Migraine - Prophylactic and Acute Migraine Treatments

An analysis of pharmacological and non-pharmacological options

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Evidence-Based Use of Supplements

ABSTRACT

The goal of this paper is to provide a comprehensive assessment of the data around migraine and relevant therapeutics. Here, we cover pros and cons of traditional treatments and analyze the published peer-reviewed clinical data supporting the use of non-pharmacological options.

Migraines affect at least 1 in 10 people worldwide, and its prevalence is on the rise.1 According to the World Health Organization (WHO), migraine ranks as the 2nd most disabling neurological condition and the 3rd most prevalent medical condition in the world.2,3 Though migraines affect approximately 15% of adults in the United States, only about one quarter of those with chronic migraines receive an accurate diagnosis, and of those who do, fewer than 50% are provided with acute or preventative treatments.4,5
Also problematic is that there is no cure for migraines, and for more than 90% of those who suffer the condition, their migraines interfere with some combination of their work, education, and social activities.6 A longitudinal study on the impact of migraines revealed that more than half of people who suffer from migraines participated in fewer family activities and believed they would be better parents and partners if they did not have migraines.7 Approximately 33% of these patients also reported worry that their migraines could compromise their long-term financial security.

What are Migraines?

A chronic neurological disorder, migraine involves moderate to severe head pain that is often described as throbbing and worsened by head movement or physical activity.4 The head pain may be unilateral and may change sides and often involves the posterior cervical and trapezius regions of the head.4,8 However, migraines can also be bilateral, in which case they may be mistaken for tension-type headaches.9 The headaches are often accompanied by other symptoms, such as sensitivity to light and sound, dizziness, tinnitus1, gastrointestinal disturbances, cognitive impairment, and cutaneous allodynia - or the presence of pain in response to non-painful stimuli being applied to the skin.4,10

The specific symptoms that may arise with migraines include:11-17

- Photophobia
- Phonophobia
- Visual aura
- Neck pain
- Dizziness
- Cutaneous allodynia
- Non-aura visual symptoms
- Vomiting
- Hyperosmia or osmophobia
- Diarrhea

What are the Classic Symptoms?

Migraines are characterized by premonitory and postdromal symptoms. Unlike many other conditions, acute migraines are often preceded by premonitory symptoms that last for hours or days.18 While the most common of these symptoms are fatigue, neck stiffness, and trouble concentrating, there is a wide variety of other symptoms that may be experienced. These symptoms include psychological symptoms, such as anxiety or depression, as well as lacrimation, photophobia, diarrhea, increased urination, food cravings, and nausea.19

Once the migraine resolves, 80% of migraine sufferers undergo a postdromal phase that can potentially last for days.20–23 Symptoms during this phase include fatigue, photophobia, nausea, irritability, and problems with concentration.4

Migraines can occur at any time, but they often occur soon after waking or early in the morning.24,25 The median time for a migraine headache to reach its peak pain intensity is 1 hour, though the median duration is 24 hours.8 There are several specific types of migraines, the details of which are beyond the scope of this review. However, this resource offers a more in-depth discussion of each type of headache.26

What are the Risk Factors for Migraines?

Genetics

Migraines run in families. For those with a parent who suffers from migraines, there is a 40% chance that they too will develop migraines.4 If both parents have migraines, that risk increases to 75%. Research into the genetic contributions to migraines is providing more information on the specific genes that may be involved in migraines. Next-generation sequencing, for instance, will likely lead to the discovery of causal genes and variants.27 Nonetheless, it is clear that the genetic underpinnings of migraine disorder is complex, much like their pathogenesis.27

Age

Early and middle adulthood appear to be the most likely time to experience migraines, though the precise ages during which one is most likely to suffer from migraines depends on how researchers group age. For instance, it has been reported that those between the ages of 25 and 55 are most

likely to suffer from migraines and also that 18- to 44-year-olds have the highest prevalence of migraines.4,28 However, it seems clear that prevalence hits a peak in people's 40s.5

Sex and Race

The lifetime prevalence of migraines is estimated at 33% for women, and 13% in men, though before puberty, migraines occur slightly more frequently in boys than in girls.4,29 Data from 2015 suggest that migraines occur most in American Indian and Alaska Native populations, with a prevalence of more than 18% in these groups. Asians were found to suffer from migraines less than not only these groups but also whites, blacks, and Hispanics. The prevalence amongst Asians was found to be approximately 11%.

