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

Danielle N. Rhyne,[1] Sarah L. Anderson,[1] Margaret Gedde,[2] and Laura M. Borgelt,[1,3,*]

[1]Department of Clinical Pharmacy, University of Colorado Anschutz Medical Campus Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado; [2]Gedde Whole Health, Littleton, Colorado; [3]Department of Family Medicine, University of Colorado Anschutz Medical Campus School of Medicine, Aurora, Colorado

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.

Key Words cannabis, marijuana, migraine, headache.

(Pharmacotherapy 2016;36(5):505–510) doi: 10.1002/phar.1673

*Address for correspondence: Laura M. Borgelt, University of Colorado Anschutz Medical Campus Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 E. Montview Blvd., Mail Stop C238, Aurora, CO 80045; e-mail: laura.borgelt@ucdenver.edu.

Cannabis encompasses three species: *Cannabis indica, Cannabis sativa,* and *Cannabis ruderalis*. Cannabis is composed of more than 400 compounds, with more than 60 being cannabinoids (CBs).[1] The most common psychoactive CB is

Δ^9-tetrahydrocannabinol (THC). Cannabidiol (CBD) is another common CB, which accounts for 40% of the plant's extract and is one of the primary constituents of medical marijuana.[1]

Phytocannabinoids are CBs that occur naturally in the plant (e.g., THC, CBD) and stimulate CB receptors throughout the body.[2] The body contains endogenous CBs and receptors, which make up the endocannabinoid system. This system is responsible for maintaining homeostasis in our bodies. Research has found that the endocannabinoid system might be a target for treatment of diseases such as migraine headache (HA), fibromyalgia, neuropathic pain, and irritable bowel syndrome.[3] The endocannabinoid system is common throughout the central nervous system and has presence in peripheral tissues as well. This system includes CB receptors, CB_1 and CB_2, and ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are located throughout the brain and influence many regulatory systems.[4] Cannabinoid$_1$ receptors are widely expressed in the central and peripheral nervous system. In the central nervous system, activation of CB_1 receptors leads to inhibition of the following neurotransmitters: γ-aminobutyric acid (GABA), glutamate, serotonin, dopamine, acetylcholine, norepinephrine, cholecystokinin, and D-aspartate.[5] Cannabinoid$_2$ receptors are widely expressed throughout the peripheral tissues, especially the immune system, and have antiinflammatory properties and analgesic effects. Anandamide is a partial agonist at CB receptors and binds to CB_1 receptors with higher affinity than CB_2 receptors. Anandamide has been shown to have inhibitory effects on serotonin type 3 (5-hydroxytryptamine $[HT]_3$) receptors, further suggesting its antiemetic and analgesic roles.[5] It is also a 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist.

Δ^9-Tetrahydrocannabinol acts as a partial agonist at CB_1 and CB_2 receptors and is structurally similar to endogenous AEA. Cannabidiol antagonizes CB_1 receptors at low levels in the presence of THC and acts as a potent analgesic. The mechanisms of CBs have been examined and suggest serotonergic and dopaminergic effects as well as providing antiinflammatory effects. Evidence suggests that THC affects serotonin and dopamine by inhibiting serotonin release from platelets, stimulates 5-HT synthesis, and modulates dopaminergic imbalances.[3] Specific conditions such as Alzheimer's disease and depression occur due to a lack of neurotransmitters.[6] As a result, it has been hypothesized that patients with central nervous system disorders might have a clinical endocannabinoid deficiency. Further evidence from one study[6] reported reduced levels of AEA in the cerebrospinal fluid of patients with migraine HA. As a result of reduced AEA levels, the trigeminovascular system is activated, resulting in a migraine HA.

