Current Pain and Headache Reports (2021) 25:16
https://doi.org/10.1007/s11916-020-00931-2

EPISODIC MIGRAINE (S NAHAS, SECTION EDITOR)

Cannabis and Migraine: It's Complicated

Laszlo L. Mechtler[1] · Fran M. Gengo[2] · Vincent H. Bargnes[1]

Accepted: 29 December 2020

Abstract

Purpose of Review The use of cannabis for the treatment of migraine has become an area of interest with the legalization of medical cannabis in the USA. Understanding the mechanisms of cannabinoids, available studies, and best clinical recommendations is crucial for headache providers to best serve patients.

Recent Findings Patients utilizing medical cannabis for migraine have reported improvement in migraine profile and common comorbidities. Reduction in prescription medication is also common, especially opioids. Side effects exist, with the majority being mild. Not enough data is available for specific dose recommendations, but THC and CBD appear to mediate these observed effects.

Summary The purpose of this article is twofold: review the limited research surrounding cannabis for migraine disease and reflect on clinical management experiences to provide recommendations that best capture the potential use of cannabis for migraine.

Keywords Migraine · Cannabis · Headache · Marijuana · Medical cannabis · Medical marijuana

Introduction

Migraine is a prevalent, female-predominant, and complex headache disorder that is the second most disabling disease worldwide, ranking number one in those under 50 years old [1]. Migraine attacks are the result of the painful activation of the trigeminovascular system [2•]. Sensory inputs from the meninges, especially meningeal blood vessels, activate the spinal trigeminal nucleus (SpV) and a vast array of second-order trigeminal projections. These projections relay pain signals to nuclei within the basal ganglia, brainstem, hypothalamus, and thalamus [3]. This constellation of projections is responsible for the distinctive symptomatology present in patients suffering from migraine, from throbbing headache to nausea to photophobia. Migraine is defined by the International Classification of Headache Disorders 3rd Edition's (ICHD-3) as a recurring disorder involving at least five headaches lasting 4–72 h; at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity; nausea and/or vomiting or photophobia and phonophobia; and is not better accounted for by another ICHD-3 diagnosis.

Neuronal transmission and neurotransmitters serve as therapeutic targets for migraine attack treatment and prevention. Voltage-gated sodium (Nav) channel blockers, including amitriptyline and topiramate, provide prophylactic therapeutic relief by attenuating the neuronal transmission of pain signals associated with the SpV [4, 5]. Triptans, including sumatriptan, provide acute therapeutic relief by preventing the release of neuropeptides associated with pain signaling while stimulating serotonin-mediated vasoconstriction of the dilated meningeal blood vessels [6]. Most recently, calcitonin gene-related peptide (CGRP) antagonists, including injectable monoclonal antibodies and oral gepants, can provide both prophylactic and acute therapeutic relief by interfering with CGRP pain signaling [7, 8].

Conventional migraine treatment and exogenous cannabinoids derived from the cannabis genus of flowering plants share considerable overlap in biochemical effects and

This article is part of the Topical Collection on *Episodic Migraine*

✉ Laszlo L. Mechtler
lmechtler@dentinstitute.com

Fran M. Gengo
fgengo@dentinstitute.com

Vincent H. Bargnes
vbargnes@dentinstitute.com

[1] Dent Neurologic Institute, 3980 Sheridan Drive, Suite 600, Amherst, NY 14226, USA

[2] Dent Neurologic Institute, 3980 Sheridan Drive, Suite 300, Amherst, NY 14226, USA

Published online: 25 February 2021

therapeutic potential. However, the wide spectrum of over 100 cannabinoids present in whole-plant medical cannabis treatment represents a substantial paradigm shift from the traditional single-compound, single-target pharmaceutical approach [9, 10]. Certain cannabinoids, including those inactive by themselves, can modulate the effects of other cannabinoids, with Raphael Mechoulam's lab labeling this modulation as the "entourage effect" [11]. Further research has confirmed different permutations of active and inactive cannabinoids are capable of both beneficial and harmful effects [12]. Beyond cannabinoids, cannabis also contains other plant metabolites, including terpenes and flavonoids, that impact how cannabis affects patients [13•]. Going forward, this article will focus on the two major bioactive cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC primarily acts as an agonist on the same cell surface receptor as the endocannabinoid anandamide (AEA), cannabinoid receptor 1 (CB1R) [14]. Activity following AEA-CB1R interaction controls many areas involved in migraine pathophysiology, including thalamic pain relays, basal ganglia activity, and cerebellar regulation [15]. Simplistically, THC enables correction of the mechanisms associated with migraine through endogenous G protein–coupled receptor (GPCR) signaling.

CBD's interactions within the body are more complex than those of THC's. While THC's effects are mediated largely by CB1R, CBD displays an inappreciable active site affinity for cannabinoid receptors [16]. CBD's action involves both metabotropic and inotropic effects. CBD's metabotropic effects include balancing excitatory cerebral signaling by inhibition of GPR55 [17•]. CBD's ionotropic effects include the reduction of sodium current by stabilizing lipid membranes associated with Nav channels [18].

As phytocannabinoids, THC and CBD can provide migraine relief beyond currently available pharmaceutical treatments by supplementing low levels of endocannabinoids, including anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The Clinical Endocannabinoid Deficiency (CED) theory suggests that endogenous cannabinoids may play a role in migraine pathophysiology, especially in chronic migraine [19•]. Evidence exists to suggest that the chronic migraine population has significantly lower levels of cerebrospinal fluid AEA compared to non-migraine controls [20]. Furthermore, significantly lower levels of AEA reuptake and metabolism enzymes have been observed in the chronic migraine population [21]. This tonic decrease in reuptake and degradation of AEA may reflect a physiologic response to adaptively increase cannabinoid levels in patients with chronic migraine. The evidence supporting CED represents an opportunity for medical cannabis to further normalize cannabinoid levels within the body. While the endocannabinoid system of a patient with chronic migraine attempts to correct low endocannabinoid levels by reducing reuptake and degradation, THC and CBD can augment this adaption by directly enhancing cannabinoid tone within the body.

CED may also explain the female predominance in migraine disease. Female patients have exhibited an increased degradation of AEA via fatty acid hydroxylase (FAAH) compared to males [22]. These findings help to assist in rationalizing individual treatment plans and properly addressing migraine pathophysiology through a physician-guided supplementation of appropriate cannabinoids within a comprehensive migraine care plan.

The encompassing perspective of basic science and clinical treatment rationale that a physician has concerning inflammatory conditions is required to understand the relevance of these deficiencies. A decrease in AEA levels can also be accomplished through a family of enzymes called cyclooxygenases (COX) that can transform AEA into pro-inflammatory mediators [23]. COX-2 is elevated during migraine attacks and is relevant in migraine treatment, with many patients successfully targeting migraine attacks with non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit COX, such as ibuprofen. However, the field of headache medicine recognizes that NSAIDs alone often provide suboptimal treatment and are aware of the adverse effects (AEs) of overuse, including gastric irritation [24]. While successful migraine treatment may warrant the replacement of AEA, the mechanism of inactivation should also be taken into consideration; otherwise, the supplementation may not affect the patient.

