet criteria for migraine without aura and/or respond to migraine-specific treatment, occurring in a patient with a lifetime history of at least five prior migraine attacks not attributed to another causative disorder and no medication overuse [4].

The relationship between EM and CM is complex. EM progresses to CM at the rate of 2.5% per year [5], and CM often remits to EM (2-year transition rate of 26%) [6]. The use of a frequency score of 15 or more days per month to classify CM is admittedly somewhat arbitrary. Nonetheless, these clinical definitions identify groups that differ in epidemiologic and symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, and rates of comorbidities. In addition, the patterns of treatment response for EM and CM differ, raising the possibility of both overlapping and distinct biological mechanisms.

Large observational studies have provided valuable information on the distinct clinical characteristics observed in CM and EM [7••, 8••, 9, 10••]. Much of the recently published data that highlight the epidemiological distinction between CM and EM have been generated by three large observational studies: the International Burden of Migraine Study (IBMS), the American Migraine Prevalence and Prevention (AMPP) study, and the German Headache Consortium (GHC) study. IBMS is a web-based, cross-sectional, multinational survey that identified and evaluated persons with CM and persons with EM [7••]. The AMPP study is a large United States (US) population–based, mail-based, longitudinal survey that identified 24,000 respondents with headache and followed them annually for 5 years (2004–2009) [8••]. The GHC study is a German population–based longitudinal survey where respondents completed questionnaires via mail ($n = 4642$) or phone ($n = 4708$) and were identified as either CM, high-frequency EM (9–14 headache d/mo), or low-frequency EM (0–8 headache d/mo) and then evaluated on an annual basis [10••].

Herein and with an emphasis on recent key findings, this article provides an update on the similarities and differences between CM and EM in their epidemiologic and symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, and rates of comorbidities.

Epidemiology of Chronic Migraine Versus Episodic Migraine

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Prevalence

Epidemiologic studies in Europe and America estimate that 6% to 8% of men and 15% to 18% of women experience migraine each year [1]. Recent prevalence data from the US population–based AMPP study reported the 1-year gender-stratified prevalence for EM was 17.1% for women and 5.6% for men [11], and for CM was 1.3% for women and 0.5% for men [12]. CM prevalence rates also varied by age, and were highest for women (1.9%) and men (0.8%) in the age range of 40 to 49 years. The authors also reported that CM represents 7.7% of the total migraine population [12].

Definitional variability of CM poses an epidemiological challenge; however, a recent systematic review summarizing 12 population-based studies using several definitions for frequent migraine determined the global prevalence of CM to be from 0.0% to 5.1% in the general population, with most estimates in the range of 1.4% to 2.2% [13•]. Most of the reviewed studies used the definition of chronic daily headache (≥ 15 headache/mo) with ICHD-1 migraine criteria [14] or the Silberstein-Lipton criteria for CM [15, 16]. None of these criteria matched the current ICHD-2R criteria [4, 13•], at least in part because of difficulties implementing the criteria.

Symptom Profiles

The IBMS provides the most robust epidemiological data comparing the symptom profiles of CM and EM (Table 1) [7••]. Findings demonstrated that, on average, persons with CM had longer duration of headache attacks than those with EM, both treated (24.1 vs 12.8 h; $P < 0.0001$) and untreated (65.1 vs 38.8 h; $P < 0.0001$) [3, 4, 7••, 8••, 17]. In addition, chronic migraineurs were more likely to experience severe pain intensity than episodic migraineurs [7••]. These population findings are confirmed by clinic-based data. For example, the Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program [18] characterized 1384 individuals as chronic

migraineurs. In a 28-day baseline period, headache occurred on 20 days on average, with 19 migraine days and 18 moderate/severe headache days [18].

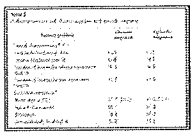

Table 1
Profiles of persons with chronic migraine and episodic migraine

Sociodemographics

The AMPP study and the IBMS demonstrated different sociodemographic findings between persons with EM and CM [7••, 8••]. Both studies demonstrated that CM and EM were most common among females in their fourth decade of life, although those with CM were slightly older (AMPP: CM = 41.7 y [mean] vs EM = 40.2 y [mean], $P = 0.005$; IBMS: CM = 47.7 y [mean] vs EM = 46.0 y [mean], $P = 0.03$ [Table 1]) [7••, 8••]. CM also was most common among Caucasians (over 80%) [7••, 8••]. However, sociodemographic profiles for persons with CM differed from EM in that those with CM reported significantly lower household income levels, were less likely to be employed full time, and were more likely to be occupationally disabled (Table 1) [8••]. In the GHC study, chronic migraineurs also were found to have significantly higher body mass index (BMI; CM = 25.9 mean BMI vs EM = 24.1 mean BMI, $P < 0.015$), have achieved lower levels of education, and were more likely to be smokers [10••].

