20 Complementary and Alternative Approaches to Chronic Daily Headache: Part III—Nutraceuticals

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Nutraceuticals

The term "nutraceutical" was coined by Dr. Stephen DeFelice in 1989 as a combination of "nutrition" and "pharmaceutical" and was defined as "a food, or part of a food, that provides medical or health benefits, including the prevention and/or treatment of a disease" [1]. Currently, this term is used loosely and has no regulatory definition. The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined the US Food and Drug Administration's (FDA) statutory authority over dietary supplements [2]. A dietary supplement is "a product that is intended to supplement the diet and may contain one or more dietary ingredients. A dietary ingredient may be any of the following: a vitamin or mineral; an herb or other botanical; amino acid; a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; a concentrate, metabolite, constituent, extract, or combination of the preceding ingredients."

Dietary supplements are used by nearly half of the US population [3]. Unlike pharmaceutical products, the FDA expects the manufacturer to maintain quality and safety standards. Thus, dietary supplements are not required to pass safety and efficacy studies in humans before production and sale. Voluntary adverse event reporting exists, and if the FDA has scientific proof and determines a product to be unsafe, the FDA can issue a warning or require that it be removed [4]. Past products have required numerous years to assemble sufficient data and prove harm prior to market removal [3]. The FDA also oversees the health claims that are used for dietary supplements. Specifically, supplements are allowed to make claims of health benefit, nutrient content, and structure/function, but not of specific disease treatment or prevention [5].

The supplement market has grown from 4000 products in 1994 to over 85,000 by 2014, and the ability to purchase them online has increased their accessibility [3]. In addition, the high cost of prescription drugs, disparities in prescription coverage, and the public's perception that all "natural" medicines are good are cited as reasons for the explosion of this market [1]. Many patients report using supplements to avoid side effects associated with some prescription medications (70%) or because they have an integrated approach to their health (52%) or are generally dissatisfied with conventional medicine (32%) [6]. However, since the FDA allows companies control over the manufacturing process, the accuracy of labeling and purity of some supplements have come into question. Investigations of supplements are ongoing for (1) claims of potential

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contaminants [7] and (2) poor quality (lack of advertised ingredient or different dosage from claim) [8]. Supplement companies can pay for third-party testing to confirm content and accuracy. Consumers can use this "stamp of approval" on bottles to confirm accuracy and quality of the product.

In the 2007 National Health Interview Survey (n = 23,393), 26.7% of adults with self-reported migraines/severe headaches reported using herbal/other supplements (even without including multivitamins in this category); usage was split across 44 different supplements [9]. Children also frequently use supplements. In an Italian survey of 124 4- to 16-year-old children with a primary headache diagnosis by IHS criteria, 64% reported use of herbal remedies (such as *Valeriana*, *Ginkgo biloba*, *Boswellia serrata*, *Vitex agnus-castus*, passionflower, linden tree), and 40% reported use of vitamins/mineral supplements (such as magnesium, 5-hydroxytryptophan, vitamin B6 or B12, multivitamin compounds); baseline CAM use in this group was 76% [6]. A larger, multicenter Italian study (n = 706 children/adolescents with a primary headache disorder using ICHD-IIIβ criteria) found a lower, but still meaningful, prevalence of nutraceutical use (32%) and melatonin use (10%) [10]. Of note, perceived efficacy of melatonin and nutraceuticals was similar to prophylactic drugs (75% vs. 68% vs. 75%, respectively). Despite such frequent use, it is estimated that 60% of patients do not report CAM use to their providers [9, 11].

Few studies have evaluated the benefit of nutraceuticals specifically for chronic daily headache. Therefore, the research evidence conducted for headache will be described, with the hope that this information can help inform use in those with chronic daily headache. Based on evidence and efficacy for headache, nutraceuticals included in this review are *Tanacetum parthenium* (feverfew), riboflavin, magnesium, CoQ10, melatonin, vitamin D, and ginkgolide B (*Ginkgo biloba*). The evidence for homeopathy is also discussed.

Although Level A evidence exists for *Petasites* (butterbur), it is not currently recommended secondary to potential for liver toxicity [4, 12, 13].