Similar to modern pharmaceutical therapy, appropriate medical supplementation of cannabinoids should exhibit caution when using high dosages, especially with compounds that contain elevated levels of certain cannabinoids. High THC levels often limit therapeutic potential within medical cannabis therapy due to a range of potentially undesirable symptoms, including euphoria, anxiety, psychosis, altered perception, and diminished memory [25].

Specific to migraine treatment, THC exhibits both a dose-dependent and time-dependent induction effect on COX, indicating that regular supplementation with high-dose THC may further exacerbate a headache [26]. This can be mitigated by allowing physicians to establish strong patient-physician relationships that enable a properly guided cannabis therapy, with the regulation of THC supplementation and the incorporation of therapeutics that complement each other, including NSAIDs.

CBD is considerably more tolerable than THC, with one study indicating no difference between placebo and 600 mg of CBD exposure in pulse rate, blood pressure, or motor and cognitive performance [27]. However, supraphysiological levels of CBD have inhibited cytochrome p450 3A4 (CYP3A4), which is responsible for the metabolism of 60–70% of drugs in humans, including CBD [28, 29]. This too can be mitigated by a physician-guided cannabis therapy, with

the regulation of CBD supplementation and monitoring levels of therapeutics that are co-metabolized.

There exist two legal parallel programs that allow patients to incorporate cannabis into migraine therapy. Patients can access chemovar type III (CBD-dominant) cannabis through the federal 2018 Farm Bill that legalized hemp-based CBD products containing ≤ 0.3% THC. In thirty-six states, 4 US territories, and the District of Columbia, physicians can legally certify patients for medical cannabis and control cannabinoid ratios specifically for the patient's condition. While state-based programs vary, most allow patients access to chemovar type I (THC-dominant), II (equal amounts of THC and CBD), and III.

While federal quality regulations for CBD are forthcoming, many state-based medical cannabis programs require strict quality analysis. For instance, New York State requires medical cannabis to be tested for cannabinoid potency, heavy metals, pesticides, and microbiology. Recent investigations on federally regulated hemp-based products have revealed high rates of CBD potency mislabeling and contamination [30–32].

The pre-clinical background of cannabis and migraine has led many physicians, scientists, and patients, alike, to incorporate cannabis into migraine therapy. However, the majority of clinical research surrounding the use of cannabis and migraine comes from retrospective or observational studies, with most relying on self-reported data through surveys. No peer-reviewed articles exist on cannabis and migraine from placebo-controlled, double-blinded, multicenter studies, the gold standard of clinical trials.

Many of the studies currently available have suggested that cannabis is helpful for migraine, but patients and physicians should be aware of side effects and limitations associated with cannabis treatment. While this article will be reviewing clinical studies in detail below, simply reflecting on pre-clinical studies accurately can conclude appropriate use of cannabis may yield relief, inappropriate use of cannabis will yield unwanted effects, and much of this controversial treatment remains undiscovered to the scientific community. This article aims to review published literature on the intersection of cannabis and migraine to provide greater clarity on the role of emerging medical cannabis therapies for migraine treatment.

Pre-Clinical Rational of Cannabis and Migraine

Pre-clinical investigations examining the use of cannabis in the treatment of migraine are promising, but their results must be carefully extrapolated in the context of clinical research and management. While cannabis was a mainstay of migraine treatment between 1842 and 1942, much of the knowledge surrounding cannabinoid treatment is a recent discovery [33]. Isolation of CBD occurred in 1963, with THC shortly after in 1964. However, the discovery of cannabinoid receptors and endogenous cannabinoids was not until the 1990s followed by evidence of cannabinoid activity through non-cannabinoid receptors in the early twenty-first century.

While both THC and CBD are considered to be psychoactive, defined as impacting brain function, THC is responsible for the euphoric effects that recreational and medicinal cannabis users may experience. THC's effects are largely based on partial agonist activity of CB1R, a GPCR found abundantly throughout the nervous system, both centrally and peripherally [14]. However, THC has also been found to act on cannabinoid receptor 2 (CB2R), GPR55, and opioid receptors [34–36].

For this article, we will focus on CB1R function within the peripheral nervous system, specifically the trigeminal ganglion. CB1R activity regulates nociception from multiple branches of the trigeminal ganglion that are comprised of medium and large diameter afferent pain nerve fibers [37]. In the presence of CB1R agonist activity, pain signals originating peripherally were not acted upon by the CNS [38]. In 2011, a study confirmed that a CB1R partial agonist diminished hyperalgesic behavior within the SpV and area postrema, a region of the brain responsible for the nausea/vomiting response associated with migraine [39]. In 2013, CB1R activity acted through ventrolateral periaqueductal gray (vlPAG) to attenuate trigeminovascular transmission and decrease the resting tone of the trigeminovascular system [40]. In 2018, THC given at 0.32 mg/kg to a female rat model was proven to exhibit an anti-migraine effect [41••]. The anti-migraine effect of THC observed in a female rat model also involves secondary partial agonist activity on CB2R.

Compared to CB1R's primary action on neuronal transmission, CB2R favors regulation of the immune system [34]. CB2R's unique immunomodulation has evidence of mitogen-activated protein kinase (MAPK) mediated gene expression with both cytoprotective and cytotoxic effects [42]. CB2R activation is associated with both anti-inflammation and pro-inflammation effects. Anti-inflammatory effects include decreasing tumor necrosis factor-α (TNF-α) and prostaglandin D2. Pro-inflammatory effects include an increase in leukocyte migration and interleukin-8 [42].

Specific to migraine, stimulation of CB2R counteracted acute migraine-like pain in rat models [43]. Additionally, following the logic of CB2R activity affecting gene expression, these immunomodulatory effects were found to be persistent with no abrupt withdrawal. While tolerance was observed in CB1R agonism, CB2R agonism did not display tolerance or reward-seeking behavior [34]. The activity that THC has on the cannabinoid system through CB1R and CB2R provides rationale in proper utilization for disease states, especially migraine.

Beyond the classically defined cannabinoid receptors CB1R and CB2R, THC also activates GPR55, a GPCR with localization similar to CB1R [35]. Unlike ion channel blocking potential that results from THC-CB1R interaction, THC's agonism on GPR55 increases intracellular calcium and enhances excitatory neuronal signaling. THC-GPR55 interaction suggests that THC at certain doses might have a pronociceptive role that should be taken into account during cannabinoid supplementation.

Another GPCR that THC has been founded to interact with is the μ opioid receptor, the target in the disruption of pain by opioids. Studies have found that THC alone does not attenuate pain through opioid receptors, but rather enhances opioid receptor signaling [36]. With the co-administration of THC, opioids can achieve higher levels of anti-nociception with less opioid exposure. Interestingly, THC's enhanced opioid signaling comes without unwanted side effects, including respiratory depression and abuse [36, 44, 45].