Individual Burden

CM has been shown to impose a greater emotional and social burden on the individual than EM in large observational studies using various validated tools [7••, 9, 19]. Using the Migraine-Specific Quality of Life (MSQ) questionnaire, which details how migraines limit daily performance, the IBMS showed individuals with CM consistently scoring worse in all categories by 6 to 13 points compared to individuals with EM [7••]. The 2009 AMPP study used the Headache Impact Test-6 (HIT-6) to assess headache impact on the lives of chronic migraineurs [19]. Conversion of HIT-6 scores to standard categories revealed that individuals with CM were much more likely to experience severe headache impact (72.9%) than those with EM (42.3%) [19]. Furthermore, those with CM had significantly higher odds of adverse headache impact than those with EM (OR 3.5; 95% CI, 2.77–4.41; $P < 0.0001$) [19]. The AMPP study also evaluated disability and similarly showed that those with CM had a greater disability according to the Migraine Disability Assessment (MIDAS) questionnaire [9], which calculates a disability score based on reduced productivity (eg, missed days of school and work).

Economic Burden

In the 2005 AMPP study data, CM respondents had lower household income levels, were nearly twice as likely to be occupationally disabled (CM 20.0% vs EM 11.1%; $P < 0.001$), and were less likely to be employed full time than EM respondents (CM 37.8% vs EM 52.3%; $P < 0.001$) [8••]. In the 2006 AMPP study data, more than half of the individuals with CM missed at least 5 days of household work over a 3-month period, compared with only one quarter of those with EM [9]. Chronic migraineurs were three times more likely to report reduced productivity in household work than those with EM (58.1% vs 18.2%; $P < 0.001$) [9]. A minimum of 5 days of missed family activities was reported by 36.9% of those with CM and only 9.5% of those with EM ($P < 0.001$) [9].

In another analysis of the 2005 AMPP study, chronic migraineurs were 19% less likely to be working for pay and lost 4.6 h per week from headache compared to 1.1 h by those with 3 or fewer headache days per month [20]. Although those with high-frequency migraine (10–14 headache d/mo) or CM only accounted for 9.1% of employed migraineurs, they represented 35% of the overall lost work time when considering medical leave and unemployment [20]. According to the 2006 AMPP study, those with CM have reported work or school productivity to be reduced by over 50% in the previous 3 months because of headaches [21].

From a societal perspective, CM is more costly per individual than EM [7••, 21, 22]. Both the AMPP study and IBMS found that those with CM had a statistically significant increase in resource utilization, as evidenced by

markedly more primary care visits, specialist visits, emergency room visits, and hospitalizations compared to those with EM [7••, 21, 22]. Regarding US estimates, the average per-person annual total costs were more than fourfold greater for those who had progressed to CM ($7750) compared with EM ($1757) [21].

Comorbidities

Those with various types of migraine share a range of comorbidities. Recent observational studies have provided insight into the distinct comorbidity profiles of those with CM versus EM. The IBMS demonstrated that those with CM were significantly more likely to report comorbidities for all groups than EM, notably in nonheadache pain (CM 39.1% and EM 18.4%; $P < 0.0001$), psychiatric disorders (CM 46.3% and EM 28.5%; $P < 0.0001$), and vascular disease events (CM 8.2% and EM 3.3%; $P < 0.0001$) [7••].

Similarly, the AMPP study [8••] revealed that those with CM were about twice as likely to be depressed (CM 30.2% vs EM 17.2%; OR 2.0; 95% CI, 1.67–2.40; $P < 0.001$) as determined by self-report on the Patient Health Questionnaire-depression module (PHQ-9) [23] and to have anxiety based on self-report of a physician's diagnosis (CM 30.2% vs EM 18.8%; OR 1.8; 95% CI, 1.51–2.15; $P \leq 0.001$ [Table 1]). Chronic pain disorders also were more than twice as frequent among persons with CM (31.5% vs 15.1%; OR 2.5; 95% CI, 2.08–2.97; $P \leq 0.001$) as well as specific pain disorders like arthritis (CM 33.6% vs EM 22.2%; OR 1.7; 95% CI, 1.43–2.05; $P \leq 0.001$). In addition, the CM population also had higher rates of cardiovascular and respiratory comorbidities, such as hypertension, high cholesterol, stroke, emphysema or chronic obstructive pulmonary disease, and asthma [8••].

