

# Diet and nutraceutical interventions for headache management: A review of the evidence

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## Abstract

**Background:** The use of complementary and alternative medicines (CAM) is common among patients with primary headaches. In parallel, CAM research is growing. Diet interventions comprise another category of non-pharmacologic treatment for primary headache that is of increasing clinical and research interest.

**Methods:** A literature search was carried out to identify studies on the efficacy of diet and nutraceutical interventions for primary headache in the pediatric and adult populations. MEDLINE, Embase and EBM Reviews—Cochrane Central Register of Controlled Trials were searched to identify studies.

**Results:** There is a growing body of literature on the potential use of CAM and diet interventions for primary headache disorders. This review identified literature on the use of a variety of diet and nutraceutical interventions for headache. Most of the studies assessed the efficacy of these interventions for migraine, though some explored their role in tension-type headache and cluster headache. The quality of the evidence in this area is generally poor.

**Conclusions:** CAM is becoming more commonplace in the headache world. Several interventions show promise, but caution needs to be exercised in using these agents given limited safety and efficacy data. In addition, interest in exploring diet interventions in the treatment of primary headaches is emerging. Further research into the efficacy of nutraceutical and diet interventions is warranted.

## Keywords

Diet, nutraceuticals, vitamins, herbal medicines, headache, migraine

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## Introduction

Complementary and alternative medicine (CAM) accounts for an ever-increasing portion of health care expenditures. The United States (US) National Institutes of Health (NIH) defines CAM as a “group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine” (1). In the US, CAM is a multibillion dollar industry, with spending estimated at \$13.9 billion to \$33.9 billion annually (2). The use of CAM has become more prevalent over the past decade (3). Recent estimates have found that more than one-third of US adults and more than 10% of US children endorse the use of CAM in the past year (4). This trend of CAM use is not unique to the US, with studies in other countries also unveiling prevalent use (5,6).

The management of chronic pain has been identified as a priority area for CAM research (7). It also appears

that patients with headache commonly turn to CAM for alternatives to traditional allopathic options. In one US headache clinic, a survey revealed that 84% of patients were using CAM interventions, with herbs, vitamins and nutritional supplements accounting for just fewer than 30% of the modalities used in this population (8). Similarly elevated estimates of CAM use in adult headache patients have been found elsewhere (9–12). A study among pediatric headache patients referred to an Italian tertiary care headache clinic revealed that 76% of the patients were using CAM

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therapies for their headaches, with 74% using herbal remedies and 40% using vitamin and mineral supplements (13). In a study drawing on data from a national sample of children representative of the US population, 30% of the children with headaches reported CAM use (14). Therefore, the use of CAM among headache patients is very prevalent.

There is a significant gap between the prevalence of CAM use and the degree to which dialogue about CAM enters into the typical physician-patient interaction. In one study carried out in an Italian headache clinic, 60.9% of the patients using CAM had not told their physician about their CAM use (12). In addition, many physicians lack familiarity with CAM and avoid the topic during routine clinical encounters. For patients interested in exploring CAM, this mutual reluctance to discuss the options may constitute a significant barrier to trust and optimal care. Given how many headache patients are resorting to CAM, headache practitioners should become well versed in the evidence behind current CAM options, so as to enable informed discussion with their patients.

Within the CAM literature, there has been a focus on nutraceutical interventions for headache. Another area of interest within the non-pharmacologic headache intervention literature pertains to diet interventions. The present review will provide an overview of the current evidence for dietary and nutraceutical interventions for headache in adults and children.

## Methods

Two separate literature searches were carried out in order to identify studies on the efficacy of dietary or nutraceutical interventions for primary headache in the pediatric and adult populations. A variety of search term combinations were used in order to identify the largest possible number of relevant studies. MEDLINE, Embase and EBM Reviews-Cochrane Central Register of Controlled Trials were searched to identify studies. Reference lists of included studies were also scrutinized for pertinent citations. Observational studies, intervention studies and systematic reviews of dietary or nutraceutical headache therapies were included.

## Dietary interventions for headache

Studies on dietary interventions for primary headache disorders are summarized in Table 1.

### *Weight-loss diets for headache*

Headache and obesity are comorbid (15). Migraine has a specific association with obesity (15) and metabolic syndrome (16,17). Furthermore, obese individuals

appear to be more likely to suffer from chronic migraine as compared to their peers (18), thereby unveiling a possible relationship between body mass index (BMI) and migraine frequency. There is increasing evidence to suggest that migraine and obesity may be linked through inflammatory mediators released by adipose tissue (19–22). Despite the increasing interest in the headache-obesity association, there is a lack of research on the use of weight loss as a treatment for headache disorders. Weight loss has been found to be an efficacious intervention for patients with idiopathic intracranial hypertension (23,24), but little is known about its potential for efficacy in the primary headaches. Two small observational studies have described a decrease in migraine frequency and disability in obese women with migraine following bariatric surgery (25,26). A large retrospective study carried out in several tertiary care pediatric headache centers uncovered an association between weight loss and reduction in headache frequency among overweight children presenting with primary headaches (27). Also, an open-label study comparing the ketogenic diet to a standard low-calorie diet found that both diets yielded a significant decrease both in BMI and headache frequency (28). The only prospective study assessing a weight-loss diet for migraine recruited obese adolescents with migraine to undergo a 12-month intervention program involving not only a dietary intervention, but also an aerobic exercise program and cognitive-behavioral training sessions. In this study, weight loss was associated with reductions in migraine frequency, intensity and disability (29). However, given the multi-intervention approach, it is not known if the dietary intervention played a role in the observed effect. A randomized controlled trial (RCT) is currently under way to assess the efficacy of a behavioral weight-loss treatment program, involving diet alterations, in a sample of overweight and obese women with migraine (30). The state of the current evidence is very limited in regards to the efficacy of weight-loss interventions for primary headaches. However, the growing interest in the association of obesity and headache is likely to compel further research in this area in the years to come.

### *Low-sodium diets for headache*

The potential role for a reduced-sodium diet in headache has been explored in only one recent study. The theoretical impetus for this study pertained to the association between hypertension and headache, and the role of a low-sodium diet in reducing blood pressure. In addition, it is well known that monosodium glutamate is a headache trigger for some patients with primary headaches (31). A detailed analysis of headache occurrence was carried out on data generated