CBD is also a phytocannabinoid that has pre-clinical evidence to justify use in disease states, especially migraine. Contrary to THC, CBD exerts effects largely independently from the currently defined cannabinoid system. The mechanisms of action behind CBD include both direct interaction with cellular targets and secondary messengers produced from GPCR signaling.

While THC and CBD both bind to CB1R, THC exhibits partial agonist activity and CBD exhibits negative allosteric modulation [46]. This unique CBD-CB1R interaction restrains both THC and endocannabinoid potential within receptor signaling. Exposure to cannabis that contains CBD has the potential to maximize THC's therapeutic effects with minimal AEs.

Similar in theory, but opposite in mechanism, CBD is a positive allosteric modulator on μ and δ opioid receptors [47]. Therefore, both THC and CBD have the potential to enhance opioid signaling with less opioid exposure and associated risk. In the setting of pain requiring opioid control, exposure to CBD has the potential to improve opioid's therapeutic efficacy and minimize AEs. CBD's therapeutic potential extends beyond allosteric receptor modulation, including GPR55 antagonism, transient receptor potential vanilloid receptor 1 (TPVR1) agonism, FAAH inhibition, and serotonin 1A receptor (5-HT_{1A}] agonism, and stabilization of inactivated Nav channels [17, 18, 48–50].

GPR55 is viewed by some as a third cannabinoid receptor (CB3R) with THC, CBD, and AEA exhibiting binding affinities, with efforts in progress to clone this receptor [51]. CBD provides an antagonism on GPR55, mitigating pronociception from THC and other pain relays on GPR55. CBD-GPR55 interaction is the proposed anti-epileptic mechanism behind CBD's effect on the hippocampal dentate gyrus of patients with Dravet syndrome [17•]. Antagonism of GPR55 by CBD results in increased inhibitory neuronal transmission, representing a calming of the brain for patients with seizures and potentially patients with migraine.

TRPV1 is also referred to as the capsaicin receptor and functions as an ion channel that serves to detect noxious stimuli and trigger pain signals [48]. While CBD serves as an agonist on TRPV1, this action does not yield noxious pain signals, but rather desensitizes the ion channel. Studies with high-dose CBD (10–50 mg/kg) have shown that CBD could act on TRPV1 to inhibit pain afferents related to the trigeminovascular system [16].

FAAH overactivity and the resultant decrease in endocannabinoid tone has been proposed as a potential pathophysiologic mechanism of migraine, especially in female patients with migraine [22, 51]. CBD has been shown to inhibit FAAH activity. Mouse models showed a 66% decrease in FAAH activity when exposed to CBD, while THC exhibited a more modest reduction of 31% [52]. CBD presents as a therapeutic that serves to both attenuate high levels of FAAH activity and permit physiologic levels of AEA.

5-HT potentiation is utilized in both headache (5-$HT_{1B/1D}$ and 5-HT_{1F} agonism] and anxiety treatment (5-HT reuptake), with CBD providing an overlapping mechanism on 5-HT_{1A} activation and increasing 5-HT tone. Anxiety is a common comorbidity in patients with migraine, especially chronic phenotypes, that is addressed in a comprehensive care plan. CBD has been found to act as an agonist on 5-HT_{1A} which serves as the autoregulatory receptor for serotonin release [50]. In 5-HT_{1A} knock out models, stressors elicited a state of fear and anxiety as neurons could not properly sense 5-HT levels [53]. Low-dose, repetitive exposure to CBD (0.1–1.0 mg/kg) has been shown to increase 5-HT firing, yielding anxiolytic effects and supplementing anti-nociceptive effects [50]. Repetitive exposure to low-dose CBD may address anxiety associated with migraine disease and compliment an anti-nociceptive regimen.

The lipophilic nature of CBD has been shown to directly interact with cell membranes by stabilizing inactivated Nav channels that conduct neuronal transmissions to synaptic terminals. This represents a unique, receptor-independent mechanism that relies on the inherent properties of CBD. This Nav inhibition is temperature-dependent and mediated by direct interactions between CBD and lipid rafts associated with Nav [18]. By keeping Nav channels closed, CBD has the potential to mimic sodium channel blockers that are commonly used in prophylactic headache medicine, including amitriptyline and topiramate.

THC and CBD have shown promise in pre-clinical trials, but given the multiple targets of both, their interaction with each other, and the possibility of other cannabinoids impacting their effects, precautions must be taken in clinical trials and with patient use of medical cannabis. This evidence serves to support the cautious excitement the authors have on medical cannabis and rationalizes an evidence-based,

physician-guided approach to medical supplementation of cannabinoids for the treatment of migraine disease..

Clinical Studies of Cannabis and Migraine

Bold investigations applying pre-clinical evidence to the clinical setting support the thoughtful excitement of cannabis for migraine treatment. Unfortunately, most clinical investigations are observational or retrospective in nature, rely on patients to self-report outcomes, and lack randomization and placebo controls. Despite the lack of these quality standards, the available research surrounding cannabis and migraine helps to formulate insights into best clinical practices.

The use of medical cannabis for the treatment of migraine has become increasingly more common. In 2016, a cross-sectional survey of patients utilizing medical cannabis in Washington State found 35.5% were using medical cannabis to treat "headache/migraine" [54]. We estimate that this number has grown as access to cannabis therapy expands. Since the 2016 survey, an additional 9 states have legalized medical cannabis and state-regulated qualifying conditions have evolved to include migraine. With the increased prevalence of cannabis treatment for migraine, research has been generated from the following patients certified for state-based cannabis programs.

Cannabis and Migraine Frequency

In 2016, a retrospective chart review of 121 patients utilizing medical cannabis for migraine disease in Colorado observed a decrease in migraine frequency among 85.1% of patients, over an average of 21.8 months [55•]. The decrease in mean monthly migraine days (MMD) across the sample population was 55.8% (10.4 to 4.6 migraines per month). Concomitant prescription migraine therapy was used in 43.1%, but no significant reduction in conventional headache medication was reported. Nearly all patients, 90.9%, utilized cannabis for both migraine prophylaxis and acute treatment.

While all forms of medical cannabis yielded positive effects, the edible form presented with the most negative effects, including somnolence. This likely occurs because of the greater production of the active metabolite 11-hydroxy-tetrahydrocannabinol via hepatic metabolism of THC that contributes to somnolence. Medical cannabis treatment was a well-tolerated migraine treatment that displayed remarkable effects on frequency. However, the lack of placebo, blinding, and randomization prohibits assigning causation between cannabis exposure and migraine improvement.

In 2020, an Israeli cross-sectional, self-reporting survey of 145 patients with migraine provided further evidence to suggest medical cannabis reduces migraine frequency, over an average of 3 years [10••]. Sixty-one percent of patients reduced their mean monthly migraines by ≥ 50%. The study classified patients with ≥ 50% reduction in mean monthly migraine days as responders. No significant differences between demographic or migraine features were present between responders and non-responders, representing a similar baseline disease burden. Similar to the 2016 chart review, 45% utilized concomitant conventional pharmaceutical analgesics.