The role of serotonin in migraine HA is supported by the efficacy of serotonin agonists such as triptans for acute treatment of migraine. Other agents used for acute migraine treatment include nonsteroidal antiinflammatory drugs, acetaminophen, and antiemetic agents. In addition to acute migraine treatment, the American Academy of Neurology 2012 guidelines recommend pharmacologic agents for preventive therapy.[7] Level A treatment recommendations include certain antiepileptic drugs, β-blockers, and triptans. Current guidelines do not address the use of cannabis for the prevention or treatment of migraine HA; however, the potential effects of CBs on serotonin in the central nervous system make it possible that cannabis could be a therapeutic alternative.[5]

Although there are no clinical trials available, to our knowledge, demonstrating the effects of marijuana on patients with migraine HA, five case reports described patients who used dronabinol with or without additional marijuana products for treatment of their vascular or migraine HAs and who experienced an overall decrease in migraine HA.[8] These case reports, however, lack scientific rigor and consistent reporting and do not provide detailed information about the positive or negative impact of marijuana.

Due to a lack of data on the efficacy and proposed mechanism of the pharmacologic benefit of medical marijuana in patients with migraine HA, clinical data describing the effectiveness of medical marijuana for the frequency of migraine HA are necessary. Other useful information would include the dose and type of medical marijuana being used and other clinical effects of marijuana. Thus, the primary purpose of this study was to determine the monthly frequency of migraine HA in patients diagnosed with migraine HA who used medical marijuana.

Methods

Study Design, Setting, and Outcomes

This was a retrospective, observational chart review of patients who were seen at Gedde

Whole Health, a private medical practice with offices located in Colorado Springs and Buena Vista, Colorado. The physician in these clinics specializes in applications of medical marijuana for various conditions and makes recommendations to patients for the use of medical marijuana when a patient has a qualifying medical condition based on state requirements. This study was approved by the Colorado Multiple Institutional Review Board.

The primary outcome of this study was monthly frequency of migraine HA with medical marijuana use. Secondary outcomes were type and dose of medical marijuana used, previous and adjunctive migraine therapies, and patient-reported effects.

Patient Chart Identification and Data Collection

Charts for adult patients, aged 18–89 years old, with a primary diagnosis of migraine HA and at least one follow-up visit were included for review. Data were extracted by a single investigator for consistency. Data collection included sex, number of years with migraine HA, medical history, previous migraine therapy, adjunctive migraine therapy, number of migraine HAs per month, types and doses of marijuana, frequency of marijuana use, number of migraine HAs per month at the follow-up visit, and patient-reported effects. Number of migraine HAs experienced each month and the amount of marijuana used each month were patient-reported data. Medical marijuana quantities were reported in ounces, with the exception of edible dosage forms, which were reported in milligrams. Edible doses were then converted to ounces per month based on a calculation of 100 mg/day of edible marijuana being considered equivalent to 1 oz/month of cannabis flower. This conversion was based on an approximated potency of CB in cannabis flower used by study patients of 10% (w/w), based on historical and contemporary data.[9] If CB potency in cannabis flower is approximated at 10% (w/w), then 1 g of cannabis flower contains 0.1 g (or 100 mg) of CB. Given that 1 oz equals 28 g, and 1 month is approximately 30 days, then 1 oz/month is approximately 28 g/30 days, or approximately 1 g/day. Then 1 oz/month of cannabis flower roughly equals 1 g/day of cannabis flower, which converts approximately to 100 mg/day of CB. The CB conversion used is illustrated in the following equation:

$$\text{No. of ounces/month} \approx (\text{no. of milligrams/day})/100$$

When ranges of doses were reported (e.g., 1–2 oz/month), the highest dose of medical marijuana was documented.

Statistical Analysis

Descriptive statistics were used to describe demographic and clinical data. The mean and standard deviation, median and interquartile range, and proportions were calculated for normally distributed data, nonparametric data, and nominal data, respectively. Two-tailed paired *t* tests were used when possible; a p value less than 0.05 was considered to indicate a statistically significant difference. All statistical tests were performed using GraphPad software (GraphPad Software, Inc., San Diego, CA).

