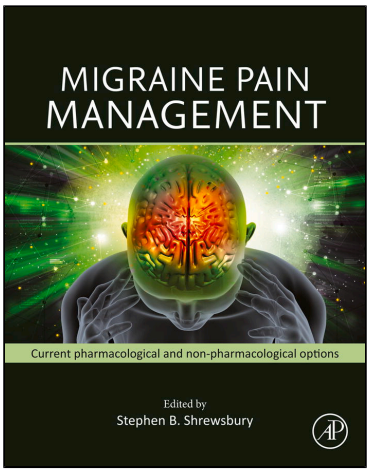

From Schoenen, J., & Lisicki, M. (2025). Nutraceuticals and diets. In S. B. Shrewsbury (Ed.), Migraine Pain Management: Current Pharmacological and Non-pharmacological Options (pp. 555–569). Academic Press: Elsevier.
ISBN: 9780443247057

Academic Press

Chapter 35

Nutraceuticals and diets

Jean Schoenen[a] and Marco Lisicki[b,c]

[a]GIGA-Neuroscience-Neuroanatomy, University of Liège, Liège, Belgium; [b]Headache Research Laboratory, Mercedes & Martín Ferreyra Institute – National Scientific and Technical Research Council (CONICET) – National University of Córdoba, Argentina; [c]Department of Biomedical Physics, School of Medicine, National University of Córdoba, Argentina

1. Introduction

The pathogenesis of migraine involves a complex interplay between genetic, environmental, and hormonal factors. There is compelling evidence that impaired brain energy metabolism due to mitochondrial dysfunction and oxidative stress has a prominent role (Del Moro et al., 2022; Gross et al., 2019) together with abnormal, energy-demanding processing of sensory information and hyperresponsivity (de Tommaso et al., 2014; Gantenbein et al., 2013; Goadsby, Holland, et al., 2017).

Although their precise mode of action is not fully understood, classical drug treatments for migraine prevention such as beta-blockers, calcium antagonists, antidepressants, and anticonvulsants are thought to normalize information processing and brain excitability (Diener et al., 1989; Noordhout et al., 1987; Sándor et al., 2000). Their efficacy/adverse effect profile is rather unfavorable so that treatment adherence and persistence are quite low (Hepp et al., 2014).

Drugs blocking CGRP neurotransmission are thought to exert their action in the peripheral trigeminovascular system, the final common pathway of migraine attack pathophysiology. As such, they act as long-lasting (the monoclonal antibodies) or daily-administered (the gepants) acute treatments without obvious influence on the central nervous system causes of migraine (Ferrari et al., 2022). CGRP-blocking drugs have an excellent efficacy/adverse effect profile, but they are expensive and inefficient in ± 40%–60% of migraine patients (Schoenen et al., 2020).

The metabolic facets of migraine pathogenesis can be targeted by so-called metabolic treatments, among which are nutraceuticals and diets. The term "nutraceutical" is derived from the words "nutrition" and "pharmaceutical," and refers to food or food products that provide health benefits beyond their basic nutritional value. As nutraceuticals are unregulated in most countries, it is often stated that they are promoted by marketing hype rather than by clinical evidence (Aronson, 2017). Nutraceuticals are indeed less rigorously and extensively studied than pharmaceuticals and, although they have undergone numerous randomized controlled trials (RCTs), many of them investigator-initiated, the relatively small sample sizes and short treatment durations tend to decrease their level of evidence in scientific literature grading systems. While nutraceuticals are chiefly "metabolic enhancers" (i.e., substances that when supplemented improve or optimize energy metabolism), "substrate-based treatments" are therapies aiming to provide the most adequate or an alternative source of fuel for energetic processes. Ketone bodies, be they provided by ketogenic diets or dietary supplements, are part of the latter. We will review here the available evidence for both nutritional strategies.

2. Metabolic enhancers

2.1 Riboflavin and its combinations

2.1.1 Riboflavin

Riboflavin (vitamin B2) is the precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are required for the activity of flavoenzymes involved in complexes I and II of the electron transport chain. It is fundamental for the adequate functioning of electron carriers in the inner membrane of the mitochondria and has neuroprotective properties, as it mitigates oxidative stress, neuroinflammation, and glutamate excitotoxicity (Gross et al., 2019).

The first proof-of-concept trial of riboflavin in migraine prevention (Schoenen et al., 1994) was prompted by the MR spectroscopy findings of a reduced phosphorylation potential in the brain of migraine patients (Barbiroli et al., 1992; Welch et al., 1989) and the known beneficial effect of

Migraine Pain Management. https://doi.org/10.1016/B978-0-443-24705-7.00035-1

high dose riboflavin in certain mitochondriopathies (Penn et al., 1992; Scholte et al., 1995). Its encouraging high 50%-responder rate of 80% led to the investigator-initiated, pivotal RCT (Schoenen et al., 1998) showing that 53% of episodic migraine patients treated for 3 months with riboflavin 400 mg qd had a ≥50% decrease in monthly migraine days compared to 15% of those receiving placebo, i.e., a number-needed-to treat of 3. Adverse events occurred in two patients treated with riboflavin (diarrhea and polyuria), and in one patient with placebo (abdominal pain). No other placebo-controlled trial was performed in adult migraine patients, most likely because of the lack of commercial interest from the pharma industry Table 35.1.

Only one randomized, single-blinded study comparing riboflavin 400 mg/day and sodium valproate 500 mg/day is available (Rahimdel et al., 2015). No significant difference in efficacy was found between the two drugs, but adverse effects were much more frequent with valproate. Four open-label studies confirmed riboflavin's effectiveness in the prevention of adult episodic migraine prevention, and in two of them, it was not inferior to a beta-blocker (Boehnke et al., 2004; Nambiar et al., 2011; Sándor et al., 2000).

By contrast, five randomized, double-blinded, placebo-controlled trials were performed in childhood and adolescence migraine, in addition to three retrospective surveys Table 35.1, the superior safety and tolerability profile of riboflavin over classical preventives being an incentive for its use in these younger patients with migraine. Two out of the 5 RCT found that riboflavin (200 or 400 mg/day) was significantly superior to placebo with a 50% responder rate up to 80% (Athaillah et al., 2012; Talebian et al., 2018). In the three other RCT there was no significant difference in outcome between riboflavin and placebo. In 2 trials, however, a low dose of 50 mg/day was used, and many included children who had headaches phenotypically resembling tension-type headache that decreased in frequency after riboflavin (Bruijn et al., 2010; Nambiar et al., 2011). The third trial used a medium dose of 200 mg/day and found an unprecedented placebo response of 67%, compared to 44% for riboflavin (MacLennan et al., 2008).

In a pharmacogenetic study assessing mitochondrial DNA haplogroups, responders to riboflavin therapy belonged in the majority to the nonH haplogroups. In contrast, nonresponders carried the H haplotype that is highly prevalent in Western Europe and known to provide superior OXPHOS performance (Di Lorenzo et al., 2009).

Overall, several *systematic* (Chen et al., 2022; Thompson & Saluja, 2017) *or narrative reviews* (Yamanaka et al., 2021) confirm the effectiveness of riboflavin in migraine prophylaxis. Considering that, in addition, it is well tolerated, nonteratogenic, and rather inexpensive, it can be considered as first-line preventive treatment in many migraine patients. Noteworthy, all published trials of riboflavin were performed in episodic migraine. The only exception is the one by Das & Qubty (2021), which comprised a majority of children or adolescents with chronic migraine and showed a ≥50% responder rate of 62%. The possible usefulness of riboflavin in chronic migraine remains therefore to be proven.

Meanwhile, the following *quality of evidence ratings* for riboflavin can be found in the guidelines for prophylaxis of migraine headache by four scientific societies: American Headache Society-American Academy of Neurology (Silberstein et al., 2012): level B (probably effective); Canadian Headache Society (Canadian Headache Society Guideline for Migraine Prophylaxis, 2012): strong recommendation, low-quality evidence; European Federation of Neurological Societies (Evers et al., 2009) level C, drug of third choice; French Headache Society (Ducros et al., 2021): moderate recommendation.

2.1.2 Riboflavin combinations

The reduction in migraine days achieved with a combination of riboflavin, magnesium 600 mg, and coenzyme Q10 150 mg did not reach statistical significance in one study (Gaul et al., 2015). Still, all secondary outcomes (i.e., pain intensity, headache impact, and patients' satisfaction) were significantly improved. For instance, patient-reported outcomes of "very good or good" were almost twice as frequent for the combination (47.3%) compared to placebo (24.6%) (Gaul et al., 2015). In another study, the effects of riboflavin combined with magnesium 300 mg and feverfew 100 mg were compared to a low dose of riboflavin (Maizels et al., 2004). A possible explanation for the poor effect of the combinations could be a decrease in riboflavin's bioavailability because of an interaction with the other components, especially with magnesium salts (Feldman & Hedrick, 1983).

2.2 Combination of B vitamins

Three double-blind, placebo-controlled, RCTs of a combination of vitamins B9 (folic acid) 1 or 2 mg/day, B6 (pyridoxine) 25 mg/day and B12 (cyanocobalamin) 400 μg/day were conducted in female migraine with aura patients by the same Australian group. Interestingly, the two trials of a combination containing 2 mg of B9 found a significant decrease of attack frequency, severity and disability over placebo (Lea et al., 2009; Menon et al., 2012) as well as a decrease in blood homocysteine (Menon et al., 2012) while there was no effect when the same doses of B6 and B12 were combined with 1 mg of B9 (Menon et al., 2016). A recent RCT of a low-dose multi-vitamin B complex in children with migraine reported a significant decrease in headache frequency after 6 months (Sadeghvand et al., 2023); in this trial, however, monthly headache days decreased by only −3 days (−1 day for placebo) from an average of 14 days/month at baseline, questioning its

TABLE 35.1 Vitamins for migraine prevention.