Other Factors

Migraine prevalence is over 21% in those who are unemployed and nearly 20% in those with an annual family income of less than $35,000.28 These associations do not, however, provide any information on if these conditions may cause migraines or vice versa. Interestingly, neurologists have been found to suffer from migraines 2 to 3 times more frequently than the general population.30 These findings may be due to better recognition amongst neurologists of the symptoms of migraine.

How are Migraines Conventionally Treated, and are Treatments Safe and Effective?

Pharmacological Interventions

Simple Analgesics

People with mild to moderate migraines are recommended to use mild analgesics like acetaminophen as a first approach to migraines because these drugs offer several relative advantages when compared with other migraine drugs. For instance, they tend to be effective in certain patients, they are less costly, and they are not as likely to lead to adverse side effects.5

Most migraine sufferers use simple analgesics, but many of these patients use a step-care approach, where they move on to migraines-specific drugs when the pain becomes severe enough to warrant something stronger than a simple analgesic.31 Acetaminophen is also often used in combination with NSAIDs and caffeine for a stronger response.32

Acetaminophen is recommended at doses ranging from 1000 milligrams (mg) to 4000 mg taken every 4 hours.32 The downside to acetaminophen is that randomized controlled trials have shown that its efficacy is mainly limited to the treatment of mild to moderate migraines.33,34 Those with more severe migraines may therefore get little relief from acetaminophen and be forced to rely on other interventions.

In addition to the potential lack of adequate efficacy, acetaminophen can lead to adverse side effects. For instance, chronic use of acetaminophen enhances the risk for gastrointestinal bleeding and increases in systolic blood pressure.35 Other risks associated with asthma, kidney injury, liver damage, and cardiovascular disease are also possible, and ongoing research is exploring the effects of in utero exposure to this drug. For these reasons, acetaminophen may not offer a safe and practical long-term solution for migraine sufferers.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used in the acute management of migraines, with some of the most effective NSAIDs being ibuprofen (400 to 2400 mg every 4 hours), acetylsalicylic acid (ASA) (975-100 mg every 4-6 hours), naproxen sodium (500-1375 mg twice a day), and diclofenac potassium (50-150 mg as a single dose for an attack or 3-4 times per day).32

Ibuprofen is used more often than other NSAIDs for migraines management, likely due to its relatively good efficacy, low cost, and availability.32 It is also thought to produce less gastric irritation than ASA. Comprehensive reviews of the efficacy and safety of naproxen sodium in the acute treatment of migraines have shown it to be more effective than placebo in treating moderate to severe migraines but has also demonstrated that it is associated with more adverse events.36

Despite their frequent use, NSAIDs are associated with adverse side effects, including cardiovascular, cerebral, gastrointestinal, hepatic, pulmonary, and renal complications.37 Troublingly, some pathologies that present asymptomatically can be life threatening.38 NSAIDs are also associated with a high rate of adverse drug reactions (ADRs) and are responsible for 30% of hospitalizations that occur due to ADRs.39

Ergots

Ergots and ergot derivatives began being used to treat migraines more than a century ago. However, the use of ergots has been controversial due to the harmful side effects associated with them and challenges with balancing efficacy and safety.40 While ergot formulations have been developed that have more tolerable side effects, including the orally inhaled dihydroergotamine, concerns about vasoconstrictive effects of ergots persist.41,42 In addition to the dangerous adverse effects, other adverse side effects frequently occur as well. Nausea is the most common adverse side effect, and light headedness and leg cramps are also common.43

Triptans

Triptans, which are highly selective serotonin receptor agonists for the 5-HT1B and 5-HT1D receptors, with some relevant activity at the 5-HT1F receptor, are considered first-line drugs for people with moderate to severe migraines.32They are also indicated for menstruation-related migraines.5 Though effective in treating headaches, they are not used preventatively.