Onset and Risk Factors for Progression from Episodic Migraine to Chronic Migraine

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Epidemiological and clinical observations support the progression of EM to CM [24] Progression from EM to CM occurs in about 2.5% of those with EM annually [5]. Because not all those with EM progress to CM, it is important to identify those at high risk for progression. Risk factors can be broken into two categories: those that are easily modified and those that are not readily modifiable (eg, age, female sex, Caucasian race, low educational level/socioeconomic status, and head injury) [25]. Identification of modifiable risk factors for progression to CM, such as obesity, depression, and medication overuse, is important because physicians can implement approaches through behavioral and pharmacologic interventions to help the patient maintain a stable, healthy lifestyle, thus reducing the risk of CM [26]. Below are brief discussions of potential modifiable risk factors and their associations with the transition between EM and CM.

Modifiable Risk Factors

Studies have linked obesity to frequent headache [26]. Although obesity (defined as having BMI > 30) is not a risk factor for the development of EM, it is a risk factor for progression of EM to CM [26]. One large population-based study reported that the prevalence of CM ranged from 0.9% in normal-weighted persons to 1.6% in the obese population (OR 1.7 [1.2–2.4]) and 2.5% in the morbidly obese population (OR 2.2 [1.5–3.2]) [27].

Depression, anxiety, and chronic pain disorders all have been associated with CM at higher rates than with EM [8••]. It has been difficult to determine the causal relationship between depression and migraine because there is a bidirectional relationship between the two disorders; thus, those experiencing either migraine or depression are at increased risk for developing the other [28]. To explain this relationship, two possible hypotheses are depression as a risk factor for CM onset or depression as a consequence of CM [29]. However, recently presented results support a casual rather than consequential relationship between depression and the onset of CM. Adjusted longitudinal modeling of the AMPP study data aimed to assess the role of depression as a predictor of new onset of CM among persons with EM and concluded that, among persons with EM, severe depression was associated with an about 1.28-fold increased risk of the subsequent onset of CM the following year, even after controlling for factors of headache-related disability and headache-day frequency [29]. Additionally, the effects of depression, anxiety, and obesity are additive, such that migraine-related disability increases when obese individuals have comorbid depression or anxiety compared to non-depressed obese migraineurs [30, 31].

Stressful life events such as divorce, moving, employment changes, or problems with children have been considered a risk factor for chronic daily headache [32]. Results from the frequent headache epidemiology study demonstrated that, compared to episodic headache control patients, those with chronic daily headache had more major life changes in the year before or the same year as the onset of chronic daily headache [32].

Traditionally, acute medication overuse (generally defined as use of medications on more than 10 or 15 d/mo, depending on the class) [5] has been considered a risk factor for poor migraine prognosis [33, 34]. Recent epidemiological data have shown that intake of (overuse or use of) certain classes of medication increase the risk of CM in those who already have EM. Specifically, follow-up data from respondents in the 2006 AMPP study demonstrated that those with EM in 2005 had an increased risk of developing CM when they used compounds that contained barbiturates (OR 2.06; 95% CI, 1.3–3.1) and opiates (OR 1.98; 95% CI, 1.4–2.8) [5]. The use of triptans or NSAIDs was not associated with increased risk for developing CM [5]. These findings support other population-based [35–37] and clinic-based studies [34] in chronic daily headache.

Another possible risk factor for progression to CM is the consumption of caffeine. A population-based study that investigated caffeine consumption among participants in a general health survey determined that high medicinal (first-choice medication containing caffeine) or dietary (287 mg/d) consumption of caffeine before chronic daily headache onset was a modest risk factor (OR 1.5; $P = 0.05$), with an increase in women (OR 1.9; $P = 0.006$) and those who were under 40 years (OR 3.4; $P < 0.001$) [38].

Risk-factor modification, such as decreasing headache frequency with behavioral and pharmacological treatment; weight loss management; avoiding medication overuse and caffeine consumption; and screening and treating depression and other psychiatric comorbidities, remains a component to optimizing care [26].

