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Headache (JR Couch, Section Editor)

Nutraceuticals in Acute and Prophylactic Treatment of Migraine

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Opinion statement

People who suffer from headaches often prefer nutraceutical treatment over traditional pharmacological approaches, due to fear of possible side effects, drug dependence, or addiction. Since treatment with nutraceuticals does not require a doctor's prescription, many patients rely on their own judgment as to when and which one to take, often without consultation or guidance from their physician. Some physicians could provide information about potential efficacy and side effects of various products, but many are not familiar with the nutraceuticals. Widespread skepticism persists among doctors about the effectiveness of these treatments. This is largely due to the lack of rigorous clinical studies. However, even when incontrovertible scientific evidence exists, many physicians remain distrustful of the evidence. The following review summarizes randomized controlled trials of some of the most commonly used non-pharmacological treatments, including magnesium, coenzyme Q_{10}, riboflavin (vitamin B2), petasites, and feverfew (Table 1).

Introduction

Migraine headache is the most common neurological disease, affecting an estimated 36 million Americans [1]. Patients suffer remarkable disability during the attacks, along with a substantial social and financial burden to the patient as well as to the society [2]. The primary goals of migraine treatment include relieving pain, restoring function, and reducing headache frequency [3]. The most common treatment protocols of migraine management include analgesics, such as triptans and over-the-counter (OTC) pain relievers, as well as prophylactic medications, such as anti-seizure drugs, cardiovascular drugs, antidepressants, and onabotulinum toxin A injections.

Despite multiple treatment options, many patients respond poorly to, or are noncompliant with, pharma-

cological preventive therapies. There is a growing body of evidence supporting the efficacy and tolerability of various nonpharmacologic therapies in the management of migraine. These treatment modalities include nutraceuticals, in addition to physical and behavioral therapies. Although controversial, the use of nutraceuticals in acute and prophylactic treatment of migraines has been on the rise, and now appears to be in widespread use among migraine sufferers, as demonstrated by several epidemiological studies [4, 5]. Up to 82 % of patients with headaches use complementary or alternative medicines, often prescribed by clinicians [6•]. Nutraceutical options include vitamins, minerals, and supplements, along with herbal preparations. [7]. Although nutraceuticals may be used instead of traditional medications, using them in conjunction with pharmacological therapies as part of a multidisciplinary treatment plan is more likely to result in an optimal response [7, 8]. While the evidence for some of these nutraceuticals is promising, many of the existing studies are small and uncontrolled, sometimes showing inconsistent results (Table 1).

Minerals and vitamins

Magnesium

Magnesium is the second most prevalent cation in intracellular fluid, and has a vital role within the cell, including ATP production and function and glucose metabolism. Magnesium binds to NMDA receptors and is also involved in the control of vascular tone [7]. Magnesium deficiency, or hypomagnesemia, is quite common, with a prevalence of approximately 14.5 % of the population [20]. Studies have consistently shown that migraineurs are often deficient in magnesium [21–25]. Low magnesium in the brain may also possibly be associated with the presence of aura, implying that magnesium supplementation may be more effective in migraineurs who experience aura [26].

A comprehensive review [8] suggests that oral supplementation of magnesium in the treatment of migraines yields mostly positive results. A study by Peikert et al. [10] in 81 patients showed significant improvement in migraineurs on active therapy with trimagnesium dicitrate 600 mg per day, compared to placebo. Attack frequency was reduced by 41.6 % in the magnesium group, compared to only by

Table 1. Summary of major studies in the article

Supplement	Major studies depicted in the article	*N*	AAN recommendation based on an extensive review
Magnesium	Peikert et al. [10]	81	Level B
	Bigal et al. [11]	120	
Coenzyme Q10	Hershey et al. [12]	1550	Level C
Riboflavin	Schoenen et al. [13]	55	Level B
Petasites	Pothmann et al. [14]	112 (children and adolescents)	Level A
	Grossmann et al.[15]	120	
	Lipton et al. [16]	223	
Feverfew	Diener et al. [17]	170	Level B
	Pfaffenrath [18]	147	
Folic acid, vitamin B_6, and vitamin B_{12}	Lea et al. [19]	52	Not evaluated

15.8 % in the placebo group. In a study ($n = 60$), patients suffering from an acute migraine received intravenous (IV) magnesium sulfate. Results showed a significant improvement in pain and symptoms in patients with migraine with aura. Furthermore, 36.7 % were pain free after 1 h in the treatment group vs. 6.7 % in the placebo group. It is interesting to point out that while patients without aura had no significant reduction in pain, there was a decrease in the intensity of photophobia and phonophobia in both groups (aura and none aura), compared to those who received placebo [11]. IV magnesium is usually administered for acute migraine, as well as for prophylaxis, while oral magnesium supplementation is given for prophylaxis. The American Academy of Neurology (AAN) Guidelines rate oral magnesium supplementation for the prophylactic therapy of episodic migraines as having level B evidence for its efficacy, or being probably effective [27••]. As far as IV magnesium, a meta-analysis [28] of five RCT evaluating the efficacy of IV magnesium in the treatment of acute migraine suggested evidence level of U, or undetermined. This is, in part, due to the exclusion of some frequently cited studies because of their flawed methodology.