The triptans that have good evidence for efficacy in treating acute migraines are almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.32 There is some debate, however, about which triptan is the best to use to combat migraines.44 Dosing can also be complicated. Both oral and non-oral formulations are available, and determining dosage is often a trial-and-error process.4 In addition, repeat dosing may be required after the initial use of triptans.

Triptans can cause vasoconstriction by binding to systemic blood vessel receptors as well as both intracranial and extracranial blood vessels, which likely contributes to their influence on migraines.4 Though effective, an analysis of the safety of triptans by the U.S. Food and Drug Administration (FDA), found that triptan is associated with aneurysms, artery dissections, and pregnancy-related vascular events. Triptans can also lead to an increase in migraine frequency

if overused, as neural adaptations that occur with triptans can increase one's sensitivity to migraine triggers.45 Given the risks, triptans are contraindicated for patients with severe hypertension or with a history of cerebrovascular disease.4,5 Triptans have also been reported to lead to fetal death and intrauterine growth retardation in those who are exposed to triptans during pregnancy and are thus not always considered a good option for pregnant women.46

Beta-Blockers

Beta-blockers whose efficacy is considered well established for preventing migraines include metoprolol, propranolol, and timolol.5 Atenolol and nadolol are also considered likely to be effective, but the evidence is not as high as for the former drugs. Nebivolol may be effective but has not been as extensively investigated as the other beta-blockers. beta-blockers with intrinsic sympathetic activity, such as acebutolol, alprenolol, oxyprenolol, and pindolol do not appear to have the prophylactic value in migraines that other beta-blockers have.47

Some research suggests that when used in combination with behavioral therapy, beta-blockers are particularly effective for improving outcomes related to frequent migraines.48 However, a recent systemic review and meta-analysis found that the trials investigating the effectiveness of beta-blockers in chronic migraines are limited in terms of the evidence they provide on the benefit of these drugs. In addition to questions of efficacy for chronic migraines, the value of beta-blockers may also be limited by potential side effects, the most common of which appear to affect the central nervous system.49,50

Antiepileptic Drugs

Migraines and epilepsy occur via similar mechanisms that involve overexcitability in neocortical cells.51 It is thus not surprising that antiepileptic drugs that target excessive neuronal activity can be effective in migraine treatment.

Divalproex sodium, sodium valproate, and topiramate are thought to be effective preventative treatments for migraines.5 Carbamzepine and lamotrigine are other antiepileptic drug with some evidence for efficacy in combatting migraines.5,52 Despite some reports that gabapentin can be effective in migraines, a recent Cochrane review found that there is insufficient evidence for the use of this antiepileptic in migraines.53

Antiepileptic drugs likely work through several mechanisms, affecting neurotransmitter receptors, neurotransmitter metabolism, and ion channels to reduce excitability and potentially protect neurons.54 These drugs, however, are associated with unwanted side[1] effects, which appear to be particularly common in migraine patients despite the low doses of antiepileptics used in migraines.55

For instance, topiramate has been shown to commonly lead to altered taste, diarrhea, paresthesia, and somnolence in migraines patients.56 In addition, several antiepileptics can lead to adverse outcomes in infants of mothers taking these drugs.52 This risk is high enough with valproate that it is not recommended that women of childbearing potential use this antiepileptic. The most common adverse effects of antiepileptic drugs, however, appear to be those that affect the central nervous system and specifically lead to psychiatric and behavioral changes.57–59

Antidepressants

Unlike depression, migraines respond to drugs that act peripherally. However, meaningful overlap exists between depression and migraines, and both conditions are associated with reduced levels of serotonin.60,61 Antidepressants, particularly those that work through the serotoninergic system have thus been explored for their potential value in migraines.

Stress often triggers migraines, so the potential for antidepressants to lower perceived stress could contribute to the value of these drugs in improving migraine symptoms.62 Research into this issue has shown that antidepressants may be a reasonable second or third line prophylactic therapy in migraine patients who have not responded adequately to other medications.63 In the case that an antidepressant approach is taken, amitriptyline monotherapy is recommended as the first choice.