Patterns of Treatment Response

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Acute Treatment

Acute medication is often required because migraine attacks are associated with severe and disabling features and usually are accompanied by other symptoms of sensory disturbance (eg, light and sound sensitivity) [39]. Because the clinical distinction between CM and EM is based primarily on the frequency of headache and migraine days rather than the attack features or symptoms, both populations use acute therapies (eg, analgesics and NSAIDs) or migraine-specific agents with vasoconstrictor properties (eg, triptans and ergot derivatives) [9, 39]. Although the patterns of treatment response to acute medication are similar between EM and CM, there are emerging differences driven by the frequency of use, response, and overall satisfaction [9]. It is important to treat CM and EM patients at the earliest onset of symptoms; however, those with CM have a less robust response to triptans than those with EM [40•]. Additionally, medication overuse of acute therapies containing barbiturates and opiates is a risk factor and an important consideration, particularly for CM [5]. It is critical to limit and monitor the use of these compounds when treating migraine and to educate patients on the risks associated with the progression to CM due to medication overuse.

Preventive Treatment

As our understanding of the clinical, epidemiological, and pathophysiological differences between EM and CM develops, it becomes highly likely that we will find the patterns of treatment or treatment response to preventive therapies to be different between the two migraine groups. Indeed, the recognition of the two disease states within the ICHD-2 guidelines is designed to facilitate the optimal treatment paradigm and the development of therapies specifically targeted at either EM or CM.

Several classes of drugs are available for migraine prevention, including antihypertensives, antiepileptics, and antidepressants [39]. Specifically, antihypertensive agents available for migraine treatment are β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. Common

choices of antiepileptics include topiramate, valproate, and gabapentin. In addition, tricyclic antidepressants are commonly used [39].

Many of these therapies also are used in the prevention of CM; however, of the aforementioned EM therapies, only topiramate has demonstrated efficacy in CM patients through randomized placebo-controlled trials [41, 42]. Additionally, while efficacy has not been demonstrated in EM, onabotulinumtoxin A injections [43] have demonstrated safety and efficacy in CM patients in randomized, double-blind, placebo-controlled studies [18, 44, 45]. Less-studied agents in CM preventive treatment include gabapentin, pregabalin, fluoxetine, tizanidine, zonisamide, and memantine [46].

Conclusions

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Migraine is a highly debilitating disease in both its episodic and chronic forms, with the latter imposing more substantial individual and socioeconomic burden as described by various population-based studies [7••, 9, 10••, 21]. Through identification of risk factors for progression to CM, clinicians can educate patients about modifiable risk factors and can begin appropriate selected therapy in a timely manner. As research continues to demonstrate, CM is a distinct disorder with clinico-epidemiological profiles and therapeutic response patterns different from that of EM. Clear definition and enhanced recognition of these two disease states can better facilitate the development of therapies specifically targeted at either EM or CM.

Acknowledgment

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References

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Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

1. World Health Organization. Headache disorders. Fact sheet N°277. http://www.who.int/mediacentre/factsheets/fs277/en/. 2004.

2. Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27:193–210. doi: 10.1111/j.1468-2982.2007.01288.x. [PubMed] [Cross Ref]

3. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004, 24 Suppl 1:9–160. [PubMed]

4. Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Gobel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Silberstein SD, Steiner TJ. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006;26:742–746. doi: 10.1111/j.1468-2982.2006.01172.x. [PubMed] [Cross Ref]

5. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache. 2008;48:1157–1168. doi: 10.1111/j.1526-4610.2008.01217.x. [PubMed] [Cross Ref]

6. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. Neurology. 2011;76:711–718. doi: 10.1212/WNL.0b013e31820d8af2. [PubMed] [Cross Ref]

7. •• Blumenfeld A, Varon S, Wilcox TK, Buse D, Kawata AK, Manack A, Goadsby PJ, Lipton RB: Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS). Cephalalgia 2011, 31:301–315. *This is the only international (nine countries) study of migraine epidemiology. A web-based survey was used to compare those with episodic migraine to those with chronic migraine on headache features, headache-related disability, health-related quality of life, health care resource utilization, and medical and psychiatric comorbidities.*

8. •• Buse DC, Manack A, Serrano D, Turkel C, Lipton RB: Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. J Neurol Neurosurg Psychiatry 2010, 81:428–432.*This population-based study from the United States demonstrates that those with chronic migraine were significantly more likely to have a lower socioeconomic status and more psychiatric/medical comorbidities than those with episodic migraine.*

9. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology. 2008;71:559–566. doi: 10.1212/01.wnl.0000323925.29520.e7. [PubMed] [Cross Ref]

10. •• Katsarava Z, Manack A, Yoon M-S, Obermann M, Becker H, Dommes P, Turkel C, Lipton RB, Diener HC: Chronic migraine: Classification and comparisons. Cephalalgia 2011, published on January 10, 2011 as doi:10.1177/0333102410383590. *This epidemiologic study of a random population in Germany used three different definitions of chronic migraine and demonstrated that the epidemiological profiles of the three groups were similar but differ significantly from those with high- or low-frequency episodic migraine. The prevalence of chronic migraine also differed depending on the definition used.*

11. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343–349. doi: 10.1212/01.wnl.0000252808.97649.21. [PubMed] [Cross Ref]

12. Reed ML, Buse DC, Manack AN, Fanning KM, Serrano D, Turkel CC, Lipton RB: Prevalence of chronic migraine (CM), headache-related disability and sociodemographic factors in the US population: Results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2011, 51:28 [abstract P58].