Responders did significantly vary in migraine disability and analgesic consumption. Responders exhibited significantly less migraine disability through validated measures, including the Migraine Disability Scale (MIDAS), Headache Impact Test (HIT-6), and Pittsburg Sleep Quality Index (PSQI). Responders also consumed fewer opioids and triptan medications. Between the improvement in disability and medication usage, the study provides evidence that cannabis utilization for migraine treatment significantly reduces disease burden.

No migraine response or side effect differences were observed between sublingual, inhalation, and vaporization administration. AEs were observed at a higher rate, 37% of patients, compared to the 2016 Colorado chart review data.

Remarkable insights into specific cannabinoid exposure and migraine outcomes were obtained, with chemovar type I treatment making up 92% of exposure in responders, despite 50 unique cannabinoid combinations. For acute inhaled cannabis therapy, two phytocannabinoids under investigation, ms_373_15c and ms_331_18d, were identified as being correlated with responders utilizing smoked or inhaled cannabis. These results, containing similar limitations to the aforementioned chart review, propose that chemovar type I exposure with certain levels of unspecified phytocannabinoids may represent optimal migraine treatment.

While the above clinical studies are peer-reviewed journal articles, the authors recognize poster presentations from established international conferences to allow insight into potential future peer-reviewed data, especially when the results match and further currently accepted data. In 2019, a retrospective chart review from New York was presented at the American Academy of Neurology's (AAN) Annual Meeting that further supported medical cannabis reducing migraine frequency [56•]. This 316 patient chart review had a narrow focus on patients with chronic migraine, diagnosed by the United Council for Neurologic Subspecialties-certified (UCNS) headache subspecialists. While this sample represented a difficult to treat population, 88% reported improvement of their migraine disease status on medical cannabis.

This chronic migraine chart review observed a 42.1% decrease (12.6 to 7.30) in mean monthly migraine days with cannabis. Patient-reported improvements in anxiety, sleep,

and mood occurred at rates of 40%, 31%, and 26%, respectively. Both chemovar types I and III yielded significantly higher rates of improvement in anxiety, sleep, and mood compared to chemovar type II treatment. Seventy-seven percent of patients utilized concomitant conventional migraine treatment, a higher rate than other studies likely due to the nature of the diagnosed disease.

After an average medical cannabis treatment of 5.63 months, no decrease in acute headache medication usage between baseline and follow-up was observed. However, there was a significant difference in the reduction of headache medication usage between chemovar type I treatment compared to both chemovar types II and III. Fifty-six percent of patients utilizing opioid medication(s) for chronic migraine-related pain decreased opioid consumption. Rates of AEs were nearly an average of the previous studies, with 25% of patients reporting AEs, no severe AEs reported, and 1.3% discontinuing due to AEs. No difference in AEs was observed between chemovar type treatment. In the context of chronic migraine, the multi-compound, multi-target therapeutic potential of medical cannabis reduced pain, addressed comorbidities, and decreased opioid consumption with minimal and tolerable AEs.

Cannabis and Migraine Severity

In 2019, the effect of inhaled medical cannabis administration on migraine severity was analyzed through a patient-reported mobile application data survey. Formative pre- and post-inhalation data were self-reported into an app. Over 16 months, 7441 4-h sessions between 653 patients showed that 88% of patients reported a decrease in migraine severity with inhaled cannabis [57••]. The sample's mean migraine severity rating decreased by 49.6% (pre 6.65, post 3.30) with significant differences between individuals and greater reductions with a higher pre-inhalation severity rating. The mean THC content was 14.9%, with a range of 0–77%, and the mean CBD content was 2.58% with a range of 0–50.7%. These wide ranges help to introduce that no significance was found in THC or CBD content for severity reduction. Severity was also reduced regardless of dose and type of cannabis preparation, flower, or concentration.

In terms of adverse effects, this study focused on the potential of tolerance over the course of a patient's treatment history. Patients using inhalation for migraine treatment did not experience a lessening of reduction across a history of sessions or a change in pre-inhalation migraine severity. These results suggest that cannabis is an appropriate repetitive acute therapy for migraines over time, without a reduction in efficacy or signs suggestive of medication overuse headache. However, the use of cannabis flower products required a higher dose over time to sustain migraine reductions. No change in dose requirement was observed among patients utilizing cannabis concentrate, although a minority of the data originated from patients utilizing concentrate.

This study suggests that inhaled cannabis concentrate may be effective for acute migraine treatment. Specific dosages, THC content, and CBD content do not appear to play a role in this severity reduction. While additional studies with prospective research quality controls are required, these results did not find evidence of tolerance in analyses of long-term effectiveness, efficiency, or pre-treatment response. Future investigations are also required to understand why patients treating migraines did not develop tolerance under concentrate use, but patients treating headaches did develop signs of tolerance with inhaled cannabis treatment.

Cannabis, Migraine, and Modern Pharmaceuticals

One of the standards to measure medical cannabis effectiveness is independence from pharmaceuticals. In 2016, a study found evidence that cannabis could replace certain medications that had clinical use overlap with cannabinoids [58]. By analyzing Medicare D prescribing patterns, states that implemented medical cannabis programs were found to use significantly less daily doses of prescriptions for pain, seizures, depression, psychosis, anxiety, nausea, and sleep disorders, in descending order. This reduction of medications across multiple condition categories was estimated to represent $165 million in 2013 when only 24 states provided access to medical cannabis.

In 2017, a survey of medical cannabis patients in New England found that 66% of patients were able to reduce migraine medications [59]. However, this survey consisted of a small, self-reported sample of patients with migraine that did not have clinical documentation of migraine. A Canadian survey initiated in 2018 set out to address these limitations. This later survey found that cannabis has the potential to reduce pharmaceuticals in patients with migraine [60••]. Utilizing a validated, patient-administered migraine diagnosis tool, the study was able to conclude with 97% confidence that 343 patients surveyed were suffering from migraine disease. Similar to results seen in the 2020 Israeli cross-sectional survey, 2019 New York chart review poster, and the 2017 New England survey, 45.1% of patients likely suffering from migraine reduced opioid consumption with similar reductions in anti-anxiety/depression medications (41%). Twenty-two percent of the study population reduced NSAIDs. Over half (59.5%) of patients likely suffering from migraine disease were able to reduce prescription drug consumption.

Gender and racial differences have been observed in medication reduction with cannabis, favoring women/girls over men/boys, and Native American/Asian/Pacific Islanders over Caucasians [61]. The differences between medical cannabis use and non-medical cannabis use are beyond the scope of this article; however, the same study found that the odds of

reduction in prescription usage is nearly five times greater among medical users than non-medical users. This data helps supports that individualized and physician-supported cannabis treatment plans are most effective.