**Table 1.** Summary of studies on dietary interventions for headache.

Diet	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Weight loss	Non-randomized	Novack et al., 2011 (25): prospective observational study	29 obese adult patients with migraine	Bariatric surgery	N/A	After bariatric surgery, migraine frequency ( $p < 0.0001$ ), duration ( $p = 0.02$ ), medication use ( $p = 0.005$ ), MIDAS and HIT-6 scores decreased ( $p < 0.005$ )
		Bond et al., 2011 (26): prospective observational study	57 severely obese adult patients with migraine	Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding	N/A	After surgery, headache frequency ( $p = 0.013$ ), severity ( $p = 0.022$ ) and disability ( $p = 0.003$ ) decreased
		Hershey et al., 2009 (27): retrospective chart review	913 pediatric patients with a variety of headache disorders	Routine care, routine dietary and nutritional counseling plus discussion about health risks of obesity for overweight patients	N/A	In overweight patients (BMI percentile $> 85$ th), change in BMI at follow-up was positively associated with change in headache frequency ( $r = 0.32$ , $p = 0.01$ )
		Di Lorenzo et al., 2015 (28): prospective open-label study	96 adult patients with migraine as diagnosed by ID-Migraine who self-referred to a dietitian for weight loss	Ketogenic diet with four-week ketogenesis period, eight-week transitional period, followed by standard low-calorie diet ( $n = 45$ ). Diet chosen based on patient preference	Standard low-calorie diet for six months ( $n = 51$ ). NB: Diet chosen based on patient preference	Both the ketogenic and standard diets yielded a reduction in BMI and both groups had a decrease in number of headache days/month ( $p < 0.0001$ )
		Verrotti et al., 2013 (29): prospective open-label study	135 Caucasian adolescents with migraine and BMI $> 97$ th percentile	12-month program involving a balanced diet, aerobic activity and cognitive-behavioral therapy group sessions	N/A	Weight, BMI and waist circumference ( $p < 0.01$ ) as well as headache frequency ( $p < 0.01$ ), headache intensity ( $p < 0.01$ ), use of acute medications ( $p < 0.05$ ) and PedMIDAS scores ( $p < 0.05$ ) were significantly reduced at six months
Low-sodium diet	RCT	Amer et al., 2014 (32): RCT	390 adult patients with hypertension	Dietary Approaches to Stop Hypertension (DASH) diet with 30-day cross-over periods of low, moderate and high sodium ( $n = 198$ )	Control diet with 30-day cross-over periods of low, moderate and high sodium ( $n = 192$ )	The low-sodium cross-over period was associated with reduced headache occurrence as compared to the high-sodium period for both groups (OR = 0.69, 95% CI = 0.49–0.99 and OR = 0.69, 95% CI = 0.49–0.98)

(continued)

Table 1. Continued.

Diet	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Low-fat diet	Quasi-experimental	Bic et al., 1999 (34): quasi-experimental pre-test/post-test protocol	54 adults with migraine	Restriction of dietary fat intake to 20 g/day and advise to limit caffeine intake for 12-week intervention period	N/A	Significant decrease in migraine frequency, intensity, headache index and frequency of medication use ( $p < 0.0001$ )
		Bunner et al., 2014 (35): open-label randomized cross-over study	42 adults with migraine	Low-fat vegan diet for four weeks followed by elimination diet for four weeks followed by reintroduction diet for eight weeks ( $n = 21$ )	Placebo (10 mcg linoleic acid and 10 mcg vitamin E) once daily for 16 weeks ( $n = 21$ )	Significant decrease in weight ( $p < 0.001$ ), number of headaches ( $p = 0.04$ ), severity of worst pain ( $p = 0.03$ ) and use of medications ( $p = 0.004$ ) over diet period as compared to placebo period
Elimination diet	Non-randomized	Egger et al., 1983 (37): prospective open-label study	99 children with migraine	Oligoantigenic diet with elimination of multiple trigger foods in non-individualized manner with subsequent double-blind cross-over period involving reintroduction of provocative foods	N/A	93% improved greatly or recovered completely on the diet
		Wantke et al., 1993 (38): prospective open-label study	28 adults with chronic headaches and a history of food intolerance	Histamine-free diet for four weeks	N/A	68% of patients had a 50% or greater reduction in headache frequency on the diet, with a decrease from $3.1 \pm 2.3$ to $1.1 \pm 1.0$ headaches/week ( $p < 0.001$ )
		Arroyave Hernández et al., 2007 (39): prospective open-label study with matched controls	56 adults with migraine and 56 age- and gender-matched controls	IgG antibodies to food antigens were measured and then culprit foods removed from the diet for six months	N/A	All migraine patients and 15% of controls had IgG immunoreactivity ( $p < 0.01$ ); 84% of migraine patients had remission of migraine or a decrease in migraine frequency and intensity during the diet period
	RCTs	Salfeld et al., 1987 (36): RCT	39 children with migraine	Fiber-rich diet with exclusion of foods with vasoactive amines for eight weeks ( $n = 19$ )	Fiber-rich diet without exclusion of foods with vasoactive amines for eight weeks ( $n = 20$ )	Both groups had a significant reduction in migraine frequency with no difference between the groups
		Alpay et al., 2010 (40): cross-over trial	35 adults with migraine without aura	IgG antibodies to food antigens were measured and then culprit foods were eliminated for six weeks	IgG antibodies to food antigens were measured and then culprit foods were continued for six weeks	During elimination diet phase, attack count ( $p < 0.001$ ), headache days ( $p < 0.001$ ), use of acute medications ( $p < 0.001$ ) and total medication intake ( $p = 0.002$ ) were reduced significantly

(continued)

Table 1. Continued.

Diet	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Ketogenic diet	Non-randomized	Mitchell et al., 2011 (41): single-blind, parallel-group RCT	167 participants with self-reported migraine-like headaches	IgG antibodies to food antigens were measured and then participants were instructed to remove culprit foods for 12 weeks (n = 84)	IgG antibodies to food antigens were measured and then participants were instructed to remove a matched number of non-culprit foods for 12 weeks (n = 83)	No significant difference in the frequency of headaches, MIDAS or HIT-6 scores between the groups
		Schnabel, 1928 (45): prospective open-label study	18 adults with migraine	Ketogenic diet	N/A	50% of patients had some relief in their headaches over the diet period
		Barborka, 1930 (46): prospective open-label study	50 adults with migraine	Ketogenic diet for three to six months	N/A	78% of patients had a response to the diet, with 28% having migraine remission on the diet
		Kossoff et al., 2010 (50): prospective open-label study	8 adolescents with chronic daily headache	Modified Atkins diet for three months. Only three participants completed the three-month period	N/A	No participant had any reduction in headache frequency
		Farkas et al., 2014 (51): prospective open-label study	18 adolescents with migraine	Ketogenic diet for three months. Only six participants completed the three-month period	N/A	38% of the original sample had some response to the diet
		Di Lorenzo et al., 2013 (52): prospective open-label study	108 adult patients with migraine	Ketogenic diet for one month (n = 52)	Standard low-calorie diet for one month (n = 56)	90% of patients in the ketogenic diet group had a response in terms of migraine frequency and reduction in medication use with no responders in the standard diet group
		Di Lorenzo et al., 2015 (28): prospective open-label study	96 adult patients with migraine as diagnosed by ID-Migraine who self-referred to a dietician for weight loss	Ketogenic diet with four-week ketogenesis period, eight-week transitional period, followed by standard low-calorie diet (n = 45). Diet chosen based on patient preference	Standard low-calorie diet for six months (n = 51). Diet chosen based on patient preference	There was a significant time by treatment interaction favoring the ketogenic diet group for clinical headache variables (p < 0.0001), with the ketogenic diet group having improvement in all headache variables during the ketogenesis phase (p < 0.0001)

(continued)

Table 1. Continued.