Feverfew

The herb *Tanacetum parthenium* (feverfew) is a perennial plant that belongs to the family Asteraceae (daisy). Its Latin origin *febrifugia* means "fever reducer" [4]. Although native to the Balkan Peninsula, it can now be seen growing along roadsides, field, and wooded areas in the USA, Africa, Australia, China, Japan, and Europe [14]. It is used for numerous medical conditions [14] and comes in a variety of formulations, but its mechanism of action is not fully understood. It is thought that parthenolide, a sesquiterpene lactone, is the principle active ingredient [4, 12, 15]. Parthenium may inhibit the release of serotonin and potentially serve as an anti-inflammatory agent by inhibiting prostaglandin and phospholipase A production, thus improving vascular contraction and relaxation [4, 12, 15]. It may also inhibit platelet secretion and histamine release [14]. Parthenolide may not be the only active ingredient; some varieties of feverfew also contain a high concentration of melatonin [15], which is also thought to be helpful in many headache types (see below).

Evidence of Feverfew for Headache

Feverfew is one of the most thoroughly studied nutraceuticals for headache prevention, and two Cochrane reviews have evaluated its efficacy [15, 16]. The first review in 2004 concluded that insufficient evidence exists to suggest an effect of feverfew over placebo in preventing migraine. The publication of a larger (n = 218) and more rigorous study [17] with a stable feverfew extract (MIG-99) resulted in a new Cochrane review in 2015. This new review evaluated all randomized, placebo-controlled, double-blind trials assessing feverfew mono-preparations for preventing migraines in all ages, resulting in an analysis of 6 studies with 561 participants. Pooled analyses were not possible due to study and dose heterogeneity; participant inclusion criteria, feverfew preparation/dosage, and length of treatment varied considerably. Of the 4 studies that found some benefit [17–20], 3 had small sample sizes (between 17 and 60 participants). Two more rigorous studies (n = 50 and 147 participants,

respectively) found no significant effects [21, 22]. The newest study [17] had the largest sample size of all studies to date ($n = 218$) and found that feverfew may reduce migraine by 0.6 headaches per month compared to placebo [17] (from 4.8 to 2.9 attacks/month vs. 4.8–3.5, respectively, $P = 0.0456$). Adverse events were mild and not significantly different from placebo, with gastrointestinal complaints the most common side effect. A "post feverfew syndrome" was reported when the substance was withdrawn in long-term users. Symptoms included joint/muscle aches and stiffness, nervousness, anxiety, and poor sleep [18]. The new study added positive evidence to the prior mixed and inconclusive findings, but the overall quality evidence is still low and not conclusive.

While the Cochrane reviews evaluated the evidence for feverfew as a prophylactic migraine treatment, a recent study evaluated feverfew plus ginger given sublingually (1 unit dose applicator; exact dose was not listed) as first-line abortive for mild headache [23]. After 2 h, 32% of patients who received active medication were pain-free versus 16% who received placebo ($P = 0.02$). However, the two groups were not randomized with respect to baseline average severity of headache (1.41 in active group, on a scale 0–3, versus 1.67 placebo group). In summary, although robust data may be lacking in support of feverfew for migraine, its side effect profile is favorable. Care must be taken to obtain a high-quality product, as the amount of parthenolide may vary among brands. Feverfew should be avoided during pregnancy because it may stimulate contractions. Thus, it should be recommended with caution for women of childbearing age.

Feverfew Guideline Recommendations

The evidence for efficacy of feverfew (studied dose, 50–300 mg bid; 2.08–18.75 tid of MIG-99) is considered Level B (probably effective) per the 2012 American Headache Society (AHS) and the American Academy of Neurology (AAN) guidelines [24]. The recent Canadian Headache Society guidelines recommend against its use [25], citing insufficient evidence of benefit. The European Federation of Neurological Societies (EFNS) considers the evidence for efficacy of feverfew as Level C [26].

Riboflavin

Riboflavin, or vitamin B2, is a water-soluble vitamin that is a cofactor in the mitochondrial electron transport chain. The name originates from "ribitol" (sugar whose reduced form provides part of the chemical structure) and "flavin" (functional group which gives patient's urine the characteristic yellow color upon oxidization) [4]. It has a 1 h half-life, so absorption is poor unless taken with food [27]. Riboflavin plays a role in the Krebs cycle, production of ATP, and mitochondrial energy metabolism and generation [12, 28]. There may be a relationship between migraine and mitochondrial dysfunction which leads to "decreased ATP production and energy metabolism, imbalance in calcium ions, increased neuronal information processing, decreased migraine threshold, and ultimately cortical spreading depression" [27].