13. • Natoli J, Manack A, Dean B, Butler Q, Turkel C, Stovner L, Lipton R: Global prevalence of chronic migraine: a systematic review. Cephalalgia 2010, 30:599–609. *This review article describes the population prevalence of chronic migraine across different populations and explores the various diagnostic criteria for chronic migraine.*

14. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988, 8 Suppl 7:1–96. [PubMed]

15. Silberstein SD, Lipton RB, Solomon S, Mathew N: Classification of daily and near-daily headaches in the headache clinic. Proposed revisions to the International Headache Society criteria. In Frontiers in Headache

Research. Edited by Olesen J. New York: Raven Press, Ltd; 1994:117–126.

16. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology. 1996;47:871–875. [PubMed]

17. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, Lipton RB. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology. 2008;70:1525–1533. doi: 10.1212/01.wnl.0000310645.31020.b1. [PMC free article] [PubMed] [Cross Ref]

18. Dodick DW, Turkel CC, DeGryse R, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF. on behalf of the PREEMPT Chronic Migraine Study Group: OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50:921–936. doi: 10.1111/j.1526-4610.2010.01678.x. [PubMed] [Cross Ref]

19. Buse DC, Manack AN, Serrano D, Varon SF, Turkel CC, Lipton RB: Headache impact of chronic and episodic migraine: Predictors of impact from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2011, in press.

20. Stewart WF, Wood GC, Manack A, Varon SF, Buse DC, Lipton RB. Employment and Work Impact of Chronic Migraine and Episodic Migraine. J Occup. Environ. Med. 2010;52:8–14. doi: 10.1097/JOM.0b013e3181c1dc56. [PubMed] [Cross Ref]

21. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, Reed M, Lipton RB. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache. 2009;49:498–508. doi: 10.1111/j.1526-4610.2009.01369.x. [PubMed] [Cross Ref]

22. Stokes M, Becker WJ, Lipton RB, Sullivan SD, Wilcox TK, Wells L, Manack A, Proskorovsky I, Gladstone J, Buse DC, Varon SF, Goadsby PJ, Blumenfeld AM. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS) Headache. 2011;51:1058–1077. doi: 10.1111/j.1526-4610.2011.01945.x. [PubMed] [Cross Ref]

23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen. Intern. Med. 2001;16:606–613. doi: 10.1046/j.1525-1497.2001.016009606.x. [PMC free article] [PubMed] [Cross Ref]

24. Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. Headache. 2008;48:7–15. doi: 10.1111/j.1526-4610.2007.00969.x. [PubMed] [Cross Ref]

25. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. Headache. 2006;46:1334–1343. doi: 10.1111/j.1526-4610.2006.00577.x. [PubMed] [Cross Ref]

26. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. Neurology. 2009;72:S3–S7. doi: 10.1212/WNL.0b013e3181974b19. [PubMed] [Cross Ref]

27. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology. 2006;67:252–257. doi: 10.1212/01.wnl.0000225052.35019.f9. [PubMed] [Cross Ref]

28. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology. 2003;60:1308–1312. [PubMed]

29. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, Reed ML, Buse DC: Depression is a risk factor for the transformation of episodic to chronic migraine. Cephalalgia 2011, under review.

30. Vargas BB, Dodick DW. The face of chronic migraine: epidemiology, demographics, and treatment strategies. Neurol Clin. 2009;27:467–479. doi: 10.1016/j.ncl.2009.01.001. [PubMed] [Cross Ref]

31. Tietjen GE, Peterlin BL, Brandes JL, Hafeez F, Hutchinson S, Martin VT, Dafer RM, Aurora SK, Stein MR, Herial NA, Utley C, White L, Khuder SA. Depression and anxiety: effect on the migraine-obesity relationship.