Authors	Trial protocol	Participants	Outcome
Riboflavin (B2)			
Adults			
Schoenen et al. (1994)	Open label, uncontrolled 400 mg/day	49 migraine without aura (MO) (23 +ASA 75 mg/day)	↓ attack frequency (−5.8 days/month)
Schoenen et al. (1998)	RCT double-blind, parallel, 3 months, 400 mg/day versus placebo	52 MO, 3 migraine with aura (MA)	≥50% responders migraine days: 59% B215% placebo
Sándor et al. (2000)	Open label, comparative, 4 months, 400 mg/day versus bisoprolol 10 mg/day or metoprolol 200 mg/day	26 MO (15 B2; 11 beta-blockers)	No difference between groups:≥50% responders attack frequency: 53% B255% beta-blocker
Boehnke et al. (2004)	Open-label, 6 months 400 mg/day	17 MO, 6 MA	↓ migraine days & abortive drug intake
Di Lorenzo et al. (2009)	Open-label, 4 months, 400 mg/day	64 MO (>MA) (subanalyzed according to mtDNA haplotypes)	↓ attack frequency-1.9/month globally-2.18/month if mtDNA haplotypes nonH-1.49/month if mtDNA haplotype H
Nambiar et al. (2011)	Open-label, randomized, comparative, 3 months, 100 mg/day versus propranolol	100 MO	↓ attack frequency (−1.2 days/month) no difference between groups side effects B2 < propranolol
Rahimdel et al. (2015)	RCT single-blind, comparative, 3 months, 400 mg/day versus sodium valproate 500 mg/day	90 MO	B2 = valproate in ↓ attack frequency, duration & intensity side effects: B2 < valproate
Children and/or adolescents			
MacLennan et al. (2008)	RCT double-blind, 3 months 200 mg/day	48 MO (>MA) children	No difference with placebo. ≥50% responders attack frequency: 67% placebo 44% riboflavin
Condó et al. (2009)	Retrospective, 3, 4, 6 months, 200 or 400 mg/day	41 MO (>MA) children & adolescents	↓ attack frequency ≥50% responders attack frequency: 68.4%
Nambiar et al. (2011)	RCT double-blind, cross-over (2 × 16 weeks), 50 mg/day versus placebo	42 MO children (14 with TTH phenotype)	No difference in migraine attack frequency ↓ TTH
Bruijn et al. (2010)	RCT double-blind, cross-over, 2 × 16 weeks 50 mg/day	42 MO children	No difference with placebo ↓ TTH
Athaillah et al. (2012)	RCT double-blind, 3 months, 400 mg/day	98 MO adolescents	↓ headache frequency versus placebo (−2.7 day/month) ↓ attack duration ↓ PedMIDAS
Talebian et al. (2018)	RCT double-blind, 3 months 100 versus 200 mg versus placebo	90 MO (>MA) children	≥50% responders monthly headache frequency: 20% 100 mg 80% 200 mg 13.3% placebo
Yamanaka et al. (2021)	Retrospective, 3 months 10 or 40 mg/day	68 MO (>MA) children	≥50% responders monthly headache frequency: 36.7%. Comorbid tension-type headache in nonresponders.

Continued

TABLE 35.1 Vitamins for migraine prevention.—cont'd

Authors	Trial protocol	Participants	Outcome
Das & Qubty (2021)	Retrospective, 2–4 months, 100 mg/day (weight 20–40 kg) 200 mg/day (weight >40 kg)	25 chronic MO (1 MA), 10 episodic MO, 2 NDPH, 2 chronic PTH, children & adolescents	≥50% responders monthly headache frequency: 61.9%. ↓ headache intensity ↓ headache duration
Riboflavin combinations			
Maizels et al. (2004)	RCT, double-blind, 3 months, comparative, B2 25 mg ("placebo") versus B2 400 mg + Mg 300 mg + feverfew 100 mg	49 MO (>MA) (25 B2 25 mg; 24 combination)	No significant difference between the 2 groups. ≥50% responders monthly migraine days: 40% B2 25 mg 33% combination
Gaul et al. (2015)	RCT, double-blind, 3 months, comparative, B2 400 mg, Mg 600 mg, Q10 150 mg versus placebo	112 MO (>MA) (55 combination; 57 placebo)	No significant difference in ↓ of migraine days ↓ maximal pain/migraine day (−0.24 vs. −0.06) PROM "very good & good": 47.3% combination 24.6% placebo
Vitamin B combinations			
Lea et al. (2009)	RCT double-blind, 6 months, B9 2 mg, B6 25 mg, B12 400 μg versus placebo	52 MA	↓ attack frequency, severity & disability
Menon et al. (2012)	RCT double-blind, 6 months, B9 2 mg, B6 25 mg, B12 400 μg versus placebo	206 female MA	Improvement versus placebo↓ blood homocysteine (varying with MTHFR & MTRR polymorphisms)
Menon et al. (2016)	RCT double-blind, 6 months, B9 1 mg, B6 25 mg, B12 400 μg versus placebo	300 female MA	No significant difference between the 2 groups
Sadeghvand et al. (2023)	RCT double-blind, 6 months, low-dose complex of B1, B2, B3, B5, B6, B7, B9, B12 versus placebo	90 MO (>MA), children, high frequency (mean: 14–15 days/month) (45 B complex, 45 placebo)	↓ headache frequency: 3 days/month B complex-1 day/month placebo ↓ blood homocysteine
Vitamin D3			
Ghorbani et al. (2020)	RCT double-blind, 3 months 2000 IU (50 μ g)/day versus placebo	74 MO (38 Vit D; 36 placebo)	−2.9 headache days/month (vs. −0.14 placebo) −3.06 attacks/month (vs. −0.36 placebo) ↓ iNOS & IL-6 serum levels versus placebo
Fallah et al. (2020)	RCT single-blind, 2 months to piramate 2 mg/kg/day + 500,000 IU/week versus topiramate	57 MO (>MA) children (29 topiramate + D3; 28 topiramate)	≥50% responders monthly headache frequency: 75.9% topiramate + D360.7% topiramate
Elmala et al. (2022)	RCT double-blind, 4 months topiramate + 5000 IU/day versus topiramate	56 MA (>MO) children (28 per group)	≥50% responders monthly headache frequency: 76.13% topiramate + D353.5% topiramate

, statistically significant decrease; *B2*, riboflavin; *B9*, folic acid; *B12*, cyanocobalamine; *MA*, migraine with aura; *MO*, migraine without aura; *MTHFR*, methylenetetrahydrofolate reductase; *MTRR*, methionine synthase reductase; *NDPH*, new daily persistent headache; *PTH*, posttraumatic headache; *RCT*, randomized controlled trial; *TTH*, tension-type headache.

clinical relevance. Along the same line, a large population-based survey showed a negative correlation between migraine and dietary intake of vitamins B6 and B9 (Tian et al., 2024).

Given that migraine with aura is an independent risk factor for ischemic stroke in women (Kurth et al., 2020), which can be aggravated by the high prevalence of metabolic syndrome (Streel et al., 2017) and thrombophilic

alterations (Cavestro et al., 2021) including MTHFR polymorphism with hyperhomocysteinemia (Liampas et al., 2020; Rubino et al., 2009), adding 2 mg of folic acid to riboflavin for migraine prophylaxis could be a worthwhile, unexplored strategy.

Another B vitamin, niacin (B3) has been studied in migraine prevention without conclusive results. The finding that dietary intake of niacin was inversely associated with migraine prevalence in a large American population sample of the National Health and Nutrition Examination Survey (NHANES) (Liu et al., 2023) could be an incentive for further trials of niacin supplementation in migraine, which, however, must be tempered considering the recent finding that niacin metabolites promote vascular inflammation and contribute to cardiovascular risk (Liu et al., 2022).

2.3 Vitamin D3

Vitamin D3 (or cholecalciferol) is synthesized in the lower layers of the epidermis through a photochemical reaction with Ultraviolet B radiation. Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol), which is further hydroxylated in the kidneys to form calcitriol (1,25-dihydroxycholecalciferol), the biologically active form of vitamin D. Besides its role in bone metabolism and regulation of concentrations of calcium and phosphate, vitamin D has antiinflammatory and antioxidant properties that could be beneficial in migraine.

Three RCTs have been performed with vitamin D3 (2000 IU/day to 500,000 IU/week), one in adults against placebo (2000 IU/day) (Ghorbani et al., 2020), two others in children as an add-on treatment to topiramate (500,000 IU/week and 5000 IU/day) (Fallah et al., 2020; Kotb Elmala et al., 2022). All three trials reported a superior beneficial effect of vitamin D3 over placebo or topiramate alone respectively. The absolute gain in 50% responders for headache frequency by adding vitamin D3 to topiramate was 15.2% (NNT: 7) and 22.6% (NNT: 4). In Elmala et al.'s trial, in which the greatest effect size was observed, most children had migraine with aura.