Evidence of Riboflavin for Headache

Dating back to 1946, a case series was published in which 19 patients with migraine reported positive results from using riboflavin for variable lengths of time [29]. In a randomized clinical trial (RCT) in 1998, 3 months of 400 mg daily riboflavin resulted in statistically significant reductions in migraine headache days ($P = 0.012$) and frequency ($P = 0.005$) compared to placebo. Treatment effect was seen at 1 month but was highest after 3 months of treatment [30]. Another study comparing 4 months of preventive use of beta-blockers ($n = 11$) to riboflavin ($n = 15$) for migraine found that treatment response (patients with ≥50% decrease in attack frequency) was similar in both groups (beta-blocker 55% and riboflavin 53%), but auditory evoked cortical responses tended to normalize only after beta-blocker use, suggesting different pathophysiological mechanisms of action [31]. A small ($n = 23$) open-label study showed that 400 mg daily riboflavin decreased migraine frequency (from 4 to 2 days/month at 3 and 6 month follow-ups,

$P < 0.05$) and use of acute medications, but not headache duration or intensity [32]. Minor side effects (diarrhea, abdominal pain, facial erythema, and polyuria) were reported by a few patients.

The few studies of riboflavin for headache in pediatric patients have yielded conflicting results. A double-blind RCT showed that 200 mg daily riboflavin did not improve headaches more than placebo in 48 children. The placebo rate was high (66.6%) and the dose used for this study was lower than typical [33]. Another double-blind, crossover RCT in 42 children with migraines also found no benefit of riboflavin (at 50 mg/day) vs. placebo, although they did find a reduction in frequency of tension-type headaches [34]. No adverse reactions were noted in this study. In a retrospective chart analysis of 41 pediatric/adolescent patients with various headache subtypes, those receiving either 200 mg or 400 mg of riboflavin daily for 3, 4, or 6 months had fewer headaches (68.4% of patients) and less intense pain (21% of patients). Full benefit was seen after 4 months of treatment. A few patients reported decreased or resolution of aura. One patient stopped due to vomiting, and another complained of increased appetite, otherwise few side effects were reported [35]. Results of this study need to be interpreted with caution, as it was retrospective and lacked a placebo group and blinding. A case study of three children reported that riboflavin significantly improved ICHD-diagnosed cyclic vomiting syndrome, a condition hypothesized to be related to deficient mitochondrial energy supplies [36].

Riboflavin Guideline Recommendations

Evidence for efficacy of riboflavin (studied dose: 400 mg daily) was categorized as Level B in the 2012 AHS and the AAN guidelines. The Canadian Headache Society guidelines report strong but low-quality evidence. The EFNS considered the evidence for riboflavin as Level C and classified it as a third-line option.

Magnesium

The essential mineral nutrient magnesium (Mg^{2+}) exists in every cell type and plays a major role in energy metabolism. Nearly half of US adults have poor dietary intake of magnesium [37]. Diets low in magnesium have been associated with type 2 diabetes, premenstrual syndrome symptoms, asthma, osteoporosis, elevated plasma levels of C-reactive protein, hypertension, cardiovascular disease, and sudden death [37, 38]. Magnesium deficiency may play a role in many factors associated with migraine pathophysiology, including cortical spreading depression, substance P release, serotonin-related vasoconstriction, *N*-methyl-D-aspartate (NMDA) glutamate transmission, and nitric oxide production [39]. Magnesium deficiency may be present in up to half of patients with migraine [38]. However, conflicting evidence exists regarding serum magnesium levels in migraineurs. In one study using a magnesium load test (3000 mg of magnesium lactate), 24 h urinary magnesium excretion was lower in the migraine group versus controls, suggesting magnesium retention occurred in the migraineurs because of systemic underlying deficiency, but baseline serum levels were similar between groups [40]. In a case control study (50 migraineurs and 50 healthy controls), serum magnesium levels were lower in migraineurs vs. controls at baseline, although there were no differences in serum magnesium during or between migraine headache events [41]. In a separate matched case-control study (40 migraineurs, 40 healthy controls), serum ionized magnesium levels were lower between attacks and during acute attacks in cases compared to controls, with odds of acute migraine significantly increasing when serum levels of magnesium were low (OR 35.3, 95% CI 12.4–95.2, $p = 0.001$) [42]. Low ionized magnesium levels have been reported during acute menstrual migraine attacks [43].

Factors limit simple magnesium blood level testing to assess for magnesium deficiency [38]. Of total body magnesium stores, 31% are intracellular, 67% in the bone, and only 2% in the extracellular space, where it could be accurately measured with a blood draw; thus, blood magnesium levels do not reflect true body stores [38]. As magnesium is depleted from the blood, it is pulled from the cells in attempts to maintain adequate levels. A magnesium test in red blood cells may be more accurate, but it is not available at all institutions and can be costly.