Headache. 2007;47:866–875. doi: 10.1111/j.1526-4610.2007.00810.x. [PubMed] [Cross Ref]

32. Scher AI, Stewart WF, Buse D, Krantz DS, Lipton RB. Major life changes before and after the onset of chronic daily headache: a population-based study. Cephalalgia. 2008;28:868–876. doi: 10.1111/j.1468-2982.2008.01634.x. [PubMed] [Cross Ref]

33. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol. 2004;3:475–483. doi: 10.1016/S1474-4422(04)00824-5. [PubMed] [Cross Ref]

34. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A, Diener HC, Limmroth V. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology. 2004;62:788–790. [PubMed]

35. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J. Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. Neurology. 2003;61:160–164. [PubMed]

36. Wang SJ, Fuh JL, Lu SR, Liu CY, Hsu LC, Wang PN, Liu HC. Chronic daily headache in Chinese elderly: prevalence, risk factors, and biannual follow-up. Neurology. 2000;54:314–319. [PubMed]

37. Lu SR, Fuh JL, Chen WT, Juang KD, Wang SJ. Chronic daily headache in Taipei, Taiwan: prevalence, follow-up and outcome predictors. Cephalalgia. 2001;21:980–986. doi: 10.1046/j.1468-2982.2001.00294.x. [PubMed] [Cross Ref]

38. Scher AI, Stewart WF, Lipton RB. Caffeine as a risk factor for chronic daily headache: a population-based study. Neurology. 2004;63:2022–2027. [PubMed]

39. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. Lancet Neurol. 2010;9:285–298. doi: 10.1016/S1474-4422(10)70005-3. [PubMed] [Cross Ref]

40. • Lipton RB, Chu MK: Conceptualizing the relationship between chronic migraine and episodic migraine. Expert Rev Neurother. 2009, 9:1451–1454. *This is the first editorial to describe that chronic migraine and episodic migraine are distinct but intimately related disorders.* [PubMed]

41. Diener HC, Bussone G, Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2007;27:814–823. doi: 10.1111/j.1468-2982.2007.01326.x. [PubMed] [Cross Ref]

42. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, Brandes JL, Bigal M, Saper J, Ascher S, Jordan DM, Greenberg SJ, Hulihan J. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache. 2007;47:170–180. doi: 10.1111/j.1526-4610.2006.00684.x. [PubMed] [Cross Ref]

43. Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1707–1714. doi: 10.1212/01.wnl.0000311390.87642.d8. [PubMed] [Cross Ref]

44. Aurora SK, Dodick DW, Turkel CC, DeGryse R, Silberstein SD, Lipton RB, Diener HC, Brin MF, on behalf of PREEMPT 1 Chronic Study Group OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30:793–803. doi: 10.1177/0333102410364676. [PubMed] [Cross Ref]

45. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse R, Lipton RB, Silberstein SD, Brin MF, on behalf of the PREEMPT 2 Chronic Migraine Study Group OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30:804–814. doi: 10.1177/0333102410364677. [PubMed] [Cross Ref]

46. Diener HC, Holle D, Dodick D. Treatment of chronic migraine. Curr Pain Headache Rep. 2010;15:64–69. doi: 10.1007/s11916-010-0159-x. [PubMed] [Cross Ref]

Section G+H

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Review Article

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

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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*

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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-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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References

Agurell, S., Halldin, M., Lindgren, J.-E., Ohlsson, A., Widman, M., Gillespie, H. and Hollister, L., Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man, Pharmacol. Rev., 38 (1986) 21–43.

AJPH, Access to therapeutic marijuana/cannabis, Am. J. Public Health, 86 (1996) 441–442.

Brunner, T.F., Marijuana in ancient Greece and Rome? The literary evidence, J. Psychedel. Drugs, 9 (1977) 221–225.

Camp, W.H., The antiquity of hemp as an economic plant, J. N. Y. Bot. Gard., 37 (1936) 110–114.

Chait, L.D. and Zacny, J.P., Reinforcing and subjective effects of oral delta-9-THC and smoked marijuana in humans, Psychopharmacology, 107 (1992) 255–262.