Unfortunately, for those who suffer from both depression and migraines, one antidepressant is often insufficient for improving symptoms of both disorders.64 Complicating this problem is that antidepressants taken in combination with other migraines medications can be dangerous and can specifically increase the risk of serotonin syndrome, which occurs when serotonin levels get too high.65 These issues are compounded by the adverse effects associated with antidepressants taken in any context, which include but are not limited to sleep disturbances, weight changes, sexual dysfunction.66

Monoclonal Antibodies

In recent years, monoclonal antibodies, namely gepants, have begun being used in migraine prevention for treatment-resistant patients to facilitate the binding to and inhibition of calcitonin gene-related peptide (CGRP), a peptide known to be involved in migraines.67–69 A meta-analysis covering data from nearly 9,000 patients has found that different forms of these antibodies are more effective than placebo in reducing the frequency of adult migraines.70 Another meta-analysis showed that in addition to helping reduce the number of days each month that migraines were experienced, monoclonal antibodies were also a safe way to prevent episodic migraines.71

Researchers have also investigated the impact of monoclonal antibodies against other migraine treatment options and found that monoclonal antibodies may be more promising than other migraine interventions. A meta-analysis comparing the impact of monoclonal antibodies versus botulinum toxin in migraines found that CGRP monoclonal antibody was slightly more efficacious and safer than botulinum toxin for preventing chronic migraines.72 Other research has shown that CGRP monoclonal antibodies appear to be more favorable from a benefit-risk perspective than other established treatments for migraines, but researchers highlight that more comparative research is needed to understand the relative risks and benefits of monoclonal antibodies versus other treatments for migraines.73 Indeed, considerable adverse effects from injectable CGRP monoclonal antibodies have been observed and demand more study before this treatment option is widely disseminated.74

How Can We Improve Migraine Prevention and Treatment?

The prevalence of migraines has remained largely unchanged over the past two decades.28 There is thus a need to improve our ability to prevent and treat migraines beyond what is possible with conventional treatments. Research into the effects of non-pharmacological interventions offers clues into how we can develop more effective prophylactic and acute treatments for migraines.

Non-Pharmacological Interventions

Pharmacological approaches to migraines remain limited, and the medications used to treat migraines cannot be used continuously. Even simple analgesics like the NSAID paracetamol are not recommended to be used more than 15 days each month, and combination analgesics as well as triptan and ergot drugs should not be used more than 10 days each month.4,75 In addition, medication overuse is a well-established cause of headache and can thus diminish the value of pharmacological interventions meant to address migraines.76,77 Non-pharmacological interventions are thus critical for the management of migraines. The research related to some of these approaches is summarized below.

Diet

Diet is implicated in migraines, and it has been suggested that the inflammation that occurs due to dietary choices plays a role in the relationship between diet and migraines.78 There are known dietary triggers for migraines, most of which involve missed meals.79 Some people, however, experience migraines in response to specific foods. The most common foods to lead to migraines are caffeine, additives, and artificial sweeteners.5

Several specific diets have been shown to provide benefits for migraineurs including ketogenic, low-fat, modified Atkins, high-folate, and high omega-3/low omega-6 diets.80 The mechanisms by which these diets may improve migraines is not well understood, but it has been proposed that some of these diets could reduce inflammation, provide neuroprotection, improve mitochondrial function, or compensate for dysfunction in the serotonergic system.

It is important to note that diets that are effective in migraines appear to in many instances work based on comorbidities. For instance, consuming less sodium appears to reduce headache occurrence in older people with hypertension, while weight loss diets are effective in obese patients.80–82

Exercise

As with many disorders, there is evidence to show that exercise can be beneficial for migraines and has been posed as an option for preventing migraines in those who do not respond to or who do not want to take daily medications.83,84 In particular, regular physical activity can help to reduce migraine frequency.85

It has been proposed that the mechanism through which exercise can decrease the frequency of migraines is by raising the threshold for which migraines tend to be triggered.83 Cardiovascular exercise for instance may modulate pain mechanisms to alter the experience of migraines.86 Other research has shown that there are several variables that impact the likelihood that a migraineur will benefit from exercise, including fitness level, psychological states, and neurochemical factors.87

While getting enough of exercise may reduce the total number of days in which migraines occur, a recent review on the link between exercise and migraines found that there is not enough evidence to determine if migraine intensity or migraine duration may be impacted by exercise.86 It is also important to note that though exercise may be protective in migraines, they can also act as triggers for migraine attacks.85

Psychotherapy

There are several psychological interventions used to manage migraines.89 The literature on the impact of these interventions on migraines suggests that they do not affect the frequency of migraines. Whether psychological interventions may impact the experience or severity of migraines is unclear.