2.4 Coenzyme Q10 (ubiquinone)

Coenzyme-Q10 is a mobile component of the electron transport chain, which transfers electrons to the respiratory complex III. It also plays a key role in several redox chemical reactions (Blanco & Blanco, 2017). When first tested as a migraine preventive agent in an open-label trial, 61.3% of patients who completed the study observed a 50% or larger reduction in the number of migraine days per month. In detail, by the end of the trial, mean monthly migraine days had decreased from 7.34 at baseline to 2.95 ($P < 0.01$) (Rozen et al., 2002). Soon after this open-label study was published, the prophylactic effects of Coenzyme-Q10 were evaluated in a double-blind, randomized, placebo-controlled, trial. In that trial, participants were allocated to receive either 300 mg/day of Coenzyme-Q in a liquid suspension or placebo. Significant reductions in the number of migraine attacks and days with nausea/vomiting were observed, and the $\geq$50% responder rate was much higher in patients receiving Coenzyme-Q (Sándor et al., 2005). More recently, another randomized controlled trial evaluating the effects of Coenzyme-Q in migraine was carried out. This study included only females, who received a higher dose (400 mg) compared to previous trials. Results showed significant benefits in attack frequency, severity, and duration, associated with better scores in patients reported outcome measures (Dahri et al., 2017). In addition, important decreases in CGRP and TNF-α blood levels were observed. Notably, Coenzyme-Q10 tolerance was excellent in all the studies mentioned above.

Coenzyme Q has also proven useful as an add-on therapy in adults (Shoeibi et al., 2017), and an open-label trial in a pediatric population showed positive results concerning attack frequency and disability (Hershey et al., 2007). Similar positive effects in children were also observed in a randomized placebo-controlled cross-over trial during weeks one-to-four, although these benefits were less important at 8 months (Slater et al., 2011).

2.5 Alpha-lipoic acid

Alpha-lipoic acid (ALA), or thioctic acid, is a cofactor of several enzymes involved in the Krebs cycle including the pyruvate dehydrogenase complex. A placebo-controlled trial dedicated to evaluating the efficacy of 600 mg of thioctic acid for migraine prevention had to be prematurely stopped due to slow recruitment (Magis et al., 2007). Although underpowered, within-group analyses showed significant improvement in attack frequency and severity in patients treated with thioctic acid for 3 months, but not in those taking placebo (Magis et al., 2007). In addition, two open-label trials, one in patients with insulin resistance (Cavestro et al., 2018) and one as an add-on therapy to topiramate (Ali et al., 2010) have shown positive results. In a recent randomized placebo-controlled trial on 92 patients suffering from episodic migraine, 300 mg ALA bid significantly decreased headache frequency, intensity and headache impact test-6 (HIT-6) compared to placebo, and also decreased serum levels of lactate and vascular cell adhesion molecule-1 (Kelishadi et al., 2022).

2.6 Magnesium

Magnesium is a mineral that plays a double role in controlling the energetic supply/demand equilibrium. Acting as a cofactor to various enzymes of both glycolytic pathways and the Krebs cycle, magnesium facilitates ATP production

and thus increases energetic supplies for neurons. In parallel, by antagonizing the NMDA receptor, it reduces neural activation which decreases energetic needs (Blanco & Blanco, 2017). Decreased magnesium levels were found in erythrocytes of patients with migraine without aura (Schoenen et al., 1991) and in posterior brain regions in migraine with aura (Boska et al., 2002).

A variety of magnesium salts and dosages have been tried for migraine prevention Table 35.2.

Three out of five double-blind RCTs reported a significant migraine frequency decrease compared to placebo (Facchinetti et al., 1991; Peikert et al., 1996) or a similar decrease compared to sodium valproate (Karimi et al., 2021). In one trial (Pfaffenrath et al., 1996) of an L-aspartate hydrochloride-trihydrate salt of magnesium, there was no significant advantage over placebo. In children suffering from high-frequency migraine there was no difference after 4 months in headache frequency decrease over time between magnesium oxide and placebo (Wang et al., 2003).

A review of preventive migraine treatment with magnesium (Teigen & Boes, 2015) came to the conclusion that "*With such limited evidence, a more advantageous alternative to magnesium supplementation, in patients willing to make lifestyle changes, may be to focus on increasing dietary magnesium intake*." This might be an appropriate suggestion, the more so that data from the National Health and Nutrition Examination Survey (NHANES) in a large American population sample, show that overall dietary magnesium intake is insufficient and inversely related to migraine (Meng et al., 2021; Slavin et al., 2021).

2.7 L-Carnitine

L-Carnitine transports fatty acids into the mitochondria, accelerating their oxidization, and thus, energy production. Currently available randomized controlled trials have shown no significant benefits for patients taking L-Carnitine alone with respect to placebo (Hagen et al., 2015), but a significantly positive effect was observed in patients taking L-Carnitine associated with Coenzyme Q (see below) (Hajihashemi et al., 2019).

It remains to be confirmed if carnitine supplementation is able to reduce migraine attacks in patients with carnitine deficiency, as suggested by one case report (Charleston et al., 2021).

2.8 Combinations

Various combinations of micronutrients have been studied for migraine prevention (see Table 35.1), but only one in a double-blind RCT. In this study, a combination of L-carnitine (500 mg/day) and coenzyme Q10 (30 mg/day) was found superior to placebo regarding clinical outcome and decrease of serum lactate levels (Hajihashemi et al., 2019).

3. Substrate-based treatments

3.1 Diets

As mentioned before, a number of dietary factors could be associated with migraine occurrence and/or its aggravation. For instance, low dietary intake of zinc (Zheng et al., 2023), iron (and low ferritin levels) (Meng et al., 2021) and potassium (Xu et al., 2023) were found to be associated with migraine prevalence in large population-based studies. It must be considered, nonetheless, that in these studies the diagnosis of migraine was simply based on the response to one question: "During the past 3 months, did you have severe headaches or migraines". Similarly, high dietary intake of sodium (Amer et al., 2014) or high oxidative score (Liu et al., 2024) and inflammatory potential of diet (Liu et al., 2023) were more frequently found in people with migraine. It remains to be proven whether dietary interventions targeting these various aspects are effective in migraine prophylaxis.

The only diet for which there is convincing evidence for an effect in migraine prevention is the **ketogenic diet** (KD). The ketogenic diet, or modified Atkin's diet, is a high fat, high protein, very low carbohydrate diet, capable of inducing ketosis, which is the increase in blood of acetoacetate, beta-hydroxybutyrate, and acetone (known as ketone bodies). These substances can be used as sources of energy in the central nervous system, particularly upon neuronal activation (Bélanger et al., 2011). In addition, ketone bodies seem to reduce cerebral reactivity (Barbanti et al., 2017; Boison, 2017), making their potential positive effects on restoration of the energy supply and demand mismatch twofold.

Several case reports, case series, open label studies and three RCTs have shown the benefits of KD on migraine prevention Table 35.3.

In the review of studies published up to 2020 by (Caminha et al., 2022), 567 migraine patients (86% females) received either classical KD, modified Atkin's diet, very low calorie ketogenic (VLCKD) or nonketogenic diet (VLCD) or low glycemic index diet (LGID). Altogether, 9 out of 10 publications demonstrated a total or partial reduction in migraine attacks per month as a result of treatment with the KD. Overall, 96% of patients had a significant decrease in migraine frequency, severity and use of rescue medication with a follow-up of 1−36 months. Adverse effects comprised GI disturbances, muscle cramps, fatigue and increased blood cholesterol levels. Since 2021, six additional trials have been published Table 35.2. Among them the only randomized controlled, cross-over trial comparing 3:1 KD and an "antiheadache dietary pattern" (based on evidence for common dietary-related migraine triggers) found no difference between the two interventions (Haslam et al., 2021). All of the remaining five studies reported a significant benefit with up to 60% of

TABLE 35.2 Other nutraceuticals for migraine prevention.

Authors	Trial protocol	Participants	Outcome
Coenzyme Q10 (CoQ10)			
Rozen et al. (2002)	Open-label, 3 months, 150 mg/day	32 M	Reduced attack frequency
Sándor et al. (2005)	RCT, double-blind, 3 months, 3 × 100 mg/day versus placebo	42 MO	Reduced attack frequency, headache days & days-with-nausea
Hershey et al. (2007)	Open-label, 3 months, 1–3 mg/kg/day	252 paediatric/adolescent MO with frequent headaches & low CoQ10 blood levels	Reduced attack frequency & disability
Slater et al. (2011)	RCT double-blind, 2 × 112 days, crossover, 100 mg/day versus placebo	120 paediatric/adolescent MO with frequent headaches	No signif. difference between Q10 and placebo after 32 weeks, (but signif. reduced from baseline for Q10 at week 4)
Shoeibi et al. (2017)	Open-label, parallel, add-on, 100 mg/day	73 MO, 3 MA	Reduced attack frequency & severity
Dahri et al. (2017)	RCT double-blind, 3 months, 400 mg/day versus placebo	38 MO, 7 MA	Reduced migraine attack frequency, severity & duration reduced blood CGRP & TNF-α
Alpha-lipoic acid (ALA)			
Magis et al. (2007)	RCT double-blind, 3 months, 600 mg/day versus placebo	43 MO, 11 MA	Reduced attack frequency, migraine days & severity No signif. difference for 50% responder rate
Ali et al. (2010)	Open-label, 1 month, comparative: ALA 300 mg/day, topiramate 50 mg/day or both	40 MO (16–20 yo)	Reduced migraine days in ALA & topiramate groups, but not in either alone
Cavestro et al. (2018)	Open-label, 6 months, uncontrolled, 400 mg b.i.d. as add-on	26 MO, 6 MA patients with insulin resistance	Reduced migraine days & abortive migraine medication ≥50% responders attack frequency: 69% at 6 months
Magnesium (Mg)			
Facchinetti et al. (1991)	RCT double-blind, 2 months, 360 mg/day (Mg pyrrolidone carboxylic acid) versus placebo	20 menstrual migraine	Reduced number of headache days & pain ratings reduced premenstrual complaints
Peikert et al. (1996)	RCT double-blind, 3 months 600 mg/day (triMg dicitrate) versus placebo	81 MO (>MA) (43 Mg; 38 plac.)	≥50% responders attack frequency: 52.8% Mg; 34.4% plac (NS) reduced migraine days: 52.3% Mg; 19.5% plac (signif.)
Pfaffenrath et al. (1996)	RCT double-blind, 3 months 486 mg/day (Mg-L-aspartate-hydrochloride-trihydrate) versus placebo	69 MO (35 Mg; 34 plac.)	Monthly migraine days: migraine duration or intensity: no difference versus placebo.
Wang et al. (2003)	RCT double-blind, 4 months 84.5 mg/day Mg oxide	86 MO (high frequency) children (42 Mg; 44 plac.)	No significant difference in headache frequency decrease over time between groups.
Köseoglu et al. (2008)	RCT double blind, 3 months 600 mg/day Mg citrate versus placebo	30 MO 10 plac.	Reduced migraine attack frequency & severity reduced VEP P1 amplitude