Chiang, C.N. and Barnett, G., Marijuana effect and delta-9-tetrahydrocannabinol plasma level, Clin. Pharm. Ther., 36 (1984) 234–238.
Chopra, I.C. and Chopra, R.W., The use of cannabis drugs in India, Bull. Narcotics, 9 (1957) 4–29.
Co, B.T., Goodwin, D.W., Gado, M., Mikhael, M. and Hill, S.Y., Absence of cerebral atrophy in chronic cannabis users by computerized transaxial tomography, J. Am. Med. Assoc., 237 (1977) 1229–1230.
Cohen, S., The 94-day cannabis study, Ann. N. Y. Acad. Sci., 282 (1976) 211–220.
Comitas, L., Cannabis and work in Jamaica: a refutation of the amotivational syndrome, Ann. N. Y. Acad. Sci., 282 (1976) 211–220.
Darmsteter, J. (trans.), The Zend-Avesta, Part I, The Vendîdâd, Oxford, London, 1895, 389 pp.
Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A. and Mechoulam, R., Isolation and structure of a brain constituent that binds to the cannabinoid receptor, Science, 258 (1992) 1946–1949.
Dwarakanath, C., Use of opium and cannabis in the traditional systems of medicine in India, Bull. Narcotics, 17 (1965) 15–19.
El-Mallakh, R.F., Marijuana and migraine, Headache, 27 (1987) 442–443.
Fan, P., Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons, J. Neurophysiol., 73 (1995) 907–910.
Ferrari, M.D. and Saxena, P.R., 5-HT1 receptors in migraine pathophysiology and treatment, Eur. J. Neurol., 2 (1995) 5–21.
Fishbein, M., Migraine associated with menstruation, J. Am. Med. Assoc., 237 (1942) 326.
Fisher, M.A. and Glass, S., Butorphanol (Stadol): a study in problems of current drug information and control, Neurology, 48 (1997) 1156–1160.
Foltin, R.W., Fischman, M.W. and Byrne, M.F., Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory, Appetite, 11 (1988) 1–14.
Fride, E. and Mechoulam, R., Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent, Eur. J. Pharmacol., 231 (1993) 313–314.
Gieringer, D., Waterpipe study, Bull. Multidisc. Assoc. Psychedel. Stud., 6 (1996) 59–63.
Goadsby, P.J. and Gundlach, A.L., Localization of [^{3}H]-dihydroergotamine binding sites in the cat central nervous system: relevance to migraine, Ann. Neurol., 29 (1991) 91–94.
Grinspoon, L. and Bakalar, J.B., Marihuana: The Forbidden Medicine, Yale University, New Haven, CT, 1993, 184 pp.
Grinspoon, L. and Bakalar, J.B., Marihuana as medicine: a plea for reconsideration, J. Am. Med. Assoc., 273 (1995) 1875.
Hall, W., Solowij, N. and Lemon, J., The Health and Psychological Consequences of Cannabis Use, National Drug Strategy Monograph Series No. 25, National Drug and Alcohol Research Centre, Australia, 1995.
Herkenham, M.A., Localization of cannabinoid receptors in brain: relationship to motor and reward systems. In: S.G. Koreman and J.D. Barchas (eds.), Biological Basis of Substance Abuse, Oxford University Press, London, 1993, pp. 187–200.
Hollister, L.E., Health aspects of cannabis, Pharmacol. Rev., 38 (1986) 1–20.
Kuehnle, J., Mendelson, J.H., Davis, K.R. and New, P.F.J., Computed tomographic examination of heavy marihuana smokers, J. Am. Med. Assoc., 237 (1977) 1231–1232.
Li, H.-L., An archaeological and historical account of cannabis in China, Econ. Bot., 28 (1974) 437–448.
Lichtman, A.H., Cook, S.A. and Martin, B.R., Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement, J. Pharmacol. Exp. Ther., 276 (1996) 585–593.
Linet, M.S., Stewart, W.F. and Celentano, D.D., An epidemiological study of headache among adolescents and young adults, J. Am. Med. Assoc., 261 (1989) 2211–2216.
Lipton, R.B. and Stewart, W.F., Migraine in the United States: epidemiology and health care use, Neurology, 43 (suppl.)(1993) 6–10.
Martin, B.R., Cellular effects of cannabinoids, Pharmacol. Rev., 38 (1986) 45–74.
Mason, A.P. and McBay, A.J., Cannabis: pharmacology and interpretation of effects, J. Forens. Sci., 30 (1985) 615–631.
Mathew, N.T., Serotonin 1D (5-HT 1D) agonists and other agents in acute migraine, Neurol. Clinics, 15 (1997) 61–83.
Mikuriya, T.H. (Ed.), Marijuana: Medical Papers 1839–1972, Medi-Comp Press, Oakland, CA, 1973, 465 pp.
Milstein, S.L., MacCannell, K., Karr, G. and Clark, S., Marijuana-produced changes in pain tolerance: experienced and non-experienced subjects, Int. Neuropsychiatr., 10 (1975) 177–182.
Noyes, R. and Baram, D.A., Cannabis analgesia, Comp. Psychiatr., 15 (1974) 531–535.
Noyes, R., Brunk, F., Baram, D.A. and Canter, A., Analgesic effect of delta-9-tetrahydrocannabinol, J. Clin. Pharmacol., 15 (1975a) 134–143.
Noyes, R., Brunk, F., Avery, D.H. and Canter, A., The analgesic properties of delta-9-tetrahydrocannabinol and codeine, Clin. Pharmacol. Ther., 18 (1975b) 84–89.
Osler, W. and McCrae, T., The Principles and Practice of Medicine, Appleton, New York, 1915, 1225 pp.
Peroutka, S.J., Developments in 5-hydroxytryptamine receptor pharmacology in migraine, Neurol. Clinics, 8 (1990) 829–839.
Ratnam, E.V., Cannabis indica, J. Brit. Med Assoc., Ceylon Branch, 13 (1916) 30–34.
Schultes, R.E., Man and marijuana, Nat. Hist., 82 (1973) 59–63, 80, 82.
Schultes, R.E., Klein, W.M., Plowman, T. and Lockwood, T.E., Cannabis: an example of taxonomic neglect, Bot. Mus. Leafl. Harvard Univ., 23 (1974) 337–367.
Sidney, S., Beck, J.E., Tekawa, I.S., Quesenberry, C.P. and Friedman, G.D., Marijuana use and mortalilty, Am. J. Public Health, 87 (1997) 585–590.
Smith, R., Editorial: the war on drugs, Br. Med. J., 311 (1995) 23–30.
Stewart, W.F., Lipton, R.B. and Celantano, D.D., Prevalence of migraine headache in the United States, J. Am. Med. Assoc., 267 (1992) 64–69.
Volfe, Z., Dvilansky, A. and Nathan, I., Cannabinoids block release of serotonin from platelets by plasma from migraine patients, Int. J. Clin. Pharm. Res., 4 (1985) 243–246.
Voth, E.A. and Schwartz, R.H., Medical applications of delta-9-tetrahydrocannabinol and marijuana, Ann. Intern. Med., 126 (1997) 791–798.
Walton, R.P., Marihuana: America's New Drug Problem: A Sociologic Question with its Basic Explanation Dependent on Biologic and Medical Principles, Lippincott, Philadelphia, PA, 1938, 223 pp.
Young, F.L., In the Matter of Marijuana Rescheduling Petition, Department of Justice, Drug Enforcement Administration. Docket 86-22, Drug Enforcement Administration, Washington, DC, September 6, 1988.