The recommended dosage of magnesium supplement is 400 mg a day, and can be increased up to 1200 mg, if tolerated. Magnesium has to be taken for at least 1 month before any results are noted [8]. Possible side effects are mainly gastrointestinal, including stomach ache, nausea, and diarrhea. Certain magnesium salts are poorly absorbed, and one of the negative studies used poorly absorbed salt which led to diarrhea in almost half of the patients in the active group [9]. Magnesium glycinate and other amino acid-chelated forms of magnesium are possibly better tolerated than other salts. It is important to note that in the presence of renal failure, magnesium can lead to serious side effects including arrhythmias, hypotension, confusion, coma, and death. Absorption of gabapentin, which is used for migraine prophylaxis, is reduced by magnesium, so these two should be taken at different times.

Coenzyme Q10

Coenzyme Q10 (CoQ10), an endogenous enzyme cofactor involved in the mitochondrial electron transport chain, has been assessed for migraine prevention, as it is a vital cofactor in sustaining mitochondrial energy stores. An open-label study [29] of 31 subjects receiving 150 mg of CoQ10 daily for 3 months was found to reduce migraine days by at least 50 % in 61 % of subjects. Another study in 42 patients [30] evaluated the efficacy of 100 mg of CoQ10 taken 3 times a day. The responder rate (more than 50 % reduction in attack frequency) was 48 % in the active treatment group, compared to 14 % in the placebo group. Minimal side effects were reported in both studies, and no significant adverse effects were noted.

Hershey et al. [12] suggested that CoQ10 supplementation might be particularly beneficial in the prophylaxis of migraine in children with low CoQ10 levels. Of the 1550 participants of this study, low CoQ10 levels were found in nearly one third of patients. After 3 months of supplementation, CoQ10 levels increased. Headache frequency improved from 19.2 ± 9.8 days per month to 12.5 ± 10.8 days per month along with related disability. The AAN Guidelines consider CoQ10 to be possibly effective in migraine prevention (level C evidence) [27••].

While the most effective dose of CoQ10 remains unclear, 1–3 mg/kg per day has been recommended [6•]. CoQ10 is well tolerated—adverse events occurred in

less than 1 % of subjects and include anorexia, dyspepsia, nausea, and diarrhea [29]. Known drug interactions include warfarin, anisindione, and dicumarol.

Riboflavin

Riboflavin, or vitamin B_2, is a cofactor in oxidation-reduction reactions in the citric acid cycle and the electron transport chain. As such, it plays a key role in the mitochondrial production of energy. Numerous studies suggest a presence of mitochondrial energy depletion in patients with migraine [22]. One RCT in 55 adults found riboflavin, 400 mg a day, to be beneficial in migraine prevention. After 3 months of daily intake, 59 % of subjects treated with riboflavin had at least a 50 % decrease in migraine attacks, compared with 15 % in the placebo group. Two minor adverse reactions, diarrhea and polyuria, were reported in the treatment group [13].

A recent pharmacogenetic study [31] suggested that riboflavin might be most effective in the treatment of migraine patients with non-H mitochondrial DNA haplogroup type. mtDNA haplogroup type H is more prevalent in Europeans, and is associated with increased mitochondrial complex 1 activity, implying that riboflavin may only help those with relatively decreased mitochondrial function.

The AAN has concluded that riboflavin is probably effective for the prophylactic treatment of migraine in adults (level B evidence) [27••]. Thus, based on clinical experience and a favorable side effect profile, many clinicians recommend the use of vitamin B_2 for management of migraines in adults [32]. The recommended dosage of riboflavin is 400 mg per day. Based on a recent systematic review, riboflavin has not been found effective in migraine prevention in children and therefore is not recommended [32]. Riboflavin is well tolerated, with minimal side effects.

Herbal preparations

Petasites

Petasites hybridus is a purified extract of the butterbur plant. *Petasites* has antihistamine properties. It also inhibits synthesis of leukotrienes and blocks calcium channels. Several studies have evaluated the efficacy of *P. hybridus* in migraine prevention. A multicenter prospective open-label study [14] in 112 children and adolescents demonstrated reduction in migraine frequency of at least 50 % in the majority of patients. Two class I studies [15, 16] showed *Petasites* to be effective in reducing the frequency and severity of migraine attacks, compared to placebo. In the first study, 120 patients treated with 100 mg once daily showed a responder rate of 45 % in the active treatment group vs. 15 % in the placebo group. The second study in 233 patients showed a 68 % responder rate in the 75 mg twice daily group vs. 49 % in the placebo group. The only adverse event reported was burping. The AAN Guidelines consider *Petasites* to be effective in migraine prevention with a level A evidence [27••].