Continued

TABLE 35.2 Other nutraceuticals for migraine prevention.—cont'd

Authors	Trial protocol	Participants	Outcome
Karimi et al. (2021)	RCT double-blind, cross-over, 2 months, 500 mg Mg oxide versus 800 mg Na valproate/day	63 MO	Similar significantly reduced migraine attack frequency, days, duration, severity & impact on quality of life
Omega-3			
Tseng et al. (2024)	Network meta-analysis of 5 trials (compared to classical preventives)	Total number of patients: 334. EPA/DHA: between 180/120 mg and 1200/720 mg	3 negative trials 2 positive trials
Wang et al. (2024)	RCT double-blind, 3 months, EPA 1.8 g/day (fish oil) versus placebo (soybean oil)	70 MO (+MA) (35 EPA, 35 plac.)	Reduced migraine days/month (EPA: −4.4; plac.: −0.6) reduced MIDAS
L-carnitine			
Hagen et al. (2015)	RCT triple-blind, 3 months cross-over, acetyl-L-carnitine 3 g/day versus placebo	49 MO, 8 MA, 15 MO + MA	No sign. difference with placebo
Combinations			
Tarighat Esfanjani et al. (2012)	Open-label, comparative, parallel groups, 3 months, L-carnitine 500 mg/day or Mg oxide 500 mg/day or both as add-onto routine preventives	133 MO (33 Mg, 35 carnit, 30 Mg + carnit, 35 none)	Reduced migraine attacks & days in all groups, but more so for Mg oxide
Guilbot et al. (2017)	Open-label, observational, 100 mg Feverfew+100 mg Coenzyme Q10 + 112,5 mg Mg/day	68 MO	≥50% responders migraine days/month: 75%reduced anxiety, depression improved quality of life
Hajihashemi et al. (2019)	RCT double-blind, 2 months, L-carnitine 500 mg/day + CoQ10 30 mg/day versus placebo	56 MO	Reduced headache severity, frequency and duration reduced serum lactate levels

CGRP, calcitonin-gene related peptide; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *M*, migraine (not otherwise specified); *MA*, migraine with aura; *MIDAS*, Migraine Disability Assessment Scale; *MO*, migraine without aura; *plac.*, placebo; *TNF-α*, tumor necrosis factor alpha; *VEP*, visual evoked potentials.

patients with ≥50% decrease in monthly headache frequency, even in those suffering from refractory chronic migraine. The clinical benefit seems to be similar for normo caloric KD and low or very low-calorie KD, and not related to weight loss. The effect of LGID was equivocal: clearly inferior to KD in one study (Lovati et al., 2022), equal to KD in another (Tereshko, Dal Bello, Di Lorenzo, Pez, et al., 2023).

The available data suggest that ketogenic diets effectively reduce migraine frequency and disability even in the most disabled migraine patients. Given the variety of dietary protocols studied, it is not clear which is the most effective, what is the optimal lipid/carbohydrate and protein ratio that should be sought, or whether it should be tailored individually to each patient. Adverse effects of KD are nonserious, but long-term adherence to the treatment is problematic in clinical practice. A multidisciplinary team seems necessary for its implementation.

In order to increase ketone bodies concentrations in the blood and brain, an alternative to the ketogenic diet is exogenous ketones supplementation. This alternative entails a high interest because a strict ketogenic diet might be hard to follow, but it is hampered by patients' tolerance. Unfortunately, results of a recent trial showed no clinical amelioration with respect to placebo for patients receiving DL-beta-hydroxybutyrate at an acceptably well tolerated dose (Putananickal et al., 2022). However, a subanalysis of this trial showed that a subgroup of patients with increased blood metabolic and inflammatory markers responded to the treatment (Gross et al., 2023). Therefore, further studies evaluating higher doses are needed.

3.2 Omega-3

The Omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may have

TABLE 35.3 Ketogenesis (diets & beta-hydroxybutyrate) for migraine prevention.

Authors	Trial protocol	Participants	Outcome
Ketogenic diets-systematic review 1928–2019			
Caminha et al. (2022)	10 studies: RCT (2); case control studies (2); cohort study (1); case reports (5) follow-up: 1–36 months diets: KD, VLCKD, VLCD, LGID, modified Atkins	567 individuals (86% females) MO (>MA)	Reduced migraine frequency/duration/severity in 96% (n = 544) reduced BMI in 13% (n = 71) adverse effects: GI disturbances, muscle cramps, fatigue or not reported. GRADE evidence: very low to moderate (1 RCT)
Ketogenic diets-recent studies			
Bongiovanni et al. (2021)	Open-label, prospective, 3 months: normo-caloric KD/LCKD/VLCKD depending on BMI	23 refractory CM	Reduced hours/day with migraine reduced monthly migraine days reduced headache intensity
Haslam et al. (2021)	Randomized, controlled, crossover, 3 months (4- week intervention separated by 4 week-washout): 3:1 KD versus "antiheadache" dietary pattern	16 MO (low frequency)	No difference between interventions in migraine frequency, duration or severity.
Valente et al. (2022)	Retrospective, 3 months: 2:1 KD	23 (15 MO, 8 MA, 10 CM) individualized KD	≥50% responders headache days: 65.2% efficacy not related to weight loss
Lovati et al. (2022)	Open-label, prospective, 2 months: 2:1 KD or LGID	53 refractory CM.Study 1: 13 KD, 8 LGID study 2: 26 KD, 6 LGID	Study 1: headache frequency: KD −6.8 day/month; LGID −1.4 day/month (effect proportional to ketonuria) study 2: ≥50% responders: 57.7% KD, 16.6% LGID
(Tereshko, Dal Bello, Di Lorenzo, Pez, et al., 2023)	Open-label, prospective, 3 months: 2.1 KD if BMI <24.9 or LGID if BMI 25–29.9 or VLCKD if BMI >25	76 MO (45 CM, 31 HFEM)	Reduced attack frequency, duration and disability after all 3 diets reduced fatigue
Tereshko, Dal Bello, Di Lorenzo, Pittino, et al. (2023)	Retrospective, 3 months: 2:1 KG if BMI <25 or LGID if BMI ≥25	60 MO (33 CM, 27 HFEM) 39 LGID 21 2:1 KD	Reduced attack frequency, duration and disability in all groups ≥50% responders migraine days: 67% after LGID or KD.
Exogenous ketones			
Putananickal et al. (2022)	Randomized, controlled, crossover, 9 months (1 month baseline, 3 months 9 g Ca-Mg-HB or placebo, 1 month wash-out, 1 month baseline, 3 months placebo or 9 g Ca-Mg-HB	41 MO (HFEM) 40 ITT; 32 PP	No difference between Ca-Mg-HB (−1.7 migraine days/month) and placebo (−1.3 migraine days/month)
Gross et al. (2023)	Posthoc analysis of Putananickal et al.	32 MO PP	9 "responders" (−5.78 migraine days/month compared to placebo) metabolic markers (higher hs-CRP & Hb1Ac, lower Pi) predict response and tend to normalize after HB.

2:1 KD, ketogenic diet with fats two × carbs + proteins; *BMI*, body mass index; *CM*, chronic migraine; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *HB*, beta-hydroxybutyrate; *HbA1c*, glycated hemoglobin; *HFEM*, high frequency episodic migraine; *hs-CRP*, high-sensitivity C-reactive protein; *ITT*, intention-to-treat analysis; *LGID*, low glycemic index diet; *MO*, migraine without aura; *PP*, per protocol analysis; *RCT*, randomized controlled trial; *VLCKD*, very low-calorie KD; *VLCnKD*, very low-calorie nonketogenic diet.

TABLE 35.4 Comparative efficacy/adverse effect profiles of preventive treatments for episodic migraine.