Section G

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Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population.

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Abstract

STUDY OBJECTIVE: No clinical trials are currently available that demonstrate the effects of marijuana on patients with migraine headache; however, the potential effects of cannabinoids on serotonin in the central nervous system indicate that marijuana may be a therapeutic alternative. Thus, the objective of this study was to describe the effects of medical marijuana on the monthly frequency of migraine headache.

DESIGN: Retrospective chart review.

SETTING: Two medical marijuana specialty clinics in Colorado.

PATIENTS: One hundred twenty-one adults with the primary diagnosis of migraine headache who were recommended migraine treatment or prophylaxis with medical marijuana by a physician, between January 2010 and September 2014, and had at least one follow-up visit.

MEASUREMENTS AND RESULTS: The primary outcome was number of migraine headaches per month with medical marijuana use. Secondary outcomes were the type and dose of medical marijuana used, previous and adjunctive migraine therapies, and patient-reported effects. Migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($p<0.0001$) with the use of medical marijuana. Most patients used more than one form of marijuana and used it daily for prevention of migraine headache. Positive effects were reported in 48 patients (39.7%), with the most common effects reported being prevention of migraine headache with decreased frequency of migraine headache (24 patients [19.8%]) and aborted migraine headache (14 patients [11.6%]). Inhaled forms of marijuana were commonly used for acute migraine treatment and were reported to abort migraine headache. Negative effects were reported in 14 patients (11.6%); the most common effects were somnolence (2 patients [1.7%]) and difficulty controlling the effects of marijuana related to timing and intensity of the dose (2 patients [1.7%]), which were experienced only in patients using edible marijuana. Edible marijuana was also reported to cause more negative effects compared with other forms.

CONCLUSION: The frequency of migraine headache was decreased with medical marijuana use. Prospective studies should be conducted to explore a cause-and-effect relationship and the use of different strains, formulations, and doses of marijuana to better understand the effects of medical marijuana on migraine headache treatment and prophylaxis.

KEYWORDS: cannabis; headache; marijuana; migraine

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