A review of non-pharmacological interventions for migraines found that there is strong evidence to support the use behavioral therapy as an adjunctive treatment to prevent migraine attacks.90 Advantages of behavioral approaches for intervening with migraines include that behavioral methods are not associated with the adverse side effects that are associated with drug treatments and that these approaches can leverage modern technological capabilities to deliver new and innovative intervention strategies.5,89 Nonetheless, the benefits of behavioral therapies are often recognized when used in combination with medications.91

Clinically Studied Dietary Supplements

Magnesium

The United States Headache Consortium (USHC) has suggested magnesium as a microelement for preventing migraines.92 Magnesium is the second most common intracellular cation in tissues that influence neurochemical processes and acts as a cofactor for more than 350 enzymes.93

Magnesium helps to maintain the electric potential of cells, and magnesium deficiencies can therefore lead to neurological problems.94 Low magnesium in both serum and cerebrospinal fluid is associated with migraines. Current data suggests that up to half of all patients suffering an acute migraine have lowered levels of ionized magnesium.95 Based on these observations, magnesium has long been used both prophylactically and as treatment for migraines.

The excessive excitability of neurons in migraines occurs in large part due to glutamate and NMDA receptors with which glutamate interacts to activate neurons. Magnesium has the potential to block NMDA receptors – a property that has been shown to affect pain transmission that is associated with the excessive excitability observed in neurons in migraineurs. Because it can block these receptors, magnesium has been hypothesized to provide therapy for migraines. Supporting this idea were the results of a placebo-controlled double-blind randomized study on the prophylactic use of oral magnesium, which showed that doses of 600 mg and lower offered prophylactic value for these patients.96

A meta-analysis on the effects of intravenous magnesium in migraine has shown that intravenous magnesium can within 15 minutes alleviate acute migraine attacks.97 Further, results show that following 24 hours of infusion combined with oral magnesium, both the frequency and intensity of migraine are reduced.

Riboflavin

Riboflavin, also known as vitamin B2, has been shown to play a role in migraines – particularly in migraine prevention. A recent review of the literature found that riboflavin supplements could reduce both the frequency and duration of migraines in adults without any serious side effects.98

One study that specifically addressed the value of riboflavin for prophylactic use against migraines showed that riboflavin treatment significantly reduced the frequency of headaches.99 Migraine patients took 400 mg riboflavin capsules each day, and the average number of days they spent suffering headaches each month decreased from 4 days to 2 days.

Research into the benefits of riboflavin for migraines and pathogenically-related illnesses like Parkinson's disease have shown that riboflavin is neuroprotective through multiple mechanisms.100 Specifically, riboflavin can improve oxidative stress, ameliorate mitochondrial cellular deficiencies, combat neuroinflammation, and reduce glutamate excitotoxicity.

Riboflavin offers its benefits at least in part through enzymes that rely on its presence. For example, riboflavin is required for methylenetetrahydrofolate reductase to ensure that the folate cycle has a normal influence on the methylation cycle. Without this regulation, homocysteine levels rise and negatively impact neurovascular functioning.101–103

Mitochondrial dysfunction is believed to play a role in migraines pathophysiology, and the efficacy of riboflavin in migraine treatment may be due to its positive effect on mitochondrial metabolism.104 Riboflavin, unlike coQ10, does indeed contribute to both the Krebs cycle and the mitochondrial electron transport chain.105,106 In fact, electron transport cannot function without riboflavin derivatives. Riboflavin generates ATP during glycolysis, which contributes to the Krebs cycle and then to the electron transport chain.107

Feverfew

Feverfew, also known as Tanacetum parthenium, is often used medicinally for migraines as well as arthritis.108 It has been hypothesized that the active ingredient of feverfew is parthenolide, which is contained in the leaves of feverfew.109 However, when parthenolide is depleted from feverfew, the feverfew maintains its anti-inflammatory capabilities, suggesting that other compounds along with parthenolide are responsible for the therapeutic benefit of feverfew.110 Thus, subsequent analysis of phytochemical profiles for components of feverfew beyond parthenolide is necessary when extracting the herb. The absence of these other vital chemical compounds could explain why certain feverfew extracts do not generate any benefit.