Beyond a reduction of pharmaceutical usage with medical cannabis, better control of treatment-resistant pain has also been observed with medical cannabis. A prospective, open-label study showed that improvement was noted in 65.9% of patients suffering from chronic pain who had already experienced treatment failures with multiple analgesics [62]. Significant decreases in pain score, social disability, emotional disability, and sleep difficulties were observed. AEs were present within the study, with 5.3% discontinuing due to AEs. These results suggest that within a setting of treatment-refractory pain, medical cannabis may have a role in mitigating the perception of refractory, chronic pain, especially applicable to treatment-resistant migraines with chronic phenotypes.

Studies that compare cannabis to conventional migraine treatments are sorely missing. As of January 2020, 40 full-text, published, double-blind, randomized clinical trials of cannabis analgesia for non-cancer pain exist and were reviewed by Wong, et al. [63]. Only one of the trials was conducted on headaches. In 2012, nabilone, a synthetic THC mimic, was used in a crossover study for medication overuse headache (MOH), a headache disorder with similarities to migraine.

Over an 8-week treatment period, daily oral nabilone (0.5 mg) was found to be more effective than NSAIDs in MOH for pain intensity, analgesic intake, and quality of life [64•]. Both nabilone and ibuprofen (daily 600 mg), a non-selective NSAID, provided a significant difference in pain intensity. However, nabilone treatment reduced pain intensity from baseline visual analogue scale significantly more than ibuprofen (27.9% reduction compared to 17.8% reduction). Both treatments also reduced daily analgesic intake (DAI) from baseline (2.1 days), but nabilone treatment was associated with significantly less DAI than ibuprofen treatment 57.7% (0.89 days) vs. 36.2% (1.34 days). Furthermore, nabilone was able to reduce DAI in both single- and multi-drug overusers, while ibuprofen only reduced DAI in single-drug overusers. Quality of life measures, including HIT-6, Short Form-36 (SF-36) Physical Component, and SF-36 Mental Component, indicated significant improvement with nabilone treatment that was not present with ibuprofen. Both treatments resulted in similar rates of discontinuation due to AEs. The AEs that led to discontinuation were mild and resolved within 1 month of discontinuation. This crossover study allowed for a higher level of observations and comparisons previously unavailable. While this crossover study was small in size, 26 patients, this prospective study suggests that cannabis treatment is effective for medication overuse headache and potentially migraine.

Similar to the rationale behind discussing the 2019 New York chronic migraine chart review, a 2017 prospective cannabis trial was presented to the European Academy of Neurology (EAN) that suggested that prophylactic medical cannabis, oral doses of 200 mg with 0.4% THC and 9% CBD, yielded a similar reduction of migraine attacks (40.4%) to amitriptyline (40.1%) [65•]. Amitriptyline treatment has level B evidence for migraine prevention from the AAN, which recommends that amitriptyline should be considered for migraine prevention. Taken acutely, this THC/CBD combination also yielded a 43.5% reduction in migraine severity. While this poster presentation data has not been published, this preliminary data is supported by the previously mentioned studies and furthers the role of medical cannabis in migraine prophylaxis with specific dosing.

While drug-drug interactions with cannabis appear to be insignificant, pre-clinical studies highlight CBD as an inhibitor of CYP3A4 [28]. This inhibition was found to be present only at levels of CBD unheard of in clinical practice. Calculations have found that 4,900 mg of daily CBD consumption is required to achieve inhibition seen in pre-clinical studies [66]. However, these calculations assume the patient is not exposed to medications that are known to inhibit or induce CYP enzymes, including azoles and rifampin, respectively. Under a physician-guided medical cannabis therapy, the patient is afforded the professional knowledge of drug-drug interactions, especially in the case of polypharmacy. Specific to migraine, gepants, and certain triptans, including eletriptan, are metabolized by CYP3A4 and should be considered in cannabis therapy. Due to the CYP-independent degradation of monoclonal antibodies, concentrations of monoclonal antibodies against CGRP or CGRP receptors should not be affected by CBD's drug interactions.

The considerable mechanistic overlap between cannabinoids and opioids, anti-depressants, NSAIDs, triptans, CGRP antagonists, and ion channel blockers is demonstrated in Fig. 1. This overlap helps to explain the findings present within recent cannabis and migraine clinical literature [67••]. Opioids act as an agonist on μ opioid receptors to decrease pain; cannabinoids act as beneficial modulators on the same receptors. Anti-depressants act to increase available serotonin within synaptic clefts by inhibiting reuptake; cannabinoids act to increase available serotonin by increasing the firing rate of serotonin from neurons. NSAIDs provide anti-inflammation by blocking COX; cannabinoids provide anti-inflammation by reducing cytokines and altering gene transcription. Triptans act to inhibit neurotransmitter release via 5-$HT_{1B/D}$; cannabinoids inhibit neurotransmitter release via cannabinoid receptor interaction. CGRP antagonists inhibit the action of neurotransmitter CGRP; cannabinoids also inhibit the activity of CGRP by inhibiting neurotransmitter release. Sodium channel blockers, including amitriptyline and topiramate, blocks propagation of migraine pain signals by inhibiting

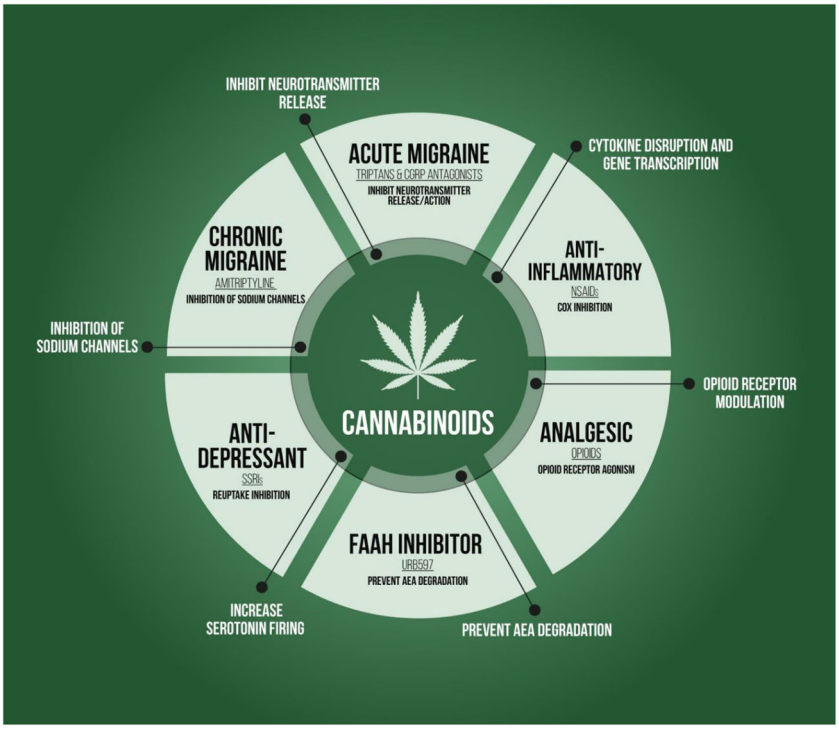

Fig. 1 Mechanistic overlap between cannabinoid and conventional pharmaceutical treatments

ion conductance; cannabinoids block propagation of migraine pain signals by inhibiting ion conductance, and excitatory nerve transmission.