Drugs	Number-needed-to treat (50% responders)	Number-needed-to-harm
Anticonvulsants		
Propranolol (160 mg/day) (Diener et al., 2004)	5	11
Topiramate (100 mg/g) (Diener et al., 2004)	7	7
Valproate (Shamliyan et al., 2013)	4	7
Metabolic treatments		
Riboflavin (Schoenen et al., 1998)	3	33
Coenzyme Q10 (Sándor et al., 2000)	3	21
Thioctic acid (Magis et al., 2007)	33	∞
Ketogenic diet (Di Lorenzo et al., 2019)	1.5	? 5 (drop-outs)
Anti CGRP therapies		
Atogepant (60 mg/day) (Ashina et al., 2023)	3.1	17 (constipation)
Rimegepant (75 mg/2 day) (Croop et al., 2021)	13	∞
Eptinezumab (100 mg/12 weeks) (Ashina et al., 2020)	8	8251
Erenumab (140 mg/4 weeks) (Goadsby, Reuter, et al., 2017)	5	319 (constipation)
Fremanezumab (225 mg/mth) (Dodick et al., 2018)	5	5665
Galcanezumab (120 mg/month) (Stauffer et al., 2018)	5	233

antiinflammatory, antinociceptive and vasodilatory actions, which could be beneficial in migraine. The evidence for a prophylactic effect of EPA/DHA is scarce and contradictory. In a recent meta-analysis of five trials (Tseng et al., 2024), three showed no benefit over placebo, while two did so Table 35.1. The doses used were, however, highly variable, ranging between 180/120 mg and 1200/720 mg. In the RCT with the largest number of participants (n = 196) and a very high dose (EPA/DHA 1080/720 mg) there was no significant difference compared with placebo (Pradalier et al., 2001).

4. Conclusions

Numerous metabolic-based approaches for the management of migraine are available. They were introduced based on findings from basic research studies investigating migraine pathophysiology. Numbers of patients necessary to treat to see a significant effect (NNT) is similar or lower as compared to the anticonvulsants effective for migraine prevention, or even some of the newer drugs blocking CGRP neurotransmission, although it must be admitted that the effect size of the metabolic treatments may be lower. On the other hand, numbers of patients necessary to treat before seeing an adverse effect (NNH) are clearly greater for metabolic treatments, and antiCGRP therapies, than for the anticonvulsants, underscoring their excellent tolerability Table 35.4.

The Nutraceuticals are evidence-supported migraine preventives and characterized by an excellent efficacy/adverse effect profile. They are thus a worthy treatment option, which, in contrast to the new treatments targeting migraine-pain transmission molecules, act at the root of migraine pathophysiology and are inexpensive. In contrast to traditional preventives, nutraceuticals are much better tolerated. All these aspects considered, nutraceuticals, in particular vitamins B2 and B9, can be offered as first line preventive treatment in migraine patients with low or moderate disability not willing to start on drugs with potential side effects, contraindications or high costs, in females without contraception or planning pregnancy, in pregnant patients, if preventive treatment is necessary, and in childhood migraine. Because of their favorable adverse effect profile, they can also be associated with other preventive treatments, but evidence for their usefulness as add-on therapy is scarce. Based on current evidence, among the metabolic treatments only ketogenic diet can be recommended for the prophylaxis of high-frequency and chronic migraine, as controlled trials of nutraceuticals in these highly disabled migraineurs are still lacking.

References

Canadian headache society guideline for migraine prophylaxis. *The Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques, 39*(S2), (2012), 63. https://doi.org/10.1017/s0317167100015109

Ali, A. M., Awad, T. G., & Al-Adl, N. M. (2010). Efficacy of combined topiramate/thioctic acid therapy in migraine prophylaxis. *Saudi Pharmaceutical Journal, 18*(4), 239−243. https://doi.org/10.1016/j.jsps.2010.07.006

Amer, M., Woodward, M., & Appel, L. J. (2014). Effects of dietary sodium and the DASH diet on the occurrence of headaches: Results from randomised multicentre DASH-Sodium clinical trial. *BMJ Open, 4*(12). https://doi.org/10.1136/bmjopen-2014-006671

Aronson, J. K. (2017). Defining 'nutraceuticals': Neither nutritious nor pharmaceutical. *British Journal of Clinical Pharmacology, 83*(1), 8−19. https://doi.org/10.1111/bcp.12935

Ashina, M., Tepper, S. J., Reuter, U., Blumenfeld, A. M., Hutchinson, S., Xia, J., Miceli, R., Severt, L., Finnegan, M., & Trugman, J. M. (2023). Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. *Headache: The Journal of Head and Face Pain, 63*(1), 79−88. https://doi.org/10.1111/head.14439

Ashina, M., Saper, J., Cady, R., Schaeffler, B. A., Biondi, D. M., Hirman, J., Pederson, S., Allan, B., & Smith, J. (2020). Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia, 40*(3), 241−254. https://doi.org/10.1177/0333102420905132

Athaillah, A., Dimyati, Y., Saing, J. H., Saing, B., Hakimi, H., & Lelo, A. (2012). Riboflavin as migraine prophylaxis in adolescents. *Paediatrica Indonesiana, 52*(3). https://doi.org/10.14238/pi52.3.2012.132-7

Bélanger, M., Allaman, I., & Magistretti, P. J. (2011). Brain energy metabolism: Focus on astrocyte-neuron metabolic cooperation. *Cell Metabolism, 14*(6), 724−738. https://doi.org/10.1016/j.cmet.2011.08.016

Barbanti, P., Fofi, L., Aurilia, C., Egeo, G., & Caprio, M. (2017). Ketogenic diet in migraine: Rationale, findings and perspectives. *Neurological Sciences, 38*(S1), 111−115. https://doi.org/10.1007/s10072-017-2889-6

Barbiroli, B., Montagna, P., Cortelli, P., Funicello, R., Iotti, S., Monari, L., Pierangeli, G., Zaniol, P., & Lugaresi, E. (1992). Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura. *Neurology, 42*(6), 1209−1214. https://doi.org/10.1212/wnl.42.6.1209

Blanco, A., & Blanco, G. (2017). *Medical biochemistry* (pp. 1−805). Argentina: Elsevier Inc.. https://www.sciencedirect.com/science/book/9780128035504.

Boehnke, C., Reuter, U., Flach, U., Schuh-Hofer, S., Einhäupl, K. M., & Arnold, G. (2004). High-dose riboflavin treatment is efficacious in migraine prophylaxis: An open study in a tertiary care centre. *European Journal of Neurology, 11*(7), 475−477. https://doi.org/10.1111/j.1468-1331.2004.00813.x

Boison, D. (2017). New insights into the mechanisms of the ketogenic diet. *Current Opinion in Neurology, 30*(2), 187−192. https://doi.org/10.1097/wco.0000000000000432

Bongiovanni, D., Benedetto, C., Corvisieri, S., Del Favero, C., Orlandi, F., Allais, G., Sinigaglia, S., & Fadda, M. (2021). Effectiveness of ketogenic diet in treatment of patients with refractory chronic migraine. *Neurological Sciences, 42*(9), 3865−3870. https://doi.org/10.1007/s10072-021-05078-5

Boska, M. D., Welch, K. M. A., Barker, P. B., Nelson, J. A., & Schultz, L. (2002). Contrasts in cortical magnesium, phospholipid and energy metabolism between migraine syndromes. *Neurology, 58*(8), 1227−1233. https://doi.org/10.1212/WNL.58.8.1227

Bruijn, J., Duivenvoorden, H., Passchier, J., Locher, H., Dijkstra, N., & Arts, W. F. (2010). Medium-dose riboflavin as a prophylactic agent in children with migraine: A preliminary placebo-controlled, randomised, double-blind, cross-over trial. *Cephalalgia, 30*(12), 1426−1434. https://doi.org/10.1177/0333102410365106

Caminha, M. C., Moreira, A. B., Matheus, F. C., Rieger, D. K., Moreira, J. D., Dalmarco, E. M., Demarchi, I. G., & Lin, K. (2022). Efficacy and tolerability of the ketogenic diet and its variations for preventing migraine in adolescents and adults: A systematic review. *Nutrition Reviews, 80*(6), 1634−1647. https://doi.org/10.1093/nutrit/nuab080

Cavestro, C., Bedogni, G., Molinari, F., Mandrino, S., Rota, E., & Frigeri, M. C. (2018). Alpha-lipoic acid shows promise to improve migraine in patients with insulin resistance: A 6-month exploratory study. *Journal of Medicinal Food, 21*(3), 269−273. https://doi.org/10.1089/jmf.2017.0068

Cavestro, C., Degan, D., Micca, G., Aloi, R., Mandrino, S., Frigeri, M. C., Pistoia, F., Molinari, F., & Sacco, S. (2021). Thrombophilic alterations, migraine, and vascular disease: Results from a case-control study. *Neurological Sciences, 42*(9), 3821−3828. https://doi.org/10.1007/s10072-020-05006-z

Charleston, L., Khalil, S., & Young, W. B. (2021). Carnitine responsive migraine headache syndrome: Case report and review of the literature. *Current Pain and Headache Reports, 25*(4). https://doi.org/10.1007/s11916-021-00936-5

Chen, Y. S., Lee, H. F., Tsai, C. H., Hsu, Y. Y., Fang, C. J., Chen, C. J., Hung, Y. H., & Hu, F. W. (2022). Effect of vitamin B2 supplementation on migraine prophylaxis: A systematic review and meta-analysis. *Nutritional Neuroscience, 25*(9), 1801−1812. https://doi.org/10.1080/1028415X.2021.1904542

Condó, M., Posar, A., Arbizzani, A., & Parmeggiani, A. (2009). Riboflavin prophylaxis in pediatric and adolescent migraine. *The Journal of Headache and Pain, 10*(5), 361−365. https://doi.org/10.1007/s10194-009-0142-2