Results

All patient visits with dates between January 1, 2010, and September 30, 2014, were screened, and 262 patient charts with a primary diagnosis of migraine HA were identified. Of these, 121 had at least one follow-up visit recorded and were eligible for inclusion. The other 141 patient charts were excluded due to the absence of a follow-up visit.

The initial visit characteristics for the 121 included patients are shown in Table 1. Fifty-two percent of patients were female, and the average duration of migraine HA was 14 years. Eighty-two (67.8%) patients had a history of previous or current marijuana use at the initial visit. Follow-up visit characteristics are also shown in Table 1.

The primary outcome of mean number of migraine HAs per month at the initial and follow-up visits were 10.4 and 4.6 ($p<0.0001$), respectively. The mean time between the initial and most recent follow-up visit was 21.8 months (range 12–37 mo). A total of 103 patients (85.1%) reported a decrease in frequency of migraine HAs per month. Alternatively, 15 patients (12.4%) reported the same number of HAs per month, and 3 (2.5%) had an increase in the number of HAs per month. More than half of the patients (62 [51.2%]) reported using two or more forms of marijuana for migraine HA treatment and/or prophylaxis at the follow-up visit. The forms of medical marijuana used included vaporized (42 patients), edible (66

Table 1. Characteristics of the 121 Study Patients

Characteristic	Initial Visit	Follow-up Visit	p Value
Female	63 (52.1)	NA	NA
Mean no. of years with migraine headache	14	NA	NA
Time between initial and most recent follow-up visit (mo)	NA	21.8 [12–37]	NA
Previous marijuana use	82 (67.8)	121 (100)	<0.0001
Mean no. of migraines/month	10.4	4.6	<0.0001
Used migraine prescription drug therapy	59 (48.8)	52 (43.0)	0.44
No. of migraine medications/patient	1.15 [0–2]	1.09 [0–2]	0.22
Used 1 form of medical marijuana	57/82 (69.5)	59/121 (48.8)	0.004
Used 2 forms of medical marijuana	20/82 (24.4)	51/121 (42.1)	0.011
Used ≥ 3 forms of medical marijuana	5/82 (6.1)	11/121 (9.1)	0.597

Data are no. (%) of patients or mean [range] values unless otherwise specified.
NA = not applicable.

patients), topical (15 patients), and smoked (65 patients). Follow-up visit mean monthly doses of each type of marijuana were 2.64 oz, 2.59 oz, 2.73 oz, and 1.59 oz for vaporized, edible, topical, and smoked forms, respectively. Reasons for use of medical marijuana included migraine HA prophylaxis (7 patients), acute treatment of migraine HA (4 patients), or both (110 patients). A post-hoc sample size calculation was performed by using PASS 14 (NCSS Statistical Software; NCSS, LLC, Kaysville, UT) to ensure the internal validity of these results. This analysis yielded a necessary sample size of 96 patients to achieve 80% power when the mean population difference in number of migraine headaches per month was 5.8 and the standard deviation for both groups was 10.0, which was exceeded in our study with a sample size of 121 patients.

Migraine HA prescription drug therapy was reported in 59 (48.8%) patients, with the average number of medications being 1.15 per patient at the initial visit. At the follow-up visit, 52 (42.9%) patients reported using migraine HA drug therapy in addition to medical marijuana. The average number of migraine HA medications was 1.09 per patient; however, the difference between the number of medications at the initial and follow-up visits was not statistically significant (p=0.22). There were 62 patient-reported effects, illustrated in Tables 2 and 3. Positive effects were recorded for 48 patients, with half (24 patients) of the effects being reported as prevention of migraine HA with decreased frequency of migraine HA (Table 2). These beneficial effects were reported for all forms of marijuana. In addition, migraine abortion was the second most common positive effect (14 patients). Negative patient-reported effects are shown in Table 3 (n=14). Patients who used the edible form (11 patients) were most likely to report negative effects, which included somnolence (2 patients) and difficulty controlling the effects of marijuana, including when the effects would occur and the intensity of effects (2 patients).