Diet	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Miscellaneous	Non-randomized	Dexter et al., 1978 (53): prospective open-label study	74 adult patients with migraine associated with fasting states	Low-sucrose, six-meal diet plus testing for diabetes with a five-hour 100 g oral glucose tolerance test	N/A	All patients with diabetic test results had a 75% or greater improvement in their headaches; 63% of those with reactive hypoglycemia had a 75% or greater improvement and 27% of them had a 50–75% improvement in their headaches
		Unge et al., 1983 (54): prospective open-label study	10 women with migraine and cutaneous symptoms	Tryptophan-reduced diet for a minimum of one month	N/A	90% had a reduction in migraine attacks during the diet
	RCT	Spigt et al., 2012 (55): RCT	Adults with recurrent headaches	Lifestyle counseling and increased dietary water intake: 1.5 l additional liters of water per day for three months (n = 52)	Lifestyle counseling only (n = 50)	No difference between the groups in terms of headache frequency or medication usage, but greater improvements in Migraine-Specific Quality of Life scores were seen for the intervention group (p = 0.007)
		Ramsden et al., 2013 (56): RCT	67 adults with chronic daily headache	Dietary intervention involving reduction of omega-6 fatty acids combined with increased omega-3 fatty acids for 12 weeks (n = 33)	Dietary intervention involving reduction of omega-6 fatty acids alone for 12 weeks (n = 34)	Both groups had significant improvement in their headaches, but the reduced omega-6-increased omega-3 diet yielded a better response: lower HIT-6 scores (p < 0.0001), fewer headache days (p = 0.02) and fewer headache hours (p = 0.01)

RCT: randomized controlled trial; BMI: body mass index; MIDAS: Migraine Disability Assessment; HIT-6: Headache Impact Test-6; Ig: immunoglobulin; OR: odds ratio; CI: confidence interval.

from the Dietary Approaches to Stop Hypertension (DASH)-sodium RCT in order to explore the effect of dietary sodium on headache. In this trial, adult participants with hypertension were randomized to the DASH diet or a control diet, with each group also having three 30-day cross-over periods to low, moderate and high sodium intakes within their assigned diet. The data showed that the odds of reporting a headache in the last seven days of the diet were lower while participants were on the low-sodium diet as compared to the high-sodium diet, with no difference between the DASH diet and the control diet overall (32). This trial was designed to assess blood pressure as a primary outcome, and the ascertainment of headache as a secondary outcome was suboptimal. However, it does provide a foundation for further exploration of the role of low-sodium diets for headache prevention in adults with hypertension.

### *Low-fat diets for migraine*

Altering dietary fat intake could effect changes in migraine patterns given the role that dietary fat composition plays in prostaglandin synthesis. Prostaglandins are thought to play a role in migraine pathogenesis through a variety of mechanisms, including their vasoactive effects on cranial arteries and their role in central and peripheral pain sensitization (33).

Two studies have investigated the role of low-fat diets for migraine prophylaxis. The first study employed a quasi-experimental design to assess the efficacy of a low-fat diet in a sample of 54 adults with migraine. Participants were instructed to reduce dietary fat intake to a maximum of 20 g per day for a 12-week intervention period and to complete headache diaries. After the intervention, there was a significant decrease not only in participant weight and dietary fat intake, but also in headache frequency, intensity and use of abortive headache medications (34). An open-label, randomized cross-over study evaluated the efficacy of a low-fat vegan diet combined with an elimination protocol to remove trigger foods as compared to placebo over a 16-week intervention period in a sample of adult migraineurs. Only 42 participants were recruited, with no a priori sample size calculations, and the participants were demographically homogeneous, with mostly Caucasian, highly educated females recruited. Participants lost an average of 3.6 kg over the dietary intervention period and had improvement in a number of headache-related outcomes as compared to placebo (35). Given methodological limitations, the lack of detail with regards to how these interventions altered dietary fat composition and given the association of the low-fat diets with weight loss, it is still unclear as to whether a simple reduction in dietary fat is efficacious for migraine.

### *Elimination diets for headache*

Dietary triggers are a well-established phenomenon in migraine. Several studies have assessed a variety of elimination diets as therapeutic interventions for migraine.

A small randomized trial evaluated the efficacy of a high-fiber diet alone vs. a high-fiber diet with elimination of foods high in vasoactive amines for migraine prophylaxis in a sample of children and found no difference in headache parameters between the groups (36). **Another study among children with migraines assessed the effect of an oligoantigenic diet on migraine through elimination of a wide variety of common trigger foods in an unselected fashion. The vast majority of children (93%) had complete or great improvement on the diet, and of those who were randomly assigned to reintroduction of provocative foods, most had relapse of their headaches (37).**

A few studies have been carried out to assess elimination diets among adult migraineurs. A sample of 28 patients with chronic headaches were placed on a histamine-free diet for four weeks, and 68% of the participants had a 50% or greater reduction in their headaches (38). Individualized approaches to elimination diets have been employed in a few studies. One open-label study tested adult migraine patients for food reactivity by measuring immunoglobulin (Ig)G antibodies to food antigens and then instructed participants to eliminate the culprit foods for six months. Complete or partial headache response was reported by 84% of the participants after the elimination diet (39). Two RCTs have also taken a targeted approach to elimination diets for migraine by measuring IgG antibodies to food antigens and then randomly assigning participants to elimination of provocative foods vs. control conditions. A small cross-over study found a six-week individualized elimination diet to be effective in reducing migraine frequency and medication use as compared to a standard diet (40). These findings were not replicated in a parallel-group trial carried out among adults with self-reported migraines, where the individualized elimination diet was no different from a sham diet after 12 weeks (41). The null results from this RCT may have been due to methodological problems with the study, namely the suboptimal selection of migraine patients, the lack of compliance monitoring and diet education and a high attrition rate. Overall, although evidence is limited in quality and quantity, it appears that targeted elimination diets for patients with concurrent migraine and food sensitivities may be effective for migraine prevention, but further evidence is required.

### The ketogenic diet for headache

In the past couple of decades, there has been a renewed interest in exploring the ketogenic diet for neurological diseases. The ketogenic diet yields multiple biochemical changes in the brain that could theoretically affect migraine propensity (42), including a shift in neuronal energy states and altered neuronal excitability in the context of acidosis and ketone body metabolism (43). Interestingly, the ketogenic diet appears to decrease cortical spreading depression in the short-term (44), making it plausible that it could have an effect in migraine with aura.

The first case series reporting use of the ketogenic diet for headache was carried out in 1928. A sample of 18 migraine patients were treated with an incremental ketogenic diet regimen, and half of those patients had some relief of their condition (45). In 1930, a sample of 50 migraineurs, most of whom had severe and refractory migraines, were followed for a period of several months on the ketogenic diet. Interestingly, 78% of the patients benefitted from the diet, with 28% of the sample achieving complete remission from their migraines (46). Since then, a few case reports have indicated promise for the ketogenic diet in migraine (47–49).