Since *P. hybridus* contains pyrrolizidine alkaloids, which are hepatotoxic and carcinogenic, patients are advised to use only products that are certified and labeled pyrrolizidine alkaloids free. Such products have been manufactured since 1992 by a known German company, which patented a technique to remove these toxic substances from the *Petasites* root. It was initially approved by the

German health regulatory authority under the brand name Petadolex®; however, this approval was later withdrawn. In 2012, the United Kingdom's Medicines and Health Care Products Regulatory Agency withdrew all butterbur products from the market due to associated cases of liver toxicity. Subsequently, other EU countries revoked the regulatory clearance of *Petasites* products due to adverse events varying from hepatitis to fulminant liver failure requiring a liver transplant [27••]. *Petasites* products are still available in the US market, and the risk to benefit ratio should be evaluated in all patients, and if a patient decides to take *Petasites*, liver function monitoring is indicated.

The recommended dose of *Petasites* is 75 mg, twice a day. It is important to note that the safety of prolonged use of *Petasites* has not been established. Just like with most herbal preparations, pregnant women should avoid *Petasites*.

Feverfew

The feverfew plant, *Tanacetum parthenium* traces its origins to the Balkan Mountains, but is now found throughout Europe, North and South America. It is commercially available as the dried leaves of the plant, and its anti-migraine action is probably related to the parthenolides within these leaves. Feverfew has long been studied for the treatment of migraines [17]. Although its mechanisms of action in migraine prevention have not been fully elucidated, parthenolides are known to inhibit nuclear factor kappa B (NF-kB), which plays a vital role in iNOS (inducible nitric oxide synthase) induction and in the parenchymal inflammatory cascade that results from cortical spreading depression [6•]. Feverfew may also produce its effect by inhibiting the release of serotonin from platelets and white blood cells. It may also function as an anti-inflammatory agent through the inhibition of prostaglandin synthesis and phospholipase A [33–36].

Treatment of migraine with the feverfew plant remains controversial, as the evidence of its efficacy is contradictory [37–42]. Inconsistent results may be attributed to the variations in the concentration of the parthenolides and to differences in the stability of the parthenolides [43]. Hence, a couple of studies with a new, more stable formula of feverfew were conducted. In the first study, 147 migraine patients, with or without aura, were divided into 4 groups: 2.08 mg, 6.25 mg, 18.75 mg of feverfew, and placebo 3 times a day. The study found no significant beneficial results at any dose of the new formula [18]. The second [17], more comprehensive study in 170 subjects demonstrated a significant reduction in the number of attacks per month, from 4.76 to 1.9, with the daily use of feverfew compared to placebo ($P = 0.0353$). The feverfew group received 6.25 mg 3 times a day for 3 months, and the 50 % responder rate in this group was 30.3 % compared to 17.3 % in the placebo group. The AAN Guidelines consider feverfew to be possibly effective in migraine prevention (level B evidence) [27••].

Feverfew is well tolerated and shows a favorable benefit–risk ratio [33], although one study noted the presence of a "post feverfew syndrome," which includes arthralgia and oral ulcers [37]. Pregnant women should not take feverfew, as it may cause uterine contractions [7]. Also, patients allergic to the daisy family of plants are more likely to be allergic to feverfew.

Boswellia serrata

B. serrata (Boswellia extract) is a genus of trees in the order of *Sapindles*. It contains a number of biologically active substances including

pentacyclic triterpene acids, which give the extract its anti-inflammatory and analgesic qualities. The presumed mechanism of action includes inhibition of cytokines and leukocyte activity [44]. Although *Boswellia* has long been evaluated for the treatment of many medical conditions, including cluster headaches [45] and indomethacin responsive headache syndrome [46], there is no scientific data regarding its benefit in the treatment of migraine.

The recommended dosage is 250 to 700 mg, 3 times a day. *Boswellia* has no toxic ingredients and is safe for consumption in any form. There is no data regarding the long-term safety of *Boswellia*.

Other

There are several other nutraceuticals that seem promising, although the scientific data is lacking and further study is required in order to fully evaluate their efficacy in migraine management.

Melatonin

The evidence for the efficacy of melatonin in migraine prevention is limited and contradictory. While some studies found no effect of melatonin in migraine prevention [47], others demonstrated mild superiority compared to placebo with daily use of melatonin 3 mg [48].

Folic acid, vitamin B_6, and vitamin B_{12}

Migraine with aura may be related to a disruption in neurovascular endothelium caused by elevated homocysteine levels [8]. One comprehensive study examined the homocysteine-lowering effect of vitamins B_6, B_{12}, and folic acid supplementation in migraine management. Fifty-two patients diagnosed with migraine with aura were administered either placebo or folic acid 2 mg, cyanocobalamin 400 mg (vitamin B_{12}), and pyridoxine 25 mg (vitamin B_6) [19]. The use of all three vitamins significantly reduced pain severity and prevalence of related disability by half.

Compliance with Ethical Standards

Conflict of Interest
Oved Daniel and Alexander Mauskop declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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