Discussion

This study is one of the first to reveal that migraine HA frequency decreased in patients using medical marijuana, and the difference in frequency between the initial and follow-up visit was statistically significant (p<0.0001). Further, 90% of patients used marijuana for both treatment and prophylaxis of migraine HA. More than half of the patients at the follow-up visit reported using two or more delivery methods of marijuana for migraine HA treatment, which demonstrates that some delivery methods might be preferred for abortive treatment versus migraine HA prevention. For example, 12 patients reported migraine abortion success while using an inhaled form of marijuana. This effect was likely due to the quick onset of action with inhaled marijuana as opposed to a slower onset of action with an edible form. Although there were more overall positive effects reported, there were more negative reports for the edible form of marijuana, likely due to variability of onset of action. As previous research has shown, the pharmacokinetics of the edible forms are variable, and it could take up to 4 hours to reach peak THC concentration, with clinical effects lasting longer (e.g., up to 8 hrs).[10, 11] These pharmacokinetic factors likely led to the reported difficulty in controlling the effects of marijuana.

This study has some limitations. First, the retrospective nature of the study limits the ability to evaluate the causality of the use of medical marijuana and decrease in migraine HA frequency, and it does not allow for controlling the

Table 2. Patient-Reported Positive Effects in the 121 Patients

Effect	No. of Patients (%)	Medical Marijuana Form (No. of Patients)			
		Vaporized	Edible	Topical	Smoked
Prevention of migraine headache with decreased frequency of migraine headache[a]	24 (19.8)	X	X	X	X
Aborts migraine headache	14 (11.6)	5	1	1	7
Relieves pain	4 (3.3)		3	1	
Reduces nausea	1 (0.8)				1
Other effects	5 (4.1)		4	1	
All positive effects	48 (39.7)				

[a]Patients used a combination of medical marijuana forms.

Table 3. Patient-Reported Negative Effects in the 121 Patients

Effect	No. of Patients (%)	Medical Marijuana Form (no. of patients)			
		Vaporized	Edible	Topical	Smoked
Somnolence	2 (1.7)		X		
Difficulty controlling effects of marijuana related to timing and intensity of the dose	2 (1.7)		X		
Increased headache and seizure	1 (0.8)	X	X		
Bad dreams	1 (0.8)				X
Jitteriness and nausea	1 (0.8)				X
Memory loss	1 (0.8)			X	
Other effects	6 (5.0)		X	X	X
All negative effects	14 (11.6)				

type of dose used. This study showed a reduction in migraine HA frequency with the use of medical marijuana; however, it demonstrates the need for performing additional studies in patients with migraine HA to explore the benefits and risks of medical marijuana in a controlled environment. Second, more than half of the patients with migraine did not have a follow-up visit and were excluded from the study. The effects of marijuana are unknown for these patients, and medical follow-up was no longer required in Colorado with the legalization of marijuana in January 2014. Third, chart documentation was not consistent across every patient. For instance, documentation of clinical effects appeared for only half of the patients. Specific directions for use of medical marijuana were not recorded in the charts. In addition, most patients reported previous use of marijuana at the initial visit; however, the duration of previous use was unknown. Given that most patients had used marijuana prior to the initial visit, this study suggests that interaction with a provider may improve how prior or current marijuana use can be optimized to improve symptoms. Documentation revealed that most patients used marijuana daily; however, it is unknown if some patients used marijuana multiple times per day. Fifty-two patients used preventive and/or abortive pharmacologic agents for migraine HA in addition to medical marijuana, but the frequency of their use was not documented. Also, information on the strains and/or amounts of CBs within medical marijuana products was not consistently documented, so this information was unable to be collected.