The modified Atkins diet, which is similar to the ketogenic diet and also results in a state of ketosis, was administered to a sample of eight adolescents with chronic daily headache. Compliance was problematic with only three of the participants completing the 12-week diet, and none of the participants had any reduction in migraine frequency over the treatment period (50). Another study among adolescents aimed to administer the ketogenic diet to 18 adolescents with migraine for a three-month treatment period. Only 38% of the patients adhered to the ketogenic diet for the entire treatment period, and some response to the diet was observed in only 38% of the original sample (51). It is therefore difficult to comment on the efficacy of the ketogenic diet in adolescents because of limited evidence and significant compliance issues observed in the published studies.

Two studies have assessed the efficacy of the traditional ketogenic diet for adult migraine prophylaxis and have shown encouraging results. The ketogenic diet was superior to a standard low-calorie diet over a four-week treatment period with a 90% responder rate in a sample of 108 migraine patients (52). A recent open-label study, during which 96 migraine patients were assigned to either the ketogenic diet or a standard diet depending on their preference, uncovered an association between migraine relief and ketosis: During the ketogenic phase of the intervention diet, a significant improvement in headache parameters was observed

(28). Based on the case reports and interventional studies described above, there is some preliminary evidence to support the use of the ketogenic diet as an intervention in the motivated adult migraine patient. Methodologically rigorous studies are needed to confirm these findings.

### Miscellaneous dietary interventions for headache

Several other dietary interventions have been explored for headache in isolated studies. A low-sucrose diet was administered to migraineurs reporting an association between migraine attacks and fasting states. A favorable response rate was observed among patients found to have diabetes or reactive hypoglycemia on an oral-glucose tolerance test (53). A small series of 10 women suffering from migraine and cutaneous symptoms consistent with food allergy demonstrated improvement in their headaches on a tryptophan-reduced diet (54). Increased dietary water intake was assessed in an RCT carried out among adult patients with recurrent headaches. Though subjective improvement in headache and disability was observed among the group with increased water intake compared to the standard intervention group, no differences were seen when assessing headache frequency and other parameters in participants' headache diaries (55). Finally, based on the theory that omega-6 fatty acids are pronociceptive and omega-3 fatty acids are antinociceptive, a group of adult patients with chronic headaches were randomized to a dietary intervention involving either reduction of omega-6 fatty acids alone or reduction of omega-6 fatty acids combined with increased omega-three fatty acids. After 12 weeks of the diet, participants on the high omega-3 and low omega-6 diet had greater improvement in their headaches as compared to participants on the reduced omega-6 diet (56).

### Nutraceutical interventions for headache

Table 2 summarizes the evidence for nutraceuticals in the treatment of primary headache disorders.

#### Feverfew (*Tanacetum parthenium* L.) for migraine

Feverfew, also known as *Tanacetum parthenium* L., is a medicinal herb that has been used for centuries for a variety of ailments. Parthenolide, a sesquiterpene lactone, appears to be feverfew's active ingredient and has multiple actions in the central nervous system. Several of its properties suggest a potential mechanism of action in migraine prevention, including evidence to suggest that parthenolide inhibits Fos-induced

**Table 2.** Summary of studies on nutraceutical interventions for headache.

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Feverfew	Systematic review	Pittler and Ernst, 2004 (60): Cochrane systematic review	Five RCTs (two parallel-group, three cross-over) of 343 patients	Riboflavin in various formulations and doses	Placebo	No convincing evidence to establish feverfew's efficacy; the two highest quality RCTs did not show benefit, and the other three RCTs did
	Non-randomized	Cady et al., 2005 (61): prospective open-label study	30 adults with migraine	Gelstat Migraine® (combination of feverfew and ginger) for acute migraine	N/A	48% of patients achieved two-hour pain freedom and 34% of participants had only mild pain at two hours
		Shrivastava et al., 2006 (64): prospective open-label study	12 adults with migraine without aura	Tanacetum parthenium (feverfew) 300 mg + Salix alba 300 mg bid for 12 weeks	N/A	70% of patients had a 50% or greater reduction in migraine frequency
	RCT	Cady et al., 2011 (62): RCT	60 adults with migraine	Gelstat Migraine® (combination of feverfew and ginger) for acute migraine (n = 45)	Placebo for acute migraine (n = 15)	32% of Getstat Migraine® group vs. 16% of placebo group were pain free at two hours (p = 0.02)
		Maizels et al., 2004 (63): RCT	49 adults with migraine	Capsules of feverfew 100 mg, magnesium 300 mg and riboflavin 400 mg two capsules daily for three months (n = 24)	25 mg riboflavin two capsules daily as placebo for three months (n = 25)	No difference in the proportion of patients achieving a 50% or greater reduction in migraine frequency (p = 0.87)
		Ferro et al., 2012 (65): RCT	68 women with chronic migraine	Tanacetum parthenium (feverfew) 150 mg daily and 20 acupuncture sessions over 10 weeks (n = 23)	Tanacetum parthenium (feverfew) 150 mg daily over 10 weeks (n = 22)	Combined feverfew + acupuncture was superior in reducing SF-36 scores (p < 0.05), MIDAS scores (p < 0.05) and mean pain scores (p < 0.05) as compared to either treatment alone
		Diener et al., 2005 (66): RCT	218 adults with migraine	Tanacetum parthenium (6.25 mg feverfew extract) CO <sub>2</sub> extract (MIG-99) tid for 16 weeks (n = 108)	Placebo for 16 weeks (n = 110)	Migraine frequency decreased more in the intervention group as compared to placebo (-1.9 vs. -1.3 attacks/month, p = 0.0148)

(continued)