Croop, R., Lipton, R. B., Kudrow, D., Stock, D. A., Kamen, L., Conway, C. M., Stock, E. G., Coric, V., & Goadsby, P. J. (2021). Oral rimegepant for preventive treatment of migraine: A phase 2/3, randomised, double-blind, placebo-controlled trial. *The Lancet, 397*(10268), 51−60. https://doi.org/10.1016/S0140-6736(20)32544-7

Dahri, M., Hashemilar, M., Asghari-Jafarabadi, M., & Tarighat-Esfanjani, A. (2017). Efficacy of coenzyme Q10 for the prevention of migraine in women: A randomized, double-blind, placebo-controlled study. *European Journal of Integrative Medicine, 16*, 8−14. https://doi.org/10.1016/j.eujim.2017.10.003

Das, R., & Qubty, W. (2021). Retrospective observational study on riboflavin prophylaxis in child and adolescent migraine. *Pediatric Neurology, 114*, 5−8. https://doi.org/10.1016/j.pediatrneurol.2020.09.009

de Tommaso, M., Ambrosini, A., Brighina, F., Coppola, G., Perrotta, A., Pierelli, F., Sandrini, G., Valeriani, M., Marinazzo, D., Stramaglia, S., & Schoenen, J. (2014). Altered processing of sensory stimuli in patients with migraine. *Nature Reviews Neurology, 10*(3), 144−155. https://doi.org/10.1038/nrneurol.2014.14

Del Moro, L., Rota, E., Pirovano, E., & Rainero, I. (2022). Migraine, brain glucose metabolism and the "neuroenergetic" hypothesis: A scoping review. *The Journal of Pain, 23*(8), 1294–1317. https://doi.org/10.1016/j.jpain.2022.02.006

Di Lorenzo, C., Pinto, A., Ienca, R., Coppola, G., Sirianni, G., Di Lorenzo, G., Parisi, V., Serrao, M., Spagnoli, A., Vestri, A., Schoenen, J., Donini, L. M., & Pierelli, F. (2019). A randomized double-blind, cross-over trial of very low-calorie diet in overweight migraine patients: A possible role for ketones? *Nutrients, 11*(8). https://doi.org/10.3390/nu11081742

Di Lorenzo, C., Pierelli, F., Coppola, G., Grieco, G. S., Rengo, C., Ciccolella, M., Magis, D., Bolla, M., Casali, C., Santorelli, F. M., & Schoenen, J. (2009). Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. *Neurology, 72*(18), 1588–1594. https://doi.org/10.1212/WNL.0b013e3181a41269

Diener, H. C., Tfelt-Hansen, P., Dahlöf, C., Láinez, M. J. A., Sandrini, G., Wang, S. J., Neto, W., Vijapurkar, U., Doyle, A., & Jacobs, D. (2004). Topiramate in migraine prophylaxis: Results from a placebo-controlled trial with propranolol as an active control. *Journal of Neurology, 251*(8), 943–950.

Diener, H., Scholz, E., Dichgans, J., Gerber, W., Jäck, A., Bille, A., & Niederberger, U. (1989). Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials. *Annals of Neurology, 25*(2), 125–130. https://doi.org/10.1002/ana.410250204

Dodick, D. W., Silberstein, S. D., Bigal, M. E., Yeung, P. P., Goadsby, P. J., Blankenbiller, T., Grozinski-Wolff, M., Yang, R., Ma, Y., & Aycardi, E. (2018). Effect of Fremanezumab compared with placebo for prevention of episodic migraine a randomized clinical trial. *JAMA, the Journal of the American Medical Association, 319*(19), 1999–2008. https://doi.org/10.1001/jama.2018.4853

Ducros, A., de Gaalon, S., Roos, C., Donnet, A., Giraud, P., Guégan-Massardier, E., Lantéri-Minet, M., Lucas, C., Mawet, J., Moisset, X., Valade, D., & Demarquay, G. (2021). Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment. *Revue Neurologique, 177*(7), 734–752. https://doi.org/10.1016/j.neurol.2021.07.006

Elmala, K., Suliman, Al-Shokary, H. A., Ibrahim, A. H., Kamal, A. O., Elshorbagy, N. M., Nasef, K. A., & El Din Fathallah, M. G. (2022). The impact of vitamin D3 supplementation to topiramate therapy on pediatric migraine prophylaxis. *Journal of Child Neurology, 37*(10–11). https://doi.org/10.1177/08830738221092882

Evers, S., Áfra, J., Frese, A., Goadsby, P. J., Linde, M., May, A., & Sándor, P. S. (2009). EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. *European Journal of Neurology, 16*(9), 968–981. https://doi.org/10.1111/j.1468-1331.2009.02748.x

Facchinetti, F., Sances, G., Borella, P., Genazzani, A. R., & Nappi, G. (1991). Magnesium prophylaxis of menstrual migraine: Effects on intracellular magnesium. *Headache: The Journal of Head and Face Pain, 31*(5), 298–301. https://doi.org/10.1111/j.1526-4610.1991.hed3105298.x

Fallah, R., Sarraf Yazd, S., & Sohrevardi, S. M. (2020). Efficacy of topiramate alone and topiramate plus vitamin D3 in the prophylaxis of pediatric migraine: A randomized clinical trial. *Iranian Journal of Child Neurology, 14*(4), 77–86. https://doi.org/10.22037/ijcn.v15i1.18017

Feldman, S., & Hedrick, W. (1983). Antacid effects on the gastrointestinal absorption of riboflavin. *Journal of Pharmaceutical Sciences, 72*(2), 121–123. https://doi.org/10.1002/jps.2600720206

Ferrari, M. D., Goadsby, P. J., Burstein, R., Kurth, T., Ayata, C., Charles, A., Ashina, M., van den Maagdenberg, A. M. J. M., & Dodick, D. W. (2022). Migraine. *Nature Reviews Disease Primers, 8*(1). https://doi.org/10.1038/s41572-021-00328-4

Gantenbein, A. R., Sandor, P. S., Fritschy, J., Turner, R., Goadsby, P. J., & Kaube, H. (2013). Sensory information processing may be neuro-energetically more demanding in migraine patients. *NeuroReport, 24*(4), 202–205. https://doi.org/10.1097/WNR.0b013e32835eba81

Gaul, C., Diener, H. C., & Danesch, U. (2015). Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: A randomized, placebo-controlled, double-blind, multicenter trial. *The Journal of Headache and Pain, 16*(1). https://doi.org/10.1186/s10194-015-0516-6

Ghorbani, Z., Togha, M., Rafiee, P., Ahmadi, Z. S., Rasekh Magham, R., Djalali, M., Shahemi, S., Martami, F., Zareei, M., Razeghi Jahromi, S., Ariyanfar, S., & Mahmoudi, M. (2020). Vitamin D3 might improve headache characteristics and protect against inflammation in migraine: A randomized clinical trial. *Neurological Sciences, 41*(5), 1183–1192. https://doi.org/10.1007/s10072-019-04220-8

Goadsby, P. J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J. H., Zhang, F., Sapra, S., Picard, H., Mikol, D. D., & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. *New England Journal of Medicine, 377*(22), 2123–2132. https://doi.org/10.1056/NEJMoa1705848

Goadsby, P. J., Holland, P. R., Martins-Oliveira, M., Hoffmann, J., Schankin, C., & Akerman, S. (2017). Pathophysiology of migraine: A disorder of sensory processing. *Physiological Reviews, 97*(2), 553–622. https://doi.org/10.1152/physrev.00034.2015

Gross, E. C., Lisicki, M., Fischer, D., Sándor, P. S., & Schoenen, J. (2019). The metabolic face of migraine — from pathophysiology to treatment. *Nature Reviews Neurology, 15*(11), 627–643. https://doi.org/10.1038/s41582-019-0255-4

Gross, E. C., Putananickal, N., Orsini, A. L., Schoenen, J., Fischer, D., & Soto-Mota, A. (2023). Defining metabolic migraine with a distinct subgroup of patients with suboptimal inflammatory and metabolic markers. *Scientific Reports, 13*(1). https://doi.org/10.1038/s41598-023-28499-y

Guilbot, A., Bangratz, M., Ait Abdellah, S., & Lucas, C. (2017). A combination of coenzyme Q10, feverfew and magnesium for migraine prophylaxis: A prospective observational study. *BMC Complementary and Alternative Medicine, 17*(1). https://doi.org/10.1186/s12906-017-1933-7

Hagen, K., Brenner, E., Linde, M., Gravdahl, G. B., Tronvik, E. A., Engstrøm, M., Sonnewald, U., Helde, G., Stovner, L. J., & Sand, T. (2015). Acetyl-l-carnitine versus placebo for migraine prophylaxis: A randomized, triple-blind, crossover study. *Cephalalgia, 35*(11), 987–995. https://doi.org/10.1177/0333102414566817

Hajihashemi, P., Askari, G., Khorvash, F., Reza Maracy, M., & Nourian, M. (2019). The effects of concurrent coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial. *Cephalalgia, 39*(5), 648–654. https://doi.org/10.1177/0333102418821661

Haslam, R. L., Bezzina, A., Herbert, J., Spratt, N., Rollo, M. E., & Collins, C. E. (2021). Can ketogenic diet therapy improve migraine frequency, severity and duration? *Healthcare (Switzerland), 9*(9). https://doi.org/10.3390/healthcare9091105