Cannabinoids may also provide benefits beyond their overlap with currently available medications, specifically their role in FAAH inhibition. Upon proper exposure, cannabinoids have been found to prevent the destruction of endogenous cannabinoids and other bioactive molecules, providing the opportunity to restore endogenous cannabinoid tone and inhibit inflammation [49]. This inhibition of FAAH represents a new frontier for migraine prevention, only available presently in pre-clinical trials.

Conclusions and Clinical Considerations

Medical cannabis is a promising therapy for migraine that requires an intricate balance of cannabinoid supplementation within a comprehensive care plan. Practicing with medical cannabis is a departure from traditional drug therapy as multiple cannabinoids are present within a state-based cannabis certification for a specific chemovar. Each cannabinoid within a cannabis compound likely targets multiple sites of action and each cannabinoid impacts the effects of others. This multi-compound, multi-target approach is a double-edged sword. Medical cannabis has the potential to yield remarkably positive effects across multiple domains of migraine symptomatology, not present in a conventional single-compound, single-target approach. However, this approach involves a dizzying number of combinations and interactions that have the potential for undesirable effects.

The lack of research standards surrounding this series of complex cannabinoid interactions represents a second departure from traditional drug therapy. Laws governing the practice of medical cannabis use in patients do not afford physicians the same standards of research data available on other therapies, rather it relies on physicians to reflect on the limited research literature available and employ the true practice of their craft. A balanced, comprehensive, physician-guided approach to this complicated therapy is the way forward.

The paucity of literature does not allow the authors to conclude any specific dosing instructions that will be the silver bullet for all migraines, nor do we believe that there is a one-size-fits-all approach to cannabis for the treatment of migraine. Medical cannabis dosing is an individualized process that depends on the underlying endocannabinoid tone. However, the evidence is clear that cannabis is a promising therapy for migraine frequency and severity. The multi-compound, multi-target approach also enables physicians to address the multifaceted nature of migraine, including anxiety, depression, and sleep.

The recommendations henceforth are evidence-based and supported by observations from the treatment of over 13,000 patients with cannabis at a Dent Neurologic Institute, a comprehensive neurologic institute in Buffalo, New York (see Fig. 2). We recommend beginning cannabinoid therapy by establishing a strong patient-physician relationship where the patient's pathophysiology is understood and treatment goals are clearly

Fig. 2 **a**–**c** Recommended clinical management of patients with migraine utilizing medical cannabis

established. Merely certifying patients based on state regulations is inadequate for advancing the legitimate use of cannabis. Only initiate medical cannabis as a part of a comprehensive migraine treatment plan if appropriate and the risks, benefits, and alternatives are agreed upon. Begin by introducing doses of cannabinoids at low doses with titration upwards to the desired effect. The mantra "start low and go slow" applies to medical cannabis.

Appreciation of cannabis' pharmacokinetics enables the clinician to choose the route of administration and concentration profile that best meets the patient's needs. If using cannabis to treat a migraine attack, sublingual or inhalation provides the patient with rapid onset of action (i.e., short T-max and half-life) to rapidly treat the migraine. If using cannabis to prophylactically treat chronic migraine, the pharmacokinetic administration profile must provide a longer half-life to provide continuing relief from migraine pathophysiology. A longer half-life can be achieved via orally absorbed formulations. It is important to point out that inhaled and sublingual absorbed formulations do not undergo first-pass hepatic metabolism, whereas orally absorbed formulations undergo extensive first-pass metabolism. The doses for inhaled and sublingual formulations are expected to be lower than oral formulations.

Inhaled concentrate presents as a treatment option for migraine attacks, but clinical considerations, including

pulmonary conditions, must be taken into account by the certifying physician. Sublingual dosing carries an intermediate half-life that may be considered for patients unable to use inhaled preparations. Oral capsule dosing carries an appreciably long half-life that should be utilized for prophylaxis and not for acute migraines.

Dose titration should be done practically, slow enough not to disturb the patient with unwanted effects but fast enough for effect. Titration steps can be accomplished in 1- or 2-week intervals depending on patient-physician comfort. Follow-up appointments should be scheduled to reflect on titration changes. Most importantly, patients must have the ability to communicate concerns with their certifying physicians between appointments.

The proper chemovar must also be matched to the patient. THC's anti-nociceptive effects may require a chemovar type I or II. CBD's anxiolytic or anti-inflammatory effects may require a chemovar type II or III. However, patient responses to each chemovar are highly individualized, including AEs. The dominating presence of THC in chemovar type I may bring an increased risk of AEs when using chemovar type I over chemovar type II or III. Patients naïve to cannabis exposure should be started on a chemovar type II or III and titrate as needed. Patients with heavy exposure to recreational cannabis containing high levels of THC may respond better to chemovar type I.

Patients can use hemp-based CBD products as chemovar type III treatment without a physician's approval. When using "over the counter" CBD products, the dosage is dependent on the chronicity of symptoms patients are seeking to treat. Chronic symptoms need around the clock treatment, including three times a day dosing. Dosing should start with 5–10 mg nightly during week 1, 5–10 mg twice a day during week 2, then 5–10 mg three times a day during week three, for a total of 30 mg. After a month, the dose may be increased to 20 mg three times a day, for a total of 60 mg. The maximum dose of CBD is patient- and illness-dependent; up to 600 mg/day has been well-tolerated in patients [66]. It is not uncommon to combine medical cannabis and hemp-based CBD products. This is a cost-effective approach and teaches patients to understand the differences between THC and CBD effects on their well-being. Trial and error may be required while gauging proper dosage and is undoubtedly dependent on the patient's age, weight, medical condition, polypharmacy, and experience with cannabis products. When choosing CBD products, ensure that each product has undergone third-party testing.

Patients should be aware of side effects previously reported on medical cannabis, including somnolence, dizziness, cognitive impairments, gastric upset, euphoria, psychosis, and worsening of headache. These represent the over-supplementation of cannabinoids, especially THC. Cannabis is generally contraindicated in pregnancy, breastfeeding, and pediatrics. While not contraindicated in the elderly, choosing a higher chemovar type is suggested to mitigate cognitive AEs associated with THC exposure. Reporting of these effects does not exclude a future care plan with medical cannabis, rather a redistribution of specific cannabinoid levels, with an emphasis on CBD to attenuate THC's negative effects.