Evidence for Treatment of Headache with Magnesium

In one study, 81 patients with migraines used 600 mg of trimagnesium dicitrate daily for 12 weeks versus placebo. Migraine attack frequency was reduced in 41.6% in the magnesium group versus 15.8% in the placebo group ($p < 0.05$). Diarrhea and gastric complaints were reported in about a quarter of participants [44].

A recent meta-analysis reviewed 21 studies of magnesium for migraine using Cochrane review criteria. In 11 studies, magnesium was given intravenously for acute treatment; in 10 studies, oral magnesium was used as a preventive [45]. The 10 studies of oral magnesium included 789 participants (6 studies in China) and used 6 different forms of the salt and/or combinations, for periods of 4–12 weeks. Overall findings were positive. Oral magnesium decreased frequency and intensity of migraine (odds ratios [ORs] 0.20 and 0.27). Intravenous magnesium aborted acute migraine within 14–45 min, 120 min, and 24 h after infusion, respectively (ORs of 1.23, 1.20, and 1.25, respectively). Only one study [46] used blinding of participants, personnel, and outcome assessments. However, the results are difficult to interpret because the treatment group received a combination of riboflavin, magnesium, and feverfew; the "placebo" group received a smaller dose of riboflavin [46].

In 1996, Pfaffenrath et al. reported the results of a randomized, double-blind, multicenter placebo-controlled phase III study of 10 mmol magnesium twice daily in patients with 2–6 migraines without aura per month. The study was stopped early due to lack of an effect (goal $n = 150$, stopped after interim analysis of 69 patients) [47]. Response rates were equivocal in the two groups (28.6% with magnesium, 29.4% with placebo). No difference was seen in numbers of migraine days or migraine attacks. Adverse events were noted in 45% of the magnesium group including diarrhea or soft stools ($n = 10$) and palpitations ($n = 3$), thus suggestive that the form of magnesium may have been poorly absorbed and patients may not have received full benefit. In addition, more than 50% of participants in both groups had previously failed one or more prophylactic agents; thus, they may have been more refractory to treatment.

Two studies have evaluated oral magnesium in children with migraine. A randomized, double-blind, placebo-controlled study tested oral magnesium oxide (9 mg/kg/day divided tid with food) versus placebo for 16 weeks among children with migraine [48]. The magnesium group reported fewer headaches of lower severity ($p = 0.0037$ and $p = 0.0029$, respectively). There was also a placebo response in headache frequency that waned after 6 weeks. In a second study of 45 children given 2.25 g of magnesium pidolate twice/daily for 3 months (in an unblinded, open-label design), treatment improved MIDAS scores, headache days (decreased by 69.9%), and use of analgesics (65.4% lower) [49]. However, only 22 participants completed the full 12-month follow-up period. Unpleasant taste was the only adverse effect noted.

Magnesium was recently reclassified from category A to D during pregnancy based on evidence that intravenous magnesium sulfate injections may have teratogenic effects on fetal bone growth. Evidence is limited on the safety of daily oral magnesium in pregnancy; given this new potential risk and categorization, precaution is advised for use in pregnancy [50].

Magnesium Guideline Recommendations

Evidence for efficacy of magnesium (studied dose: 600 mg trimagnesium dicitrate daily) is considered Level B by the AHS and AAN guidelines. The Canadian Headache Society guidelines made a strong recommendation for its use, whereas the EFNS considered the evidence as a Level C, denoting a third-line option. According to the 2015 American Headache Society Evidence Assessment, 1–2 g of magnesium given intravenously as abortive relief of migraine with aura has Level B evidence. There is no evidence of significant adverse reactions with oral magnesium in those without pre-existing severe renal disease.

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (ubiquinone) is a hydrophobic substance found in all cell membranes that serves critical roles in the electron transport chain [39]

and in mitochondrial function [39, 51] by helping convert fats and sugar into energy. As a free radical scavenger, it is an antioxidant with numerous anti-inflammatory properties [39, 52]. CoQ10 has long been studied for its cardiovascular benefits, such as blood pressure reduction, hypothesized to be secondary to improved endothelial function. Severe CoQ10 deficiencies are found in mitochondrial diseases (neonatal encephalopathy with nephropathy, Leigh syndrome, lactic acidosis, infantile nephropathy, recessive ataxia, cerebellar atrophy ± retardation) [53], and CoQ10 supplementation can significantly reduce symptoms. Ubiquinol was recently approved by the FDA as an orphan drug to treat primary CoQ10 deficiencies. Some hypothesize that migraine may be a disorder of mitochondrial energy deficiency [54] and that inflammation present during a migraine leads to depletion of CoQ10 [55].