The ideal study design to further investigate the effects of medical marijuana on the frequency of migraine HA would be a randomized, placebo-controlled clinical trial with a marijuana washout period prior to study start. The ideal study would also provide participants with standardized quantities and potencies of medical marijuana while tracking their adherence, number of migraine HAs, and adverse effects in a systematic fashion analogous to that of a prescription drug study. Based on current federal regulations regarding research of this type and lack of consistency among cannabis and cannabis compounds, substantial changes in legislation and product manufacturing would need to occur before a study with this scientific rigor could feasibly be performed.

As health care providers enter into shared decision-making with patients experiencing

migraine HA and using marijuana, this chart review provided some insight about key messages for patients. For example, providers need to be prepared to discuss potential benefits and risks of marijuana use. In addition, given the difference in strains, doses, and formulations, it may be difficult to establish a standardized dosing schedule, and marijuana use should be accurately documented. Edible formulations have a longer onset of action and variable patient responses, so patients should be advised to start with a low dose, carefully monitor response, and titrate slowly, if needed. Use of prescription and over-the-counter medications for migraine HA should also be documented to optimize medication use.

Conclusion

Patients using medical marijuana for migraine HA reported a statistically significant decrease in the number of migraine HAs per month. Almost all patients used marijuana daily for migraine HA prevention. Inhaled forms of marijuana were commonly used for acute migraine treatment and were reported to abort migraine HA. Overall, more positive than negative effects were reported with medical marijuana use. Edible marijuana was reported to cause more negative effects compared with other forms. Further research should be performed to determine if there is a preferred delivery method, dose, and strain of medical marijuana for migraine HA therapy as well as the potential long-term effects of medical marijuana.

Disclosure

Danielle Rhyne and Sarah Anderson have no conflicts of interest to disclose. Margaret Gedde is the medical director and owner of Gedde Whole Health. Laura Borgelt has served as a member of the following working groups: Colorado Department of Public Health and Environment Retail Marijuana Public Health Advisory Committee (2014–present), Marijuana Pregnancy and Lactation Guidance for Colorado Health Care Providers Committee (2014–2015), and Amendment 64 (Marijuana Legalization) Task Force Working Group: Consumer Safety and Social Issues (2013); Colorado Department of Revenue Marijuana Enforcement Division: Retail Marijuana Product Potency and Serving Size Working Group (2014); and member of the State Licensing Authority/Colorado Department of Revenue: Medical and Retail Marijuana Mandatory Testing and Random Sampling Working Group (2013) and Amendment 64 (Marijuana Legalization) and HB13-1317 stakeholder working group for rulemaking: Labeling, Packaging, Product Safety and Marketing (2013). She declares no financial conflict of interest.

References

1. **Guzman M.** Cannabinoids: potential anticancer agents. Nat Rev Cancer 2003;3:745–55.
2. Russo EB, Grotenhermen F, eds. Handbook of Cannabis Therapeutics: From Bench to Bedside. Binghamton, NY: Haworth Press; 2006:69–116.
3. **Russo E.** Clinical endocannabinoid defieciency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett 2008;29 (2):192–200.
4. **McGeeney B.** Cannabinoids and hallucinogens for headache. Headache 2013;53:447–58.
5. **Baron EP.** Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been. Headache 2015;55:885–916.
6. **Sarchielli P, Pini LA, Coppola F, et al.** Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology 2007;32:1384–90.
7. **Silberstein S, Holland S, Freitag F, et al.** Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults. Neurology 2012;78:1337–45.
8. **Mikuriya TH.** Chronic migraine headache: Five cases successfully treated with marinol and/or illicit cannabis. 1991. Available from http://druglibrary.org/schaffer/hemp/migrn1.htm.
9. **Mehmedic Z, Chandra S, Slade D, et al.** Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci 2010;55:1209–17.
10. **Colorado Department of Public Health and Environment.** Monitoring health concerns related to marijuana in Colorado. 2014. Available from https://www.colorado.gov/pacific/cdphe/retail-marijuana-public-health-advisory-committee. Accessed September 29, 2015.
11. **Grotenhermen F.** Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42(4):327–60.