Unlike many supplements that work only prophylactically or acutely in migraines, feverfew has been shown to decrease the frequency of migraines as well as their severity in more than 70% of migraines sufferers who have consumed it.108

A randomized, double-blind, placebo-controlled study published in The Lancet has shown that 2 months of feverfew supplementation improved both the frequency and the severity of migraine attacks and that when taken for an additional 2 months, these benefits were further enhanced.111

In many cases, the people who respond to feverfew have failed to respond to conventional treatments.108. Some work suggests that feverfew extracts work through a mechanism that reduces the impact of CGRP, much the way that monoclonal antibodies have been designed to work. While there has long been anecdotal evidence for the advantages of using feverfew to combat migraines, double blind placebo-controlled trials have also demonstrated that those who take the herb experience reduced frequency and severity in migraines compared to those taking a placebo.

Research into the prophylactic value of feverfew has been promising. One randomized, double-blind, placebo-controlled study on 170 migraine sufferers showed that the number of migraine attacks per month decreased with feverfew consumption from nearly 5 attacks per month to fewer than 2 per month.112

The literature on the value of acute intervention with feverfew also paints a positive picture for the use of feverfew to treat migraines. One double-blind study showed that feverfew consumption reduced the severity of classic migraines symptoms, including pain, nausea, vomiting, and sensitivity to noise and light.113 The ability of feverfew extracts to function both prophylactically and acutely is likely due to its combination of anti-inflammatory benefits, CGRP benefits, and anti-platelet benefits.

Boswellia Serrata

Boswellia serrata, or Indian frankincense, has been used in Ayurvedic medicine for thousands of years.114 Its therapeutic value comes from its anti-inflammatory properties, which have been shown to be effective in patients with the inflammatory diseases like osteoarthritis and inflammatory bowel disease.115,116

Boswellia serrata works through multiple pathways including the cyclooxygenase pathway. 117 It also inhibits 5-lipoxygenase enzyme activity.114

Though there is little data on the specific effects of Boswellia serrata on migraines, experts have suggested that this substance may be particularly helpful when used acutely for those with cluster and indomethacin-responsive headaches.118 The substance have also been shown to have a favorable safety profile.

Doses that have been shown to improve symptoms in patients with chronic cluster headaches ranged from 350 to 700 mg taken 3 times per day. Boswellia serrata was shown to reduce both the frequency and the intensity of the migraines.119 However, certain Boswellia extracts like Aflapin have been shown to have 5-lipoxygenase anti-inflammatory activity at doses as low as 100 mg per day. This dose has translated to clinically meaningful reductions in pain as well.120

Ginger

For decades, ginger has been considered for its potential use to both prevent and treat migraines without unwanted side effects.121 Though ginger does not appear to confer prophylactic benefits against migraines, it does appear to be valuable when used acutely.122,123 A recent meta-analysis on the effects of ginger on migraine patients found that ginger improved pain and was associated with a reduced incidence of nausea and vomiting.122

A study comparing the effects of ginger powder and a triptan (sumatriptan) found that the interventions were comparable in their efficacy for reducing headache severity.124 Importantly, though, ginger had a superior profile in terms of side effects.

A double-blind placebo-controlled randomized clinical trial performed in a general hospital's emergency room showed that 400 mg of ginger extract that contained 5% active ingredient improved headaches within an hour of administration.125

Melatonin

Though melatonin has been proposed as a potential treatment strategy in migraines, its benefits in migraines are likely due to its ability to improve sleep.126 Sleep is indeed often dysfunctional in migraines, which may exacerbate symptoms. Improving sleep in those who suffer migraines may thus also improve migraines symptoms.