Evidence for CoQ10 for Headache

In a double-blind, randomized, placebo-controlled study published in Neurology, CoQ10 100 mg tid improved attack frequency ($p = 0.05$) and days with nausea after 3 months of treatment ($p = 0.02$) in 42 participants with episodic migraine with and without aura, compared to placebo. The 50% responder rate for attack frequency was greater for those receiving CoQ10 than placebo (47.6% CoQ10 vs. 14.4%; $p = 0.05$). Mean duration, severity, and abortive medication use did not differ between groups. One patient reported cutaneous allergy, but otherwise no other adverse reactions were noted [56].

A randomized, double-blind, placebo-controlled, crossover study (in addition to a multidisciplinary clinic approach) of 100 mg CoQ10 was conducted in 6- to 17-year-old participants with episodic or chronic migraine with and without aura. Both groups improved from baseline, without a difference between coenzyme Q10 and placebo [57]. Chronic migraine patients taking CoQ10 did have a greater initial reduction in headache frequency from baseline to week 1–4 compared to placebo. Similarly, episodic migraineurs who crossed over from placebo to CoQ10 improved after the first 4 weeks (but declined with the opposite crossover). There was a high dropout rate; the authors suggest that after rapid improvement, patients may not have felt a need for continued therapy. The study was also limited because baseline headache frequency was based on report, whereas treatment headache frequency was based on headache diaries. The dose used in this study was lower than in the adult studies (only 100 mg daily rather than 100 mg tid) and was an add-on to an already effective multidisciplinary clinic approach; CoQ10 as monotherapy was not evaluated. Based on evidence from an open-label study in 32 adults [58], 150 mg daily of CoQ10 reduced average number of days with migraine from 7.34 to 2.95 in the last 60 days of treatment ($P < 0.0001$). These findings are supported by a recent study done by Shoeibi et al. [59]. No adverse effects were reported in either study [58, 59].

Some authors suggest testing coenzyme Q10 levels in patients prior to supplementation [4]. One-third of 1550 patients aged 3 to 22 with diagnoses of migraine with and without aura, probable migraine, and chronic migraine had CoQ10 deficiency [52]. Once diagnosed, they were then started on 1–3 mg/kg/day of CoQ10. Although there was no control group for comparison, at follow-up evaluation (mean 97 + _56 days later), headache frequency (46.3% with 50% reduction; $p < 0.001$) and headache disability scores both improved significantly (from 47.4 ± 50.6 to 22.8 ± 30.6; $p < 0.001$).

CoQ10 Guideline Recommendations

Coenzyme Q10 (studied dose 100 mg tid) was given Level C evidence and judged as possibly effective by the AHS and AAN guidelines. The Canadian Headache Society guidelines strongly encouraged offering it based on low-quality evidence but low adverse effects. The EFNS considered the evidence for efficacy of coQ10 as Level C, denoting a third-line option.

Melatonin

Melatonin is a hormone produced by the pineal gland associated with regulation of the circadian rhythm. Melatonin is thought to have anti-inflammatory properties, inhibits both nitric oxide synthesis and dopamine, and may have a role in

glutamate transmission. Its safety profile for short-term use has been established in both human and animal studies, but data are lacking during pregnancy and lactation. Melatonin may enhance opioid efficacy; thus, caution should be used in prescribing melatonin to patients using opioids. Supplements produced in a lab may be safer than products made from animal sources, which may contain contaminants. Lower doses are proposed to have a greater phase-shifting effect on human circadian rhythms [60, 61].