Remarkable barriers that have effectively prevented the gold standard of trials for cannabis and migraine, and thus cannot be ignored by this article. One of the many barriers has been set in place since 1970, as cannabis was classified as a Schedule I drug, alongside substances such as heroin. This classification has existed despite the National Commission on Marihuana and Drug Abuse report, "Marihuana, a Signal of Misunderstanding," inability to defend the Schedule I status. The national commission compared cannabis to alcohol and viewed cannabis use with a level of risk that can safely be deferred to individuals while the country can effectively minimize misuse.

Medical cannabis in the present format has alienated entire populations, especially those of low socioeconomic status that cannot afford this out-of-pocket treatment. As legislation expands the legality of cannabis, we must allow all patient populations a cost-effective opportunity for cannabis treatment. As this country progresses towards utilization and legalization of cannabis, professional perspectives, including those in public health and policy, must be incorporated to complement physician guidance.

Addressing the many barriers present with modern medical cannabis use will help to guide the migraine community of patients, family members, physicians, and researchers in best-utilizing cannabis. In addition to the appropriate supplementation of cannabis for the treatment of migraine, the authors cannot emphasize enough the need for rescheduling to facilitate a better understanding of cannabis for migraine disease and other disorders. We hope that the next review of recent literature can reflect on additional, high-quality clinical trial data.

Acknowledgments The authors would like to thank Christopher C. Ralyea, Jr., MBA, (Dent Neurologic Institute) of the Dent Cannabis Research Center for editorial assistance.

Compliance with Ethical Standards

Conflict of Interest

(1) Dr. Mechtler reports advisory board appointment, speakers bureau participation, and/or research support from the following: Amgen, Avanir Pharmaceuticals, Biohaven Pharmaceuticals, Boston Biomedical Inc., CellDex Pharmaceuticals, Delmar Pharmaceuticals, electroCore, Novartis, Orbis Pharmaceuticals, Promius Pharma, Teva Pharmaceuticals, The Harry Dent Family Foundation, Inc. Dr. Mechtler also reports being the Medical Director/Consultant for Jushi, Inc.

(2) Dr. Gengo declares no conflict of interest.

(3) Mr. Bargnes has received research support from the Harry Dent Family Foundation, Inc. a 501(c)(3) nonprofit organization dedicated to supporting neuroscience research.

Human/Animal Right or Informed Consent Statement This article is a review and does not contain any studies with human or animal subjects performed by any of the authors.

References

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

1. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain [Internet]. 2018 Feb 21 [cited 2020 Jul 29];19(1). **Available from:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5821623/
2. • Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system—40 years and counting. Lancet Neurol. 2019 Aug 1;18(8):795–804. **Review on migraine pathophysiology.**
3. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain. 2013 Dec;154(Suppl 1):S44–53.
4. Xu X, Liu Y, Dong M, Zou D, Wei Y. Tricyclic antidepressants for preventing migraine in adults. Medicine (Baltimore) [Internet]. 2017 Jun 2 [cited 2020 Jul 18];96(22). **Available from:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5459715/
5. Naegel S, Obermann M. Topiramate in the prevention and treatment of migraine: efficacy, safety and patient preference. Neuropsychiatr Dis Treat. 2010;6:17–28.
6. Levy D, Jakubowski M, Burstein R. Disruption of communication between peripheral and central trigeminovascular neurons mediates the antimigraine action of 5HT1B/1D receptor agonists. Proc Natl Acad Sci. 2004 Mar 23;101(12):4274–9.
7. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017 Nov 30;377(22):2113–22.
8. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, et al. Ubrogepant for the treatment of migraine. N Engl J Med. 2019 Dec 5;381(23):2230–41.
9. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005 Dec 22;78(5):539–48.
10. •• Aviram J, Vysotski Y, Berman P, Lewitus GM, Eisenberg E, Meiri D. Migraine frequency decrease following prolonged medical cannabis treatment: a cross-sectional study. Brain Sci. 2020 Jun 9;10(6). **Cannabis on migraine frequency reduction with cannabinoid specifications.**
11. Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. Eur J Pharmacol. 1998 Jul 17;353(1):23–31.
12. Baram L, Peled E, Berman P, Yellin B, Besser E, Benami M, et al. The heterogeneity and complexity of cannabis extracts as antitumor agents. Oncotarget. 2019 Jun 25;10(41):4091–106.
13. • Baron EP. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: an update on current evidence and cannabis science. Headache J head face pain. 2018;58(7):1139–86. **Review of terpene and flavonoid effects.**
14. Jung SW, Cho AE, Yu W. Exploring the ligand efficacy of cannabinoid receptor 1 (CB1) using molecular dynamics simulations. Sci Rep. 2018 Sep 13;8(1):13787.
15. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci [Internet]. 2018 Mar 13 [cited 2020 Jul 20];19(3). **Available from:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5877694/
16. Bisogno T, Hanuš L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001 Oct;134(4):845–52.
17. • Kaplan JS, Stella N, Catterall WA, Westenbroek RE. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2017 17;114(42):11229–34. **Characterization of CBD mechanism of action.**
18. Ghovanloo M-R, Shuart NG, Mezeyova J, Dean RA, Ruben PC, Goodchild SJ. Inhibitory effects of cannabidiol on voltage-dependent sodium currents. J Biol Chem. 2018 Oct 26;293(43):16546–58.
19. • Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis Cannabinoid Res. 2016 Jul 28;1(1):154–65. **Cannabinoid deficiency and migraine.**
20. Sarchielli P, Pini LA, Coppola F, Rossi C, Baldi A, Mancini ML, Calabresi P Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 2007 Jun;32(6):1384–1390.
21. Cupini LM, Costa C, Sarchielli P, Bari M, Battista N, Eusebi P, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiol Dis. 2008 May;30(2):186–9.
22. Cupini LM, Bari M, Battista N, Argirò G, Finazzi-Agrò A, Calabresi P, et al. Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. Cephalalgia Int J Headache. 2006 Mar;26(3):277–81.
23. Gatta L, Piscitelli F, Giordano C, Boccella S, Lichtman A, Maione S, et al. Discovery of prostamide F2α and its role in inflammatory pain and dorsal horn nociceptive neuron hyperexcitability. PLoS ONE [Internet]. 2012 Feb 21 [cited 2020 Jul 20];7(2). **Available from:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283613/
24. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Neurology. 2012 Apr 24;78(17):1346–53.
25. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 2004 Aug;29(8):1558–72.
26. Chen R, Zhang J, Fan N, Teng Z, Wu Y, Yang H, et al. Δ9-THC-caused synaptic and memory impairments are mediated through COX-2 signaling. Cell. 2013 Nov 21;155(5):1154–65.
27. Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, Borgwardt S, et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Des. 2012;18(32):4966–79.