Corroborating this notion, for instance, is research into the effects of melatonin in pediatric migraines that showed that napping after treatment predicted greater improvements.127 Further, melatonin has been shown to play a role in circadian rhythm regulation and sleep.128 Though melatonin can have anti-inflammatory effects and scavenge free radicals, if its specific effects in migraines occur due to its impact on sleep, then improving sleep habits without the use of melatonin should be equally effective. It is possible that the value of melatonin for migraine extends beyond its influence on sleep due to multiple pleiotropic mechanisms.

Butterbur

Butterbur extract, which comes from the butterbur plant, Petasites hybridus has been suggested as a treatment for migraine, including in children.129 Unfortunately, evidence has suggested that the use of butterbur could be associated with liver toxicity, which has led several countries, including the UK, Switzerland, and Italy to take butterbur products off the market.130 Germany also retracted its approval of butterbur as a result, and the FDA currently does not approve butterbur for any indications.131 The toxicity may result from the pyrrolizidine alkaloids that butterbur leaves and stems can contain, which are known to be toxic to humans.132

A recent update on the safety and efficacy of Petadolex, which is a butterbur extract, revealed that according to post-marketing surveillance of the product, data on Petadolex only supports its safety at lower doses, which led some European countries to withdraw the product.133 The authors thus suggested that only lower doses and shorter treatment periods may be appropriate for the use of butterbur in migraine, severely limiting its potential value.

Though the American Academy of Neurology once recommended butterbur, it later retracted this recommendation based on the safety data.131 Given the efficacy of other ingredients like feverfew in combatting migraines, there is little reason to impose the risks associated with butterbur by incorporating it into a formulation aimed at addressing migraines.

CoQ10

Coenzyme Q10 (coQ10) is an electron carrier in the mitochondrial respiratory chain and is hydrophobic.134 It serves as an antioxidant and has been observed to deficient in adolescents and children with migraines.135 These observations initially led to the notion that coQ10 supplementation may be beneficial in migraines. Today, the American Academy of Neurology recommends coQ10 supplementation for migraine prevention.136

One double-blind, randomized, placebo-controlled trial involving 42 migraine patients showed that compared to those taking placebo, those taking 100 mg of coQ10 3 times per day had significantly less frequent migraine attacks, significantly fewer days with headaches, and significantly fewer days with nausea.138 The frequency, severity, and duration of headache attacks were shown in another study to be reduced in women taking 400 mg/day of coQ10 when compared to placebo.139

One study that found that coQ10 as a monotherapy was comparable to placebo with respect to the level of migraines severity each day and the number of migraines attacks each month found that coQ10 was superior to placebo in reducing the number of migraines days each month.140

Though coQ10 may offer some efficacy in combatting migraines, reducing frequency and duration of migraines, coQ10 also affects energy metabolism in a similar manner as riboflavin, making its effects potentially redundant in a formulation that already includes riboflavin.141,142

In addition, some studies that point to the value of coQ10 in migraine prophylaxis have used coQ10 in combination with other potentially more beneficial substances like magnesium, feverfew, and riboflavin.143 Given that these studies involved combination treatments, they have done little to clarify the efficacy of coQ10 as a monotherapy. Other CoQ10 studies used an open-label design, limiting the value of their results because of high rates of placebo effects that are observed in pain-related trials.

When coQ10 is studied as a monotherapy and shown to reduce the number of migraine days, the intervention fails to reduce the total number of migraines experienced. To reduce the absolute number of headaches, studies include doses ranging from 300 mg to 600 mg per day, which greatly exceeds the doses in combination migraine supplements that tout migraine prophylactic capabilities.

Vitamin B12

There are multiple studies that have observed that migraine patients suffer vitamin B12 deficiencies.144 Further, when children with low serum B12 have been given B12, their headache symptoms have resolved.145

These observations have led to research to systematically study the potential therapeutic effect of cyanocobalamin - the substance used to treat vitamin B12 deficiency - in migraines. Though a small proportion of study participants appeared to benefit from cyanocobalamin in the initial studies, researchers concluded that there was no therapeutic effect of cyanocobalamin in migraines.144

There has since been research on the specific effects of vitamin B12 in migraines, and a recent literature review on the utilization of vitamin B12 in chronic migraine concluded that vitamin B12 is a promising treatment for chronic migraines.144 The vitamin acts as a cofactor for certain enzymes and converts homocysteine to methionine, which is critical for building essential proteins.144,146,147 Vitamin B12 may also affect migraines by scavenging nitric oxide.