**Table 2.** Continued.

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Riboflavin (vitamin B <sup>2</sup> )	Non-randomized	Smith, 1946 (84): case series	19 adults with migraine	Riboflavin 5 mg tid for variable durations	N/A	95% of the patients improved on riboflavin
		Boehnke et al., 2004 (85): prospective open-label study	23 adults with migraine	Riboflavin 400 mg daily for three to six months	N/A	Migraine frequency decreased from mean of four days/month to two days/month ( $p < 0.001$ )
		Schoenen et al., 1994 (86): prospective open-label study	44 adults with migraine	Riboflavin 400 mg daily (23 of the 44 patients were also given aspirin 75 mg daily) for a minimum of three months	N/A	Mean improvement of 68.2% in their migraine severity scores, with no difference between those who received ASA and those who didn't (no $p$ given)
		Sándor et al., 2000 (88): prospective open-label study	26 adults with migraine	Riboflavin 400 mg daily for four months	Bisoprolol 10 mg daily or metoprolol 200mg daily for four months	Both groups had a significant decrease in headache frequency ( $p < 0.05$ ), but no difference between the groups
		Condo et al., 2009 (91): retrospective chart review	41 children and adolescents with a variety of headache disorders	Riboflavin 200 mg or 400 mg PO daily for three, four or six months	N/A	Significant reduction in headache frequency after treatment for three or four months ( $21.7 \pm 13.7$ vs. $13.2 \pm 11.8$ , $p < 0.01$ ), which was not sustained at six months ( $19.3 \pm 13.4$ vs. $11.4 \pm 9.6$ , $p > 0.05$ )
		Markley, 2009 (92): retrospective chart review	32 adolescents with chronic daily headache	Riboflavin 400 mg daily for at least six weeks	N/A	73% of patients had some response to riboflavin
	RCT	Schoenen et al., 1998 (89): RCT	55 adults with migraine	Riboflavin 400 mg daily for four months ( $n = 28$ )	Placebo for four months ( $n = 27$ )	Riboflavin lead to a greater reduction in migraine frequency by month 4 ( $p = 0.0001$ ), NNT = 2.8
		Nambiar et al., 2011 (90): open-label RCT	100 adults with migraine	Riboflavin 100 mg daily for at least three months ( $n = 50$ )	Propranolol 80 mg daily for at least three months ( $n = 50$ )	The propranolol group had a greater reduction in migraine frequency in first month ( $p < 0.001$ ), but there were no group differences at three and six months
		MacLennan et al. 2008 (93): RCT	48 children and adolescents with migraine	Riboflavin 200 mg daily for 12 weeks ( $n = 27$ )	Placebo for 12 weeks ( $n = 21$ )	No difference between the groups in terms of the proportion of participants with 50% or greater reduction of migraine frequency (44.4% of the riboflavin vs 66.6% of the placebo group, $p = 0.125$ )
		Bruinj et al., 2010 (94): cross-over RCT	42 children with migraine	Riboflavin 50 mg daily for four months ( $n = 20$ )	Placebo for four months ( $n = 22$ )	No difference between groups in terms of change in migraine frequency ( $p = 0.44$ ); the riboflavin group had a greater reduction in the frequency of tension-type headaches as compared to placebo ( $p = 0.04$ )

(continued)

**Table 2. Continued.**

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Intravenous magnesium	Non-randomized	Martinez Cardenas et al., 2012 (97): retrospective chart review	31 refractory headaches in 23 admitted children and adolescents	Intravenous magnesium sulfate (MgSO <sup>4</sup> ) with intravenous diphenhydramine. Many of the patients received several doses of MgSO <sup>4</sup>	N/A	51% of headaches improved with treatment
		Gertsch et al., 2014 (98): retrospective chart review	20 children with acute headache in the ED	Intravenous magnesium	N/A	77% of the patients treated in the ED were admitted for further headache management
		Mauskop et al., 1996 (99): prospective open-label study	40 adult patients with a variety of acute headache disorders	Intravenous MgSO <sup>4</sup> 1 g	N/A	80% of patients had complete pain relief within 15 minutes
		Mauskop et al., 1995 (100): prospective open-label study	22 adult patients with cluster headache for a total of 38 infusions	Intravenous MgSO <sup>4</sup> 1 or 2 g	N/A	60.5% of the infusions resulted in improvement in the headaches (at least two days headache free)
	Systematic review	Orr et al., 2014 (101): systematic review	4 RCTs of 247 adult patients with acute migraine	Intravenous MgSO <sup>4</sup> 1 or 2 g	Placebo or metoclopramide	Authors concluded that MgSO <sup>4</sup> is likely not effective; one small RCT found MgSO <sup>4</sup> superior to placebo, two RCTs found no difference between placebo and MgSO <sup>4</sup> and one RCT found MgSO <sup>4</sup> inferior to placebo
		Choi and Parmar, 2014 (102): systematic review and meta-analysis	5 RCTs of 295 adult patients with acute migraine	Intravenous MgSO <sup>4</sup> 1 or 2 g	Placebo, prochlorperazine or metoclopramide	Authors concluded that MgSO <sup>4</sup> showed no benefit over comparators; 7% fewer patients on MgSO <sup>4</sup> had headache relief as compared to comparators in meta-analysis (95% CI: -0.23 to 0.09)
	RCT	Shahrami et al., 2015 (103): RCT	70 adult patients with acute migraine	Intravenous MgSO <sup>4</sup> 1 g	Intravenous metoclopramide 10 mg + dexamethasone 8 mg	MgSO <sup>4</sup> was more effective in decreasing pain severity 20 minutes, one hour and two hours after treatment than metoclopramide and dexamethasone ( $p < 0.0001$ )

(continued)

**Table 2.** Continued.

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Oral magnesium	Non-randomized	Castelli et al., 1993 (109): prospective open-label study	40 children with periodic syndromes (25 migraine, 12 recurrent abdominal pain, three fever of unknown origin)	Magnesium pidolate, doses ranging from 122 to 266 mg of elemental magnesium for various durations	N/A	72.5% of patients had a reduction in migraine frequency to 33% or less of baseline after one month of treatment
		Grazzi et al., 2005 (112): prospective open-label study	9 children with TTH	Magnesium pidolate 2.25 mg bid for two months	N/A	Headache frequency decreased at one year in 80% of episodic TTH participants and 100% of chronic TTH participants at 12-month follow-up and 100% of all participants had a reduction in medication usage by 12 months
		Grazzi et al., 2007 (113): prospective open-label study	45 children and adolescents with episodic TTH	Magnesium pidolate 2.25 mg bid for three months. Only 49.1% completed follow-up and treatment as planned	N/A	Headache days ( $p = 0.001$ ), analgesic consumption ( $p = 0.0001$ ) and MIDAS scores ( $p = 0.001$ ) decreased significantly at 12-month follow-up
	RCT	Facchinetti et al., 1991 (104): RCT	20 women with menstrual migraine	Magnesium pyrrrolidone carboxylic acid (360 mg/day) for two months ( $n = 10$ )	Placebo for two months ( $n = 10$ )	Both groups had reduced pain, with magnesium group having a larger decrease in pain magnitude ( $p < 0.03$ ); only magnesium group had less headache days
		Köseoglu et al., 2008 (105): RCT	40 adults with migraine without aura	Magnesium citrate 1830 mg (295.7 mg elemental) PO bid for three months ( $n = 30$ )	Placebo for three months ( $n = 10$ )	The magnesium group had a lower median post-/pre-treatment attack frequency ratio (0.55 vs. 1.00, $p = 0.005$ )
		Esfanjani et al., 2012 (106): single-blind RCT	133 adults with migraine or similar headaches	Magnesium oxide 500 mg PO daily for three months ( $n = 33$ ) L-carnitine 500 mg PO daily for three months ( $n = 35$ )	Magnesium oxide 500 mg PO daily + L-carnitine 500 mg PO for three months ( $n = 30$ )	Statistically significant reduction in all groups except for the no treatment group ( $p < 0.001$ for all); after post-hoc analyses, only the magnesium group as compared to the no treatment group had a greater reduction ( $p < 0.006$ )
		Peikert et al., 1996 (107): RCT	81 adults with migraine	Tri-magnesium dicitrate 600 mg daily for three months ( $n = 43$ )	Placebo for three months ( $n = 38$ )	Greater reduction in migraine frequency in the magnesium group as compared to the placebo group (41.6% vs. 15.8%, $p = 0.0303$ )

(continued)