Hepp, Z., Bloudek, L. M., & Varon, S. F. (2014). Systematic review of migraine prophylaxis adherence and persistence. *Journal of Managed*

Care Pharmacy, 20(1), 22–33. https://doi.org/10.18553/jmcp.2014.20.1.22

Hershey, A. D., Powers, S. W., Vockell, A. L. B., LeCates, S. L., Ellinor, P. L., Segers, A., Burdine, D., Manning, P., & Kabbouche, M. A. (2007). Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache, 47*(1), 73–80. https://doi.org/10.1111/j.1526-4610.2007.00652.x

Köseoglu, E., Talaslioglu, A., Gönül, A. S., & Kula, M. (2008). The effects of magnesium prophylaxis in migraine without aura. *Magnesium Research, 21*(2), 101–108. https://doi.org/10.1684/mrh.2008.0132

Karimi, N., Razian, A., & Heidari, M. (2021). The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: A randomized, controlled, double-blind, crossover study. *Acta Neurologica Belgica, 121*(1), 167–173. https://doi.org/10.1007/s13760-019-01101-x

Kelishadi, M. R., Naeini, A. A., Khorvash, F., Askari, G., & Heidari, Z. (2022). The beneficial effect of Alpha-lipoic acid supplementation as a potential adjunct treatment in episodic migraines. *Scientific Reports, 12*(1). https://doi.org/10.1038/s41598-021-04397-z

Kotb Elmala, M., Suliman, H. A., Al-shokary, A. H., Ibrahim, A. O., Kamal, N. M., Elshorbagy, H. H., Nasef, K. A., & El Din Fathallah, M. G. (2022). The impact of vitamin D3 supplementation to topiramate therapy on pediatric migraine prophylaxis. *Journal of Child Neurology, 37*(10–11), 833–839. https://doi.org/10.1177/08830738221092882

Kurth, T., Rist, P. M., Ridker, P. M., Kotler, G., Bubes, V., & Buring, J. E. (2020). Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA, the Journal of the American Medical Association, 323*(22), 2281–2289. https://doi.org/10.1001/jama.2020.7172

Lea, R., Colson, N., Quinlan, S., Macmillan, J., & Griffiths, L. (2009). The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability. *Pharmacogenetics and Genomics, 19*(6), 422–428. https://doi.org/10.1097/fpc.0b013e32832af5a3

Liampas, I., Siokas, V., Mentis, A. F. A., Aloizou, A. M., Dastamani, M., Tsouris, Z., Aslanidou, P., Brotis, A., & Dardiotis, E. (2020). Serum homocysteine, pyridoxine, folate, and vitamin B12 levels in migraine: Systematic review and meta-analysis. *Headache, 60*(8), 1508–1534. https://doi.org/10.1111/head.13892

Liu, H., Wang, D., Wu, F., Dong, Z., & Yu, S. (2023). Association between inflammatory potential of diet and self-reported severe headache or migraine: A cross-sectional study of the National Health and Nutrition Examination Survey. *Nutrition, 113*. https://doi.org/10.1016/j.nut.2023.112098

Liu, H., Wang, L., Chen, C., Dong, Z., & Yu, S. (2022). Association between dietary niacin intake and migraine among American adults: National Health and Nutrition Examination Survey. *Nutrients, 14*(15). https://doi.org/10.3390/nu14153052

Liu, X., Liu, R., Liu, W., Hua, R., & Xu, H. (2024). Association between oxidative balance score and self-reported severe headache or migraine based on NHANES 1999 to 2004 data: A cross-sectional study. *Heliyon, 10*(6). https://doi.org/10.1016/j.heliyon.2024.e27426

Lovati, C., d'Alessandro, C. M., Ventura, S. D., Muzio, F., & Pantoni, L. (2022). Ketogenic diet in refractory migraine: Possible efficacy and role of ketone bodies—a pilot experience. *Neurological Sciences, 43*(11), 6479–6485. https://doi.org/10.1007/s10072-022-06311-5

MacLennan, S. C., Wade, F. M., Forrest, K. M. L., Ratanayake, P. D., Fagan, E., & Antony, J. (2008). High-dose ribof lavin for migraine prophylaxis in children: A double-blind, randomized, placebo-controlled trial. *Journal of Child Neurology, 23*(11), 1300–1304. https://doi.org/10.1177/0883073808318053

Magis, D., Ambrosini, A., Sándor, P., Jacquy, J., Laloux, P., & Schoenen, J. (2007). A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis. *Headache, 47*(1), 52–57. https://doi.org/10.1111/j.1526-4610.2006.00626.x

Maizels, M., Blumenfeld, A., & Burchette, R. (2004). A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: A randomized trial. *Headache, 44*(9), 885–890. https://doi.org/10.1111/j.1526-4610.2004.04170.x

Meng, S. H., Zhou, H. B., Li, X., Wang, M. X., Kang, L. X., Fu, J. M., Li, X., Li, X. T., & Zhao, Y. S. (2021). Association between dietary iron intake and serum ferritin and severe headache or migraine. *Frontiers in Nutrition, 8*. https://doi.org/10.3389/fnut.2021.685564

Menon, S., Lea, R. A., Roy, B., Hanna, M., Wee, S., Haupt, L. M., Oliver, C., & Griffiths, L. R. (2012). Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. *Pharmacogenetics and Genomics, 22*(10), 741–749. https://doi.org/10.1097/FPC.0b013e3283576b6b

Menon, S., Nasir, B., Avgan, N., Ghassabian, S., Oliver, C., Lea, R., Smith, M., & Griffiths, L. (2016). The effect of 1 mg folic acid supplementation on clinical outcomes in female migraine with aura patients. *The Journal of Headache and Pain, 17*(1). https://doi.org/10.1186/s10194-016-0652-7

Nambiar, N. J., Aiyappa, C., & Srinivasa, R. (2011). Oral riboflavin versus oral propranolol in migraine prophylaxis: An open-label randomized controlled trial. *Neurology Asia, 16*(3).

Noordhout, M.de, Timsit-Berthier, M., Timsit, M., & Schoenen, J. (1987). Effects of beta blockade on contingent negative variation in migraine. *Annals of Neurology, 21*(1), 111–112. https://doi.org/10.1002/ana.410210125

Peikert, A., Wilimzig, C., & Köhne-Volland, R. (1996). Prophylaxis of migraine with oral magnesium: Results from a prospective, multicenter, placebo-controlled and double-blind randomized study. *Cephalalgia, 16*(4), 257–263. https://doi.org/10.1046/j.1468-2982.1996.1604257.x

Penn, A. M. W., Lee, J. W. K., Thuillier, P., Wagner, M., Maclure, K. M., Menard, M. R., Hall, L. D., & Kennaway, N. G. (1992). MELAS syndrome with mitochondrial tRNA Leu[UUR] mutation: Correlation of clinical state, nerve conduction, and muscle 31P magnetic resonance spectroscopy during treatment with nicotinamide and riboflavin. *Neurology, 42*(11), 2147. https://doi.org/10.1212/WNL.42.11.2147

Pfaffenrath, V., Wessely, P., Meyer, C., Isler, H. R., Evers, S., Grotemeyer, K. H., Taneri, Z., Soyka, D., Göbel, H., & Fischer, M. (1996). Magnesium in the prophylaxis of migraine - a double-blind, placebo-controlled study. *Cephalalgia, 16*(6), 436–440. https://doi.org/10.1046/j.1468-2982.1996.1606436.x

Pradalier, A., Bakouche, P., Baudesson, G., Delage, A., Cornaille-Lafage, G., Launay, J. M., & Biason, P. (2001). Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: A double-blind study versus placebo. *Cephalalgia, 21*(8), 818–822. https://doi.org/10.1046/j.1468-2982.2001.218240.x

Putananickal, N., Gross, E. C., Orsini, A. L., Schmidt, S., Hafner, P., Gocheva, V., Nagy, S., Henzi, B. C., Rubino, D., Vogt, D. R., Cichon, S., Sandor, P., & Fischer, D. (2022). Efficacy and safety of exogenous beta-hydroxybutyrate for preventive treatment in episodic

migraine: A single-centred, randomised, placebo-controlled, double-blind crossover trial. *Cephalalgia, 42*(4−5), 302−311. https://doi.org/10.1177/03331024211043792

Rahimdel, A., Zeinali, A., Yazdian-Anari, P., Hajizadeh, R., & Arefnia, E. (2015). Effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis: A randomized clinical trial. *Electronic Physician*. https://doi.org/10.14661/1344

Rozen, T. D., Oshinsky, M. L., Gebeline, C. A., Bradley, K. C., Young, W. B., Shechter, A. L., & Silberstein, S. D. (2002). Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia, 22*(2), 137−141. https://doi.org/10.1046/j.1468-2982.2002.00335.x

Rubino, E., Ferrero, M., Rainero, I., Binello, E., Vaula, G., & Pinessi, L. (2009). Association of the C677T polymorphism in the MTHFR gene with migraine: A meta-analysis. *Cephalalgia, 29*(8), 818−825. https://doi.org/10.1111/j.1468-2982.2007.01400.x

Sándor, P. S., Áfra, J., Ambrosini, A., & Schoenen, J. (2000). Prophylactic treatment of migraine with β-blockers and riboflavin: Differential effects on the intensity dependence of auditory evoked cortical potentials. *Headache, 40*(1), 30−35. https://doi.org/10.1046/j.1526-4610.2000.00005.x