Deficiencies in vitamin B12 are known to not only to lead to dysregulation of the metabolism of methionine but to also manifest neurologically, resulting in fatigue, nerve damage, anemia, and developmental delay.144,148–150 Though data show that vitamin B12 supplementation may help combat migraine symptoms, the studies are limited, mainly because the research on the impact of vitamin B12 on migraine patients usually involves vitamin B12 supplementation along with other prophylactic interventions, making it difficult to tease out the specific effects of vitamin B12.144 The current evidence for a therapeutic role of vitamin B12 in migraines is thus weak. Given the contradictions in the literature, more research is needed to determine if vitamin B12 can offer value to migraine patients.

Folic Acid

Folic acid can act as a vasodilator for small arteries, suggesting it could be an effective intervention for migraines.151 Research on the effects of folic acid on women with migraines showed an inverse relationship between folate consumption and migraine frequency, suggesting that folate intake may affect migraine frequency in female migraneurs.152

Its use as a slow intravenous injectable at a dose of 15 mg has led to reduced headache intensity within an hour on average following injection for about 60% of patients.151 A second injection was given to those who still felt head pain the following day, and the majority of patients responded to this second dose. Pulse wave studies showed that the folic acid therapy restored elasticity in the involved artery and reduced relevant edema. However, folic acid injections were less effective in older patients and were also associated with some side effects including nausea and vomiting. Overall, studies on folic acid in migraines are contradictory and show weak evidence for its value.

Vitamin D

The role of vitamin D in headache and migraine has been controversial, as some studies have shown what seem to be clear benefits of vitamin D for reducing suffering from headaches, while other studies have failed to demonstrate those benefits. Recent meta-analyses aimed at clarifying the potential link between vitamin D and headaches have revealed that the inconsistencies observed in prior research likely arise from variability in the populations of headache patients included in studies, as well as the specific outcomes that are investigated.

A deeper look into the role vitamin D may play for those suffering from headaches has revealed that compared with those suffering other types of headaches, migraineurs seem to benefit significantly more from vitamin D supplementation. This revelation is consistent with robust findings that 25-hydroxyvitamin D 25(OH)D concentrations, which represent the most reliable marker of vitamin D levels, are lower in people with migraines compared to their healthy counterparts.153

A meta-analysis covering 22 studies corroborates this notion, demonstrating that vitamin D supplementation may not benefit people with certain types of headaches, but that it is helpful for migraineurs, particularly when they are deficient in vitamin D.154 Similarly, another meta-analysis, which analyzed data from over 300 patients across 3 randomized controlled trials, revealed that though vitamin D supplementation did not have a substantial impact on the severity or duration of headaches, it significantly decreased the frequency of headaches in those with migraines.155 These data help to explain why results have appeared to conflict and how those suffering from migraines are likely to benefit from vitamin D ,.

CONCLUSION

Migraines present a medical challenge for patients and healthcare providers, with none of the conventional treatment options offering a reliable, long-term, safe solution that works for migraine symptoms. Though often tedious, trial-and-error is often a necessary process for individual migraine patients to determine the best way to deal with their symptoms. For those who have not tried pharmacological interventions or for whom migraine drugs do not work or cause unwanted side effects, supplements that combine ingredients that have been shown to have potentially beneficial effects in migraine patients may be a good first or next step, respectively.
For those interested in such an approach, committing to a 3-month regimen can help to determine any potential impact of a supplement and provide actionable insights for patients and their healthcare providers. Given that feverfew, riboflavin, and magnesium have well-established prophylactic effects against migraines and favorable safety profiles, a migraine supplement that includes these ingredients could help migraineurs circumvent pharmacological interventions while still achieving symptom relief.

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