**Table 2. Continued.**

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
		Paffenrath et al., 1996 (108): RCT	69 adults with migraine without aura	Magnesium L-aspartate-trihydrate 10 mmol (121.5 mg elemental) PO twice daily for three months (n = 35)	Placebo for three months (n = 34)	No difference in proportion of patients with 50% or greater reduction in duration or intensity of migraines (28.6% of the magnesium group vs. 29.4% of the placebo group)
		Wang et al., 2003 (110): RCT	118 children and adolescents with headaches suggestive of migraine	Magnesium oxide containing 9 mg/kg of elemental magnesium PO tid for four months (n = 58)	Placebo for four months (n = 60)	Both groups had a downward trend in headache days, with only the magnesium group sustaining the trend past six weeks; no significant difference between groups after regression analyses (p = 0.88)
		Gallelli et al., 2014 (111): single-blind RCT	160 children and adolescents with migraine without aura	Magnesium 400 mg daily + acetaminophen 15 mg/kg to be taken with acute migraine episodes for up to 18 months (n = 40)	Acetaminophen 15 mg/kg to be taken with acute migraine episodes for up to 18 months (n = 40)	Treatment with magnesium reduced pain intensity acutely when combined with acetaminophen or ibuprofen (p < 0.01) and resulted in a reduction of migraine frequency (p < 0.01)
Coenzyme Q <sup>10</sup>	Non-randomized	Rozen et al., 2002 (114): prospective open-label study	32 adults with migraine	Coenzyme Q <sup>10</sup> 150 mg daily for three months	N/A	61.3% of patients had 50% or greater reduction in migraine attack frequency
		Hershey et al., 2007 (116): prospective open-label study	252 children and adolescents with migraine and coenzyme Q <sup>10</sup> deficiency	Coenzyme Q <sup>10</sup> 1–3 mg/kg daily for average of three months	N/A	Significantly less headache days/month after treatment period (19.2 ± 9.8 vs. 12.5 ± 10.8, p < 0.01)
RCT		Sándor et al., 2005 (115): RCT	43 adults with migraine	Coenzyme Q <sup>10</sup> 100 mg tid for four months (n = 22)	Placebo for four months (n = 21)	Coenzyme Q <sup>10</sup> group had a greater reduction in migraine attack frequency compared to placebo (–1.19 ± 1.9 vs. –0.09 ± 1.9, p = 0.05)
		Slater et al., 2011 (117): cross-over; add-on RCT	120 children and adolescents with migraine	Coenzyme Q <sup>10</sup> 100 mg daily for four months (n = 60)	Placebo for four months (n = 60)	Significant reduction in headache frequency in both groups, but repeated-measures ANOVA failed to show a time × condition interaction (p > 0.05)

(continued)

**Table 2.** Continued.

Nutraceutical	Type of studies	Individual studies and design	N/patients	Intervention	Comparison	Outcomes
Miscellaneous	Non-randomized	Wagner et al., 1997 (118): prospective open-label study	168 adults with migraine	γ-lipolenic acid + α-linolenic acid 1800 mg + vitamin B <sup>6</sup> , niacin + D-α-tocopherol + β-carotene + various other lifestyle interventions for six months	N/A	Significant reduction in migraine frequency in 86% of patients
		D'Andrea et al., 2009 (122): prospective open-label study	50 women with migraine with aura	60 mg ginkgo biloba terpenes phytosome + 11 mg coenzyme Q <sup>10</sup> + 8.7 mg vitamin B <sup>6</sup> for four months	N/A	Migraine frequency decreased significantly from 3.7 ± 2.2 to 2.0 ± 1.9 attacks per month (p < 0.05)
		Esposito and Carotenuto, 2011 (123): prospective open-label study	119 children with migraine without aura	Ginkgolide B + coenzyme Q <sup>10</sup> + riboflavin + magnesium bid for three months (doses unspecified)	N/A	Migraine frequency decreased from 9.71 ± 4.33 to 4.53 ± 3.96 (p < 0.001)
		Esposito et al., 2012 (124): prospective open-label study	374 children with migraine without aura	Ginkgolide B 80 mg, coenzyme Q <sup>10</sup> 20 mg, riboflavin 1.6 mg + magnesium 300 mg for six months (n = 187)	L-tryptophan 250 mg, 5-hydroxy-tryptophan 50 mg, vitamin PP 9 mg + vitamin B <sup>6</sup> 1 mg for six months (n = 187)	Greater reduction in migraine frequency in ginkgolide group compared to other group (9.128 ± 2.842 to 1.734 ± 1.231 vs. 8.778 ± 2.512 to 3.032 ± 1.072)
		Usai et al., 2010 (125): prospective open-label study	24 children and adolescents with migraine without aura	Ginkgolide B 80 mg + coenzyme Q <sup>10</sup> 20 mg + vitamin B <sup>2</sup> 1.6 mg + magnesium 300 mg for three months	N/A	Migraine frequency decreased from 7.4 ± 5 to 2.2 ± 2.8 attacks/month (p = 0.0015)
	RCT	Pradalier et al., 2001 (119): RCT	196 adults with migraine	Omega-3 polyunsaturated fatty acid 6 g daily for four months (n = 100)	Placebo for four months (n = 96)	No difference in migraine frequency when comparing omega-3 group to placebo (1.20 ± 1.4 vs. 1.26 ± 1.11, NS)
		Harel et al., 2002 (120): cross-over RCT	27 adolescents with migraine	Marine n3-ethyl ester concentrate (EPA 378 mg, DHA 249 mg and tocopherol 2 mg) 1 g two capsules daily for two months	Placebo (oleic acid 691 mg, palmitic acid 106 mg, linoleic acid 62 mg and tocopherol 2 mg) 1 g two capsules PO daily for two months	Significant reduction in migraine frequency for both groups but no significant difference between the groups (mean number of migraines during treatment 4 ± 1/month for both groups)

MgSO<sup>4</sup>: intravenous magnesium sulfate; ASA: acetylsalicylic acid; PO: orally; bid: twice daily; tid: three times daily; ED: emergency department; RCT: randomized controlled trial; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; ANOVA: analysis of variance; TTH: tension-type headache; MIDAS: Migraine Disability Assessment; CI: confidence interval; NA: not available; NS: not significant.

activation of the nucleus trigeminalis caudalis (57), a nucleus central to migraine pathogenesis, and evidence for partial agonist activity of parthenolide at TRPA1 channels (58), which have been implicated in migraine pathogenesis (59).