28. Zendulka O, Dovrtělová G, Nosková K, Turjap M, Šulcová A, Hanuš L, et al. Cannabinoids and cytochrome P450 interactions. Curr Drug Metab. 2016;17(3):206–26.
29. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013 Apr 1;138(1):103–41.
30.•• Gurley BJ, Murphy TP, Gul W, Walker LA, ElSohly M. Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the state of Mississippi. J Diet Suppl. 2020 May 20;0(0):1–9. **Highlights hemp-based CBD quality concern.**
31. Freedman DA, Patel AD. Inadequate regulation contributes to mislabeled online cannabidiol products. Pediatr Neurol Briefs. 32: 3.
32. Hazekamp A. The trouble with CBD oil. Med Cannabis Cannabinoids. 2018 Jun 12;1(1):65–72.
33. Russo E. Hemp for headache. J Cannabis Ther. 2001 Mar 1;1(2): 21–92.
34. Dhopeshwarkar A, Mackie K. CB2 cannabinoid receptors as a therapeutic target—what does the future hold? Mol Pharmacol. 2014 Oct;86(4):430–7.
35. Lauckner JE, Jensen JB, Chen H-Y, Lu H-C, Hille B, Mackie K. GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci U S A. 2008 Feb 19;105(7):2699–704.
36. Maguire DR, France CP. Impact of efficacy at the μ-opioid receptor on antinociceptive effects of combinations of μ-opioid receptor agonists and cannabinoid receptor agonists. J Pharmacol Exp Ther. 2014 Nov;351(2):383–9.
37. PRICE TJ, HELESIC G, PARGHI D, HARGREAVES KM, FLORES CM. The neuronal distribution of cannabinoid receptor type 1 in the trigeminal ganglion of the rat. Neuroscience. 2003;120(1):155–62.
38. Clapper JR, Moreno-Sanz G, Russo R, Guijarro A, Vacondio F, Duranti A, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci. 2010 Oct;13(10):1265–70.
39. Greco R, Mangione AS, Sandrini G, Maccarrone M, Nappi G, Tassorelli C. Effects of anandamide in migraine: data from an animal model. J Headache Pain. 2011 Apr;12(2):177–83.
40. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and "triptan" receptors: implications in migraine. J Neurosci. 2013 Sep 11;33(37): 14869–77.
41.•• Kandasamy R, Dawson CT, Craft RM, Morgan MM. Anti-migraine effect of Δ9-tetrahydrocannabinol in the female rat. Eur J Pharmacol. 2018 Jan 5;818:271–7. **Pre-clinical cannabis for migraine model.**
42. Turcotte C, Blanchet M-R, Laviolette M, Flamand N. The CB2 receptor and its role as a regulator of inflammation. Cell Mol Life Sci. 2016;73(23):4449–70.
43. Greco R, Mangione AS, Sandrini G, Nappi G, Tassorelli C. Activation of CB2 receptors as a potential therapeutic target for migraine: evaluation in an animal model. J Headache Pain. 2014;15(1):14.
44. Cooper ZD, Bedi G, Ramesh D, Balter R, Comer SD, Haney M. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. Neuropsychopharmacology. 2018 Sep;43(10):2046–55.
45. Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacology. 2017 Aug;42(9):1752–65.
46. Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172(20):4790–805.
47. Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. Naunyn Schmiedeberg's Arch Pharmacol. 2006 Feb 1;372(5):354–61.
48. De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, et al. Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011 Aug;163(7):1479–94.
49. Greco R, Demartini C, Zanaboni AM, Tumelero E, Reggiani A, Misto A, et al. FAAH inhibition as a preventive treatment for migraine: a pre-clinical study. Neurobiol Dis. 2020 Feb 1;134:104624.
50. De Gregorio D, McLaughlin RJ, Posa L, Ochoa-Sanchez R, Enns J, Lopez-Canul M, et al. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain. 2019 Jan;160(1):136–50.
51. Mackie K, Stella N. Cannabinoid receptors and endocannabinoids: evidence for new players. AAPS J. 2006 Jun 1;8(2):E298–306.
52. Watanabe K, Kayano Y, Matsunaga T, Yamamoto I, Yoshimura H. Inhibition of anandamide amidase activity in mouse brain microsomes by cannabinoids. Biol Pharm Bull. 1996 Aug;19(8):1109–11.
53. Toth M. 5-HT1A receptor knockout mouse as a genetic model of anxiety. Eur J Pharmacol. 2003 Feb 28;463(1):177–84.
54. Sexton M, Cuttler C, Finnell JS, Mischley LK. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res. 2016;1(1):131–8.
55.• Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of medical marijuana on migraine headache frequency in an adult population. Pharmacother J hum Pharmacol drug Ther. 2016;36(5):505–10. **Cannabis on migraine frequency reduction.**
56.• Mechtler L, Bargnes V, Hart P, McVige J, Saikali N. Medical cannabis for chronic migraine: a retrospective review (P3.10-015). Neurology [Internet]. 2019 Apr 9 [cited 2020 Jul 20];92(15 Supplement). Available from: https://n.neurology.org/content/92/15_Supplement/P3.10-015. **Cannabis for chronic migraine.**
57.•• Cuttler C, Spradlin A, Cleveland MJ, Craft RM. Short- and long-term effects of cannabis on headache and migraine. J Pain [Internet]. 2019 Nov 9 [cited 2020 Jul 20]; Available from: http://www.sciencedirect.com/science/article/pii/S152659001930848X. **Cannabis on migraine severity reduction.**
58. Bradford AC, Bradford WD. Medical marijuana Laws reduce prescription medication use in Medicare part D. Health Aff (Millwood). 2016 Jul 1;35(7):1230–6.
59. Piper BJ, DeKeuster RM, Beals ML, Cobb CM, Burchman CA, Perkinson L, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep: J Psychopharmacol (Oxf) [Internet]. 2017 Apr 4 [cited 2020 Jul 20]; **Available from:** https://journals.sagepub.com/doi/10.1177/0269881117699616
60.•• Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain [Internet]. 2018 May 24 [cited 2020 Jul 20];19(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5968020/. **Cannabis for medication reduction.**
61. Corroon JM, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs – a cross-sectional study. J Pain Res. 2017 May 2;10:989–98.
62. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016 Dec;32(12):1036–43.
63. Wong SSC, Chan WS, Cheung CW. Analgesic effects of cannabinoids for chronic non-cancer pain: a systematic review and meta-

analysis with meta-regression. J Neuroimmune Pharmacol Off J Soc NeuroImmune Pharmacol. 2020 Mar;14.

64.• Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677–84. **Clinical trial of cannabis compared to conventional headache medications.**

65.• Nicolodi M, Sandoval V, Torrini A. Therapeutic use of cannabinoids-dose finding, effects and pilot data of effects in chronic migraine and cluster headache. In EUROPEAN JOURNAL OF NEUROLOGY 2017 Jul 1 (Vol. 24, pp. 287-287). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY. **Clinical trial of cannabis compared to conventional prophylactic migraine medication.**

66. Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. Cannabis Cannabinoid Res. 2017 Jun 1;2(1):139–54.

67.•• Tassorelli C, Greco R, Silberstein SD. The endocannabinoid system in migraine: from bench to pharmacy and back. Curr Opin Neurol. 2019 Jun;32(3):405–412. **Review of cannabinoids and conventional migraine medication overlap.**