Evidence for Melatonin for Headache

Studies evaluating melatonin for headache are challenging to summarize given the variety of headache diagnoses, melatonin dosages, forms (immediate versus extended release), and duration of treatments. In a randomized, double-blind, placebo-controlled trial of amitriptyline 25 mg, melatonin 3 mg, and placebo for 12 weeks in 196 participants with episodic migraine with and without aura [62], the amitriptyline and melatonin groups had fewer migraine headache days per month compared to placebo. Compared to baseline, after 12 weeks, headache frequency was reduced by 2.7 days in the melatonin group, 2.2 days in the amitriptyline group, and 1.1 days in the placebo group. Melatonin reduced headache frequency compared to placebo ($p = 0.009$) but not compared to amitriptyline ($p = 0.19$). As a secondary end point, more patients taking melatonin had >50% reduction in headache frequency versus amitriptyline ($p < 0.05$) and placebo ($p < 0.01$). Those receiving both melatonin and amitriptyline had reductions in migraine duration and intensity and less analgesic use compared to placebo. Adverse effects were similar in the melatonin and placebo groups but significantly higher in the amitriptyline group. In contrast, a randomized, double-blind, placebo-controlled crossover study in 48 participants with migraine with and without aura found no difference in migraine attack frequency between extended-release melatonin 2 mg for 8 weeks and placebo [61]. However, placebo response was high. Adverse reactions were mild (fatigue, dizziness, nervousness, nightmares) and not significantly different than placebo. One open-label study ($n = 49$; 41 completed study) showed that 6 months of 4 mg melatonin resulted in less frequent migraines ($p < 0.001$) and chronic tension-type headaches ($p = 0.033$) and lower HIT-6 scores for both groups ($p < 0.001$ and $p = 0.002$, respectively) [60].

Melatonin benefited a small series of patients with indomethacin-responsive headaches, both hemicrania continua ($n = 11$) [63] and idiopathic stabbing headache ($n = 3$) [64]. The similar chemical structures of melatonin and indomethacin may explain the benefits seen [64]. Other studies have cited gastric protection with melatonin, suggesting it might be beneficial combined with nonsteroidal anti-inflammatory agents [65]. Although only a few studies have evaluated melatonin for cluster headache, with conflicting results, melatonin is considered a second-line therapy in cluster headache [66]. The evidence that melatonin levels may be low during a cluster attack strengthens the hypothesis that melatonin may act on cluster headaches [67]. One study of 20 participants (18 with episodic cluster and 2 with chronic cluster headaches) reported improvement after 14 days of 10 mg of melatonin taken once per day in the evening during a cluster period, compared to placebo [68]. Headache frequency was reduced in the melatonin group (ANOVA, $p < 0.03$) although no response was seen in the patients with chronic cluster. However, another study of nine participants (six with chronic cluster, three with episodic headaches) did not report a benefit from 2 mg melatonin given during a cluster period [69].

In an open-label trial of melatonin, 14 of 21 children with migraine with and without aura and chronic tension-type headache reported a >50% reduction of headache attack frequency compared to baseline [70]. One child complained of excessive daytime sleepiness. Clinical recommendations in the Journal of the European Paediatric Neurology Society state "there is still no definitive consensus about the therapeutic use of melatonin for headaches in children" [71].

Vitamin D

Vitamin D deficiency is prevalent in the USA despite its presence in food sources and exposure

to sunlight. Vitamin D functions as a hormone, with receptors in nearly all cells of the body with many functions, including cell growth, bone health, immunity, and reducing inflammation [72]. A large cross-sectional population-based study (n = 5938) found an interaction with vitamin D levels and statin's benefit on migraine, such that statin use was associated with lower odds of having severe headaches/migraines only in those with high serum vitamin D levels [73]. Based on this observation, a RCT in migraineurs was conducted of simvastatin 20 mg twice daily plus vitamin D3 1000 IU twice daily vs. placebo. Patients continued their current migraine preventative. Those in the treatment group experienced approximately 3 less migraine days per month compared to placebo ($p < 0.001$) [74]. Unfortunately, given the intervention involved both vitamin D3 and simvastatin, it is unclear which treatment had the greatest effect or if both are required. A pediatric study (n = 53) demonstrated a decreased frequency of migraine days with supplementation of vitamin D plus amitriptyline, but the study was limited by the lack of control group [75]. A small case study (n = 3) reported the presence of severe vitamin D deficiency mimicking chronic tension-type headaches in children, with resultant improvement/near resolution after vitamin D supplementation [76].

Ginkgolide B (Ginkgo biloba)

Ginkgo biloba has been used in herbal medicine for thousands of years to treat dementia, anxiety, asthma, and schizophrenia, although with conflicting evidence. It is made from leaves from the maidenhair tree originating from China [77]. *Ginkgo* may have an effect through its impact on glutamate [78] and antiplatelet-activating factor [79].