Feverfew is one of the best-studied nutraceutical agents for migraine prophylaxis in adults. A 2004 Cochrane review identified five RCTs on this topic. The studies were quite heterogeneous in terms of quality and methodology, with notable variations in feverfew dosages. Results from the trials were mixed with regards to the efficacy of feverfew: Whereas the two highest quality trials were negative, the other three trials suggested that feverfew is effective in migraine prophylaxis. Feverfew was well tolerated in all five studies. The authors concluded that the evidence available was unconvincing for feverfew's efficacy in migraine (60). Since the Cochrane review, six new studies have been published. Five of these studies involved combinations of feverfew with other active interventions: One open-label study and one RCT have suggested that a combination of feverfew and ginger might be effective for acute migraine relief (61,62), an RCT found no difference between placebo and a combination of feverfew, magnesium and riboflavin for migraine prophylaxis (63), a small open-label study demonstrated promise for a combination of feverfew and *Salix alba* in the prevention of migraine with aura (64) and finally a randomized trial found a combination of feverfew and acupuncture to be superior to either intervention alone for chronic migraine (65). A methodologically rigorous RCT comparing a formulation of feverfew to placebo has also been published since the Cochrane review, and suggested that feverfew is superior to placebo for migraine prophylaxis in adults (66). In 2012, the American Academy of Neurology (AAN) concluded that feverfew is probably effective for migraine prevention based on level B evidence (67). Based on the state of the evidence, it appears that feverfew might be effective for migraine prophylaxis in adults, but the heterogeneity of the literature, especially with regards to feverfew preparations and dosages, makes definite conclusions challenging.

### ***Butterbur (*Petasites hybridus*) for migraine***

Butterbur is a shrub with a long history of use for medicinal purposes. It demonstrates a variety of properties that render it a candidate for migraine prophylaxis, including anti-inflammatory action through inhibition of cyclooxygenase-2 (68) and vasodilatory effects through inhibition of L-type voltage-gated calcium channels (69).

Although butterbur has been studied for migraine prophylaxis both in adults and children with promising

results reviewed elsewhere (67,70,71), increasing concerns about its safety are emerging. Butterbur contains hepatotoxic compounds by the name of pyrrolizidine alkaloids. Many of the butterbur formulations available on the market contain detectable and potentially hazardous levels of these compounds (72). Petadolex<sup>®</sup>, a formulation of butterbur that is marketed for its safety based on undetectable levels of pyrrolizidine alkaloids, has traditionally been the formulation of butterbur that is used clinically. Initial data suggested that Petadolex<sup>®</sup> is safe for use in animals and humans (73). However, cases of hepatotoxicity linked to Petadolex<sup>®</sup> have been reported post-marketing and some regulatory authorities, namely European authorities including the Swiss Agency for Therapeutic Products and the German Federal Institute of Medical Devices, have banned its use (74). Therefore, uncertainty about the safety of Petadolex<sup>®</sup> precludes recommendations for its use based on recent data.

### ***Riboflavin (vitamin B<sub>2</sub>) for migraine***

Riboflavin is a vitamin that plays an important role in cellular energy production through its two active coenzyme forms that are involved in oxidation-reduction reactions during a variety of cellular processes (75). Given evidence hinting at mitochondrial energy depletion in migraine (76–83), riboflavin's essential role in mitochondrial energy metabolism suggests that it could be effective in treating migraine.

Riboflavin has demonstrated efficacy and tolerability for migraine prevention in adults based on a case series (84) and several open-label studies (85–88). One small RCT found riboflavin to be superior to placebo for migraine prophylaxis in a sample of 55 adult migraineurs (89). Riboflavin was comparable to propranolol after three months and six months of administration in an RCT assessing its efficacy for adult migraine prophylaxis (90). Another RCT among adults with migraine explored the efficacy of high-dose riboflavin, combined with feverfew and magnesium as compared to low-dose riboflavin and found that both interventions yielded modest responder rates (63). All of the available studies indicate that riboflavin is well tolerated among adults with migraine. The AAN has determined that riboflavin is probably effective for migraine prophylaxis based on B-level evidence (67). Therefore, studies on the efficacy of riboflavin are consistent in their findings and suggest that riboflavin is well tolerated and efficacious for adult migraine prophylaxis.

Riboflavin has also been studied in the pediatric population, but results are conflicting. A retrospective case series among children with a variety of headache disorders found riboflavin to be effective in the first

three months of treatment, but efficacy appeared to wane over time and results were not sustained beyond three months (91). Another retrospective case series that similarly investigated the role of riboflavin for the prophylaxis of a variety of headache disorders found that adolescents with chronic migraine, but not other headache disorders, responded well to riboflavin (92). An underpowered RCT found no difference between riboflavin and placebo for pediatric migraine prophylaxis after 12 weeks of treatment (93). A small cross-over RCT using a lower dose of riboflavin as compared to previous studies found that children had a reduction in the number of tension-type headaches (TTHs), but not migraines, on riboflavin (94). In the pediatric population, riboflavin lacks adequately powered and methodologically rigorous studies. Although preliminary results are disappointing, further studies should explore the efficacy of riboflavin in this population.

### *Magnesium for migraine*

Magnesium is ubiquitous in the human body and plays an important role in a multitude of biological processes, some of which are linked to migraine pathogenesis (95). There is a large body of evidence, reviewed elsewhere (96), that points to a state of magnesium deficiency among migraineurs. There is therefore a plausible biological reason to explore magnesium as a migraine intervention.

Intravenous magnesium sulfate ( $\text{MgSO}_4$ ) has been used to treat acute headaches. Two retrospective case series among children with acute headaches contradicted each other with regards to conclusions on the efficacy of intravenous magnesium for acute headache relief (97,98). In adults, open-label studies have shown promise for intravenous  $\text{MgSO}_4$  in acutely relieving various headache types (99) and cluster headache in patients with low magnesium levels (100). A recent systematic review of published trials identified four eligible RCTs on the efficacy of  $\text{MgSO}_4$  for migraine relief in adults, and results were heterogeneous, with one small trial finding  $\text{MgSO}_4$  superior to placebo, two trials finding no difference between placebo and  $\text{MgSO}_4$  in terms of the primary outcome and one trial finding  $\text{MgSO}_4$  inferior to placebo. The authors concluded that intravenous  $\text{MgSO}_4$  is not likely to be effective for acute migraine relief (101). Similar conclusions were reached in a recent meta-analysis on the same topic (102). Since publication of these reviews, one further RCT has been published. In this trial, 1 g of intravenous  $\text{MgSO}_4$  was superior to a combination of 10 mg of metoclopramide and 8 mg of dexamethasone for acute migraine relief in adults (103). Given the relatively low doses of metoclopramide and dexamethasone, as well as the small

sample size ( $N=70$ ) relative to the rest of the literature, this study is unlikely to change conclusions about the efficacy of  $\text{MgSO}_4$  for acute migraine relief.

Oral magnesium supplementation has been studied for adult and pediatric migraine prevention. In a sample of women with low magnesium levels, magnesium was superior to placebo for menstrual migraine prophylaxis (104). Three separate RCTs with varying methodologies, comparison groups, magnesium dosages and formulations have found oral magnesium to be effective for migraine prophylaxis in adults (105–107). Another RCT contradicted these findings and found oral magnesium to be no different from placebo on interim analysis in a sample of refractory migraine patients and thereby halted recruitment prior to achieving the planned sample size (108). The AAN guidelines conclude that magnesium is probably effective for migraine prophylaxis in adults based on level-B evidence (67). Three studies have assessed magnesium prophylaxis for pediatric migraine. One open-label study found oral magnesium supplementation to be beneficial in a variety of childhood periodic syndromes (109). A small RCT found a significant downward trend in headache frequency for children treated with magnesium but not with placebo (110). Finally, an RCT found that daily oral magnesium had a synergistic effect with acetaminophen or ibuprofen in achieving better acute pain relief than either analgesic alone and also found magnesium to be effective in reducing migraine frequency (111). These magnesium studies have consistently uncovered minor gastrointestinal side effects associated with oral magnesium, namely soft stools and diarrhea, but no major magnesium-associated adverse events. The balance of evidence seems to be in favor of oral magnesium for migraine prophylaxis, but further research should be carried out in order to confirm these findings and assess differential efficacy based on baseline magnesium levels, given that magnesium-deficient patients would intuitively benefit more from supplementation or increased dietary intake of magnesium.