Sándor, P. S., Di Clemente, L., Coppola, G., Saenger, U., Fumal, A., Magis, D., Seidel, L., Agosti, R. M., & Schoenen, J. (2005). Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. *Neurology, 64*(4), 713−715. https://doi.org/10.1212/01.wnl.0000151975.03598.ed

Sadeghvand, S., Barzegar, M., Shiva, S., Tarmahi, V., Khodaie, H., Rahimi Khamaneh, E., Golchinfar, Z., & Raeisi, S. (2023). The effects of vitamin B-complex supplementation on serum homocysteine levels and migraine severity in children A randomized controlled trial. *Iranian Journal of Child Neurology, 17*(3), 141−153. https://doi.org/10.22037/ijcn.v17i3.40053

Schoenen, J., Lenaerts, M., & Bastings, E. (1994). High-dose riboflavin as a prophylactic treatment of migraine: Results of an open pilot study. *Cephalalgia, 14*(5), 328−329. https://doi.org/10.1046/j.1468-2982.1994.1405328.x

Schoenen, J., Sianard-Gainko, J., & Lenaerts, M. (1991). Blood magnesium levels in migraine. *Cephalalgia, 11*(2), 97−99. https://doi.org/10.1046/j.1468-2982.1991.1102097.x

Schoenen, J., Jacquy, J., & Lenaerts, M. (1998). Effectiveness of high-dose riboflavin in migraine prophylaxis A randomized controlled trial. *Neurology, 50*(2), 466−470. https://doi.org/10.1212/WNL.50.2.466

Schoenen, J., Manise, M., Nonis, R., Gérard, P., & Timmermans, G. (2020). Monoclonal antibodies blocking CGRP transmission: An update on their added value in migraine prevention. *Revue Neurologique, 176*(10), 788−803. https://doi.org/10.1016/j.neurol.2020.04.027

Scholte, H. R., Busch, H. F. M., Bakker, H. D., Bogaard, J. M., Luyt-Houwen, I. E. M., & Kuyt, L. P. (1995). Riboflavin-responsive complex I deficiency. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1271*(1), 75−83. https://doi.org/10.1016/0925-4439(95)00013-T

Shamliyan, T. A., Choi, J. Y., Ramakrishnan, R., Miller, J. B., Wang, S. Y., Taylor, F. R., & Kane, R. L. (2013). Preventive pharmacologic treatments for episodic migraine in adults. *Journal of General Internal Medicine, 28*(9), 1225−1237. https://doi.org/10.1007/s11606-013-2433-1

Shoeibi, A., Olfati, N., Soltani Sabi, M., Salehi, M., Mali, S., & Akbari Oryani, M. (2017). Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: An open-label, add-on, controlled trial. *Acta Neurologica Belgica, 117*(1), 103−109. https://doi.org/10.1007/s13760-016-0697-z

Silberstein, S. D., Holland, S., Freitag, F., Dodick, D. W., Argoff, C., & Ashman, E. (2012). Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults report of the quality standards subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology, 78*(17), 1337−1345. https://doi.org/10.1212/WNL.0b013e3182535d20

Slater, S. K., Nelson, T. D., Kabbouche, M. A., Lecates, S. L., Horn, P., Segers, A., Manning, P., Powers, S. W., & Hershey, A. D. (2011). A randomized, double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of pediatric and adolescent migraine. *Cephalalgia, 31*(8), 897−905. https://doi.org/10.1177/0333102411406755

Slavin, M., Li, H., Khatri, M., & Frankenfeld, C. (2021). Dietary magnesium and migraine in adults: A cross-sectional analysis of the National health and nutrition examination survey 2001−2004. *Headache, 61*(2), 276−286. https://doi.org/10.1111/head.14065

Stauffer, V. L., Dodick, D. W., Zhang, Q., Carter, J. N., Ailani, J., & Conley, R. R. (2018). Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurology, 75*(9), 1080−1088. https://doi.org/10.1001/jamaneurol.2018.1212

Streel, S., Donneau, A. F., Dardenne, N., Hoge, A., Albert, A., Schoenen, J., & Guillaume, M. (2017). Screening for the metabolic syndrome in subjects with migraine. *Cephalalgia, 37*(12), 1180−1188. https://doi.org/10.1177/0333102416672494

Talebian, A., Soltani, B., Banafshe, H. R., Moosavi, G. A., Talebian, M., & Soltani, S. (2018). Prophylactic effect of riboflavin on pediatric migraine: A randomized, double-blind, placebo-controlled trial. *Electronic Physician, 10*(2), 6279−6285. https://doi.org/10.19082/6279

Tarighat Esfanjani, A., Mahdavi, R., Ebrahimi Mameghani, M., Talebi, M., Nikniaz, Z., & Safaiyan, A. (2012). The effects of magnesium, l-carnitine, and concurrent magnesium−l-carnitine supplementation in migraine prophylaxis. *Biological Trace Element Research, 150*(1−3), 42−48. https://doi.org/10.1007/s12011-012-9487-5

Teigen, L., & Boes, C. J. (2015). An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. *Cephalalgia, 35*(10), 912−922. https://doi.org/10.1177/0333102414564891

Tereshko, Y., Dal Bello, S., Di Lorenzo, C., Pittino, A., Filippi, F., Belgrado, E., Lettieri, C., Merlino, G., Gigli, G. L., & Valente, M. (2023). The effect of three different ketogenic diet protocols on migraine and fatigue in chronic and high-frequency episodic migraine: A pilot study. *Nutrients, 15*(20). https://doi.org/10.3390/nu15204334

Tereshko, Y., Dal Bello, S., Di Lorenzo, C., Pez, S., Pittino, A., Sartor, R., Filippi, F., Lettieri, C., Belgrado, E., Garbo, R., Merlino, G., Gigli, G. L., & Valente, M. (2023). 2:1 ketogenic diet and low-glycemic-index diet for the treatment of chronic and episodic migraine: A single-center real-life retrospective study. *The Journal of Headache and Pain, 24*(1). https://doi.org/10.1186/s10194-023-01635-9

Thompson, D. F., & Saluja, H. S. (2017). Prophylaxis of migraine headaches with riboflavin: A systematic review. *Journal of Clinical Pharmacy and Therapeutics, 42*(4), 394−403. https://doi.org/10.1111/jcpt.12548

Tian, S., Yu, X., Wu, L., Zheng, H., Zhong, X., Xie, Y., & Wu, W. (2024). Vitamin B6 and folate intake are associated with lower risk of severe headache or migraine in adults: An analysis based on NHANES 1999−2004. *Nutrition Research, 121*, 51−60. https://doi.org/10.1016/j.nutres.2023.11.008

Tseng, P. T., Zeng, B. Y., Chen, J. J., Kuo, C. H., Zeng, B. S., Kuo, J. S., Cheng, Y. S., Sun, C. K., Wu, Y. C., Tu, Y. K., Stubbs, B., Carvalho, A. F., Liang, C. S., Chen, T. Y., Hsu, C. W., Suen, M. W., Yang, C. P., Hsu, S. P., Chen, Y. W., … Lin, P. Y. (2024). High dosage omega-3 fatty acids outperform existing pharmacological options for migraine prophylaxis: A network meta-analysis. *Advances in Nutrition, 15*(2). https://doi.org/10.1016/j.advnut.2023.100163

Valente, M., Garbo, R., Filippi, F., Antonutti, A., Ceccarini, V., Tereshko, Y., Di Lorenzo, C., & Gigli, G. L. (2022). Migraine prevention through ketogenic diet: More than body mass composition changes. *Journal of Clinical Medicine, 11*(17). https://doi.org/10.3390/jcm11174946

Wang, F., Van Den Eeden, S. K., Ackerson, L. M., Salk, S. E., Reince, R. H., & Elin, R. J. (2003). Oral magnesium oxide prophylaxis of frequent migrainous headache in children: A randomized, double-blind, placebo-controlled trial. *Headache, 43*(6), 601−610. https://doi.org/10.1046/j.1526-4610.2003.03102.x

Wang, H.-F., Liu, W.-C., Zailani, H., Yang, C.-C., Chen, T.-B., Chang, C.-M., Tsai, I.-J., Yang, C.-P., & Su, K.-P. (2024). A 12-week randomized double-blind clinical trial of eicosapentaenoic acid intervention in episodic migraine. *Brain, Behavior, and Immunity, 118*, 459−467. https://doi.org/10.1016/j.bbi.2024.03.019

Welch, K., Levine, S. R., D'Andrea, G., Schultz, L. R., & Helpern, J. A. (1989). Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy. *Neurology, 39*(4), 538−541. https://doi.org/10.1212/wnl.39.4.538

Xu, L., Zhang, C., Liu, Y., Shang, X., & Huang, D. (2023). Association between dietary potassium intake and severe headache or migraine in US adults: A population-based analysis. *Frontiers in Nutrition, 10*. https://doi.org/10.3389/fnut.2023.1255468

Yamanaka, G., Suzuki, S., Morishita, N., Takeshita, M., Kanou, K., Takamatsu, T., Morichi, S., Ishida, Y., Watanabe, Y., Go, S., Oana, S., & Kawashima, H. (2021). Experimental and clinical evidence of the effectiveness of riboflavin on migraines. *Nutrients, 13*(8). https://doi.org/10.3390/nu13082612

Zheng, H., Tian, S., Wu, L., Zhong, X., Liu, M., Yu, X., Xie, Y., & Wu, W. (2023). Dietary zinc intake in relation to migraine among adults: A cross sectional study of NHANES 1999−2004. *Nutritional Neuroscience*. https://doi.org/10.1080/1028415X.2023.2243678