Ginkgo biloba had some benefit as potential acute abortive for migraine aura in a small (n = 25) open preliminary trial [78]. Another open-label trial of *Ginkgo biloba* terpenes phytosome 60 mg plus coenzyme Q10 11 mg plus vitamin B2 8.7 mg was given twice daily for 4 months in 50 women with migraine with aura or migraine aura without headache [79]. Improvement in aura frequency and duration was seen. Abdominal complaint and vertigo were reported (n = 3), but overall was well tolerated. Two pediatric studies (n = 119 and n = 24) using combination products containing ginkgolide B, coenzyme Q10, riboflavin, and magnesium in migraine without aura found decreased migraine attack frequency [80, 81]. Another study compared Preparation A (ginkgolide B 80 mg, coenzyme Q10 20 mg, riboflavin 1.6 mg, and magnesium 300 mg) with Preparation B (L-tryptophan 250 mg, 5-hydroxytryptophan [*Griffonia simplicifolia*], vitamin PP, and vitamin B6 1 mg) in 374 school-aged children diagnosed with migraine without aura [82]. Both groups showed improvement in headache duration, pain intensity, disability, and behavioral reactions. Both groups had fewer headaches, especially the Preparation A group. However, the use of combination treatments makes it challenging to detect which component may be most helpful for migraine.

Combination Treatments

In a recent RCT, participants (n = 130) were given 400 mg riboflavin, 600 mg magnesium, and 150 mg coenzyme Q10, along with a multivitamin (containing 750 mg vitamin A, 200 mg vitamin C, 134 mg vitamin E, 5 mg thiamin, 20 mg niacin, 5 mg vitamin B6, 6 mg vitamin B12, 400 mg folic acid, 5 mg vitamin D, 10 mg pantothenic acid, 165 mg biotin, 0.8 mg iron, 5 mg zinc, 2 mg manganese, 0.5 mg copper, 30 mg chromium, 60 mg molybdenum, 50 mg selenium, 5 mg bioflavonoids) for 3 months [83]. Reduction in migraine days per month was not significant. However, reductions in migraine pain ($p = 0.03$) and HIT-6 scores ($p = 0.01$) were seen. In 1 RCT of 49 participants, no differences were seen between the treatment group (who received riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg) and the placebo group (who received placebo containing 25 mg riboflavin) regarding headache reduction, migraine days, migraine index, or triptan dose [46].

Homeopathy

Homeopathic remedies are based on the idea that giving minute amounts of a harmful substance will trigger the body's natural healing response against the harmful agent. Thousands of different homeopathic remedies/substances are used worldwide. Homeopathic treatments are created by "alternating steps of diluting and agitating a starting substance; the resulting "potencies" quickly reach dilutions beyond Avogadro's number where the probability that one molecule of the starting substance is still present approaches zero [84]." Although homeopathic experts claim that many remedies are helpful for migraine, there is currently a paucity of evidence-based research supporting its use. A systematic literature review found no evidence to support or refute the use of homeopathy for migraine, tension-type, or cervicogenic headache, [85] and the studies had numerous methodologic problems. A more recent meta-analysis included four RCTs of homeopathy and headache [86]; these showed a positive trend but no statistically significant benefit beyond placebo. Despite the lack of evidence, a survey of 124 Italian children with chronic headaches demonstrated that 47% use homeopathy [6]. Caution should be used with these products, as they have not been evaluated by the FDA for evidence, safety, or effectiveness [86].

Summary: Supplements and Chronic Daily Headache

The FDA has limited oversight on supplements, and given potential allegations of poor quality and safety of supplements, consumers need to look for the "stamp of approval" of third-party testing on bottles to confirm accuracy and quality of the product. Almost one-third of adults with severe headaches/migraines report using nutraceuticals. Many may seek herb/supplements for their supposed natural and safe profiles, although side effects also occur with supplements [87]. Few studies have evaluated the benefit of nutraceuticals specifically for chronic daily headache. Several supplements have Level B evidence of efficacy according to the 2012 AHS and the AAN guidelines, including feverfew (studied dose, 50–300 mg bid; 2.08–18.75 tid of MIG-99), riboflavin (studied dose, 400 mg daily), and magnesium (studied dose, 600 mg trimagnesium dicitrate daily). Coenzyme Q10 (studied dose 100 mg tid) was considered to have Level C evidence. Melatonin, vitamin D, and *Ginkgo biloba* have limited evidence of potential efficacy for headache. Homeopathy has limited evidence for use in headache. Despite its Level A evidence, controversy exists over the concern for hepatotoxicity with *Petasites* (butterbur); it is therefore not currently recommended [4, 12, 13]. Additional research is needed to further clarify benefits of supplements for chronic daily headache.

Conclusions to Parts I, II, and III: CAM and Chronic Daily Headache

Chronic daily headaches are often refractory to conventional treatment options, and CAM treatments may provide much-needed relief. However, research of CAM treatments specifically for chronic daily headaches is limited, so we have reviewed the research evidence for CAM for headache. Most of the studies have significant methodologic concerns, and larger, more rigorous studies are needed for all CAM modalities. Studies are limited by small sample sizes, heterogeneous interventions, limited headache outcomes, lack of active controls, and short-term follow-up. Despite these limitations, evidence for mind/body options such as meditation, yoga, tai chi, and deep breathing is promising, with the most research to date for mindfulness meditation. The strongest evidence for acupuncture is for chronic migraine, and cost analyses suggest it may have an overall cost benefit. There is some evidence for spinal manipulative therapy for chronic cervicogenic headache or chronic tension-type headache, but the potential for major adverse events, such as cervical dissection, limits more widespread recommendation for its use. No data support the use of massage for any chronic headache conditions. Other complementary therapies (aromatherapy, homeopathy, daith piercing,

and oxygen administration) have minimal evidence to support their use for chronic daily headache. The supplements with the strongest level of evidence for benefit for headache (Level B) include feverfew, riboflavin, and magnesium, with CoQ10 having Level C evidence. Additional evidence is emerging for the potential benefits of supplemental vitamin D, melatonin, and *Ginkgo biloba*.

The research for CAM in general, and for headache, has been limited by methodologic concerns that reduce study quality, leading to challenges in interpreting and assessing interventions. Treatment modalities are often poorly defined and heterogeneous in delivery format, leading to difficulty in understanding what intervention was administered and how to replicate, recommend, or assess options for patients. Many studies had wait-list comparisons without an active control group, making it challenging to interpret the effect of the intervention above the placebo effect. Few studies have long-term follow-up. Most were conducted with the CAM therapy as an "add-on" therapy to usual care, making it difficult to compare it against usual care treatment options. Side effects are not always reported.

Unfortunately, many of the limitations with this research are inherent with this type of research (Table 20.1). Evaluating non-pharmacologic treatment options with research standards created for pharmacologic treatments is difficult. For example, although the "placebo" pill is the standard accepted control for drugs, there is no ideal placebo group for most CAM therapies. Blinding participants to active non-pharmacologic treatment options is challenging, if not impossible. Participants interested in this type of research may be different from most patients, leading to selection bias. Interventions may not be easily reproduced, and non-drug treatments are often not comparable with medical treatments [88].

Table 20.1 Difficulties with non-pharmacological research

Limited ability to blind participants
Difficulty finding a credible control
Small sample sizes
Selection bias
Behavioral treatments often not comparable with medical treatments
Inability to reproduce intervention

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Since the research into most CAM therapies has really just begun, few studies specifically evaluate CAM for chronic daily headache syndromes, so extrapolation of the information from headache studies is required. Many studies done in headache evaluating CAM therapies were not conducted with well-defined headache research parameters. For example, many studies did not clarify if the intervention was assessing episodic or chronic headaches. Most did not use ICHD diagnostic criteria.

Despite these limitations and challenges, the research suggests that many CAM therapies may be beneficial, with minimal side effects. Patients with headaches, especially chronic daily headaches, are especially desperate. Although CAM treatments may be helpful, the placebo rates are quite high in many studies. Further, broad recommendations of potentially non-therapeutic interventions may damage the trust instilled in the doctor-patient relationship. Further research is critical to having a better understanding of the value of these types of therapies for chronic daily headache.

For pregnant or nursing women, CAM therapies may be quite helpful at a time when pharmacologic options are much more dangerous [50]. Pediatric patients are often open and willing to consider CAM therapies to avoid medications. Sometimes more traditional treatment options, even non-pharmacologic options such as biofeedback, are difficult for patients due to cost and availability. This point is illustrated with data from the 2007 NHIS analyses that demonstrated that <1% of patients with severe headaches/migraines used the well-researched intervention of biofeedback, while 9% used yoga, 17% meditated, and 24% did deep breathing exercises [88].

While most CAM therapies have minimal side effects compared to pharmacologic options, the potential side effects from CAM are not negligible. The time, energy, and cost associated with

many of these interventions are an important consideration in the recommendation and adherence to CAM therapies, especially since many of these treatment options are out of pocket. While several of the cost analysis studies for acupuncture demonstrated increased costs of the procedure, when the entire condition is considered and