In addition to the evidence for oral magnesium prophylaxis in migraine, two studies have assessed its efficacy in pediatric TTH. In a prospective case series of nine pediatric patients with tension-type headaches, oral magnesium appeared to be quite effective for the majority of the patients (112). The same author group later carried out a larger prospective study in 45 pediatric TTH patients, and found magnesium to be effective among the patients completing follow-up as prescribed (113). These preliminary results are promising but studies with more rigorous designs should be carried out prior to making recommendations on the use of magnesium for pediatric TTH.

### *Coenzyme Q<sub>10</sub> for migraine*

Coenzyme Q<sub>10</sub> acts as an electron carrier in the mitochondrial electron transport chain and therefore plays an important role in cellular energy metabolism. Hence, similarly to riboflavin, its potential mechanism of action in migraine would relate to the evidence that migraine results in mitochondrial energy deficiency (76–83).

In a small open-label prospective study, four months of treatment with coenzyme Q<sub>10</sub> showed promising results for the prophylaxis of migraine in adults, with no significant side effects observed (114). An RCT later found coenzyme Q<sub>10</sub> to be superior to placebo in a small sample of adults with migraine, with one patient in the coenzyme Q<sub>10</sub> group reporting a cutaneous allergy (115), but no other notable side effects. Based on the adult data, the AAN concludes that coenzyme Q<sub>10</sub> is possibly effective for migraine prophylaxis in adults based on level C evidence (67). An open-label study among pediatric migraineurs found a favorable response to coenzyme Q<sub>10</sub> among patients with low coenzyme Q<sub>10</sub> levels at baseline (116). The same group later carried out a cross-over RCT in a sample of pediatric patients and did not find any notable differences between the treatment periods with coenzyme Q<sub>10</sub> as compared to placebo (117). The study was limited by a small sample size in the context of a high drop-out rate, and the authors did not selectively treat patients with low baseline coenzyme Q<sub>10</sub> levels. Overall, it seems that coenzyme Q<sub>10</sub> might be effective and safe for migraine prophylaxis, but future high-quality studies that take into consideration baseline coenzyme Q<sub>10</sub> levels should be endeavored.

### *Miscellaneous nutraceuticals for headache*

Although the nutraceuticals described above demonstrate the most promise in headache management, several other agents have been investigated in smaller numbers of studies or with lower-quality evidence. Supplements of polyunsaturated fatty acids (PUFAs) do not appear to be effective for migraine prophylaxis (70). The evidence for their use in migraine derives from one open-label study finding improvement in adult migraine with a multi-pronged intervention including PUFAs (118), two RCTs finding no difference in efficacy comparing PUFAs to placebo in adults (119) and adolescents (120) and one RCT, with unblinded patients, finding that addition of PUFAs to sodium valproate resulted in greater reduction in migraine frequency after one month of treatment, which was not sustained after three months (121). Ginkgolide B, in combination with a variety of other nutraceutical agents, appears to improve migraine status in adults

(122) and children (123–125) based on open-label studies. However, the methodologic limitations and heterogeneity of the compounds studied make the evidence difficult to apply to clinical recommendations. Relief of cluster headache with intranasal capsaicin has been documented in several studies, reviewed elsewhere (126). In addition, limited studies have been carried out to assess the efficacy of a variety of other nutraceuticals for headache (127), including phytoestrogens for menstrual migraine, caffeine for migraine and a variety of topical botanical therapies for headache.

### **Conclusions**

Perhaps in response to the growth of the CAM industry, an increasing number of studies are exploring the role of CAM for headache. In this review, the current state of evidence for dietary and nutraceutical interventions in headache disorders is described. Several interventions show promise as potential headache treatments, although the limited number of adequately powered studies and low quality of the evidence have made it difficult to apply the findings to routine clinical practice. Because of limited data, caution needs to be taken when considering use of these interventions in clinical practice.

When discussing nutraceuticals with patients, several issues need to be considered. Patients tend to perceive herbal supplements as safe for a variety of reasons, including their non-prescription availability, and their natural properties (128). However, as with pharmaceutical agents, physicians must be aware of potential toxicities and side effects when counseling patients about these interventions. In fact, society would benefit from nutraceuticals being conceptualized, scrutinized and regulated in the same manner as pharmaceuticals, given that they have the potential for both similar efficacy and harm. The case of butterbur illustrates the need for ongoing caution and long-term monitoring of safety data in relation to nutraceuticals. Nonetheless, several of the dietary and nutraceutical interventions above warrant further investigation given promising preliminary efficacy and safety data.

When considering CAM therapies for patients with headache disorders, several factors must be weighed. As highlighted above, the quality of the evidence for efficacy and tolerability should be at the forefront of the decision-making process. In addition, headache practitioners should consider patient comorbidities, as some of the CAM therapies have been used in other circumstances and may therefore offer a twofold benefit. For example, patients with menstrual migraine and premenstrual syndrome may experience relief of both conditions with magnesium, phytoestrogens or ginkgolide B (129). In this way, clinicians need to weigh the

risks and benefits from the evidence, and consider individual patient characteristics and preferences when prescribing CAM, in the same manner as is currently the standard with pharmacological interventions.

Given the prevalence of CAM use among patients with headaches, it is imperative that practitioners develop an understanding of CAM therapies and the state of evidence for their use. At a minimum, knowledge of CAM allows the practitioner to engage in educated discussions about the efficacy and safety of CAM and is likely to foster information sharing and shared decision making between the practitioner and the

patient. In one study, patients seeing general practitioners with additional CAM training had lower health care costs and lower mortality as compared to patients seeing general practitioners without additional CAM training (130). Thus, physicians who are educated about CAM may provide better care to their patients. Hence, we owe it to our patients to become engaged in this area and to advocate for high-quality intervention studies, where justified by plausible mechanisms of action and preliminary data, that will allow us to better comment on the safety and efficacy of these interventions.

### Clinical implications

- A majority of patients with primary headache disorders have explored complementary and alternative medicines (CAM) for headache relief.
- In this article, an overview of the evidence for dietary and nutraceutical headache interventions is provided.
- A growing number of studies are assessing nutraceutical and diet interventions for headache.
- Several dietary and nutraceutical interventions have been studied for headache, with limitations in the number of studies and the quality of the evidence.
- Further evidence is required to further explore the safety and efficacy of some of the more promising dietary and nutraceutical headache interventions.

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### Conflict of interest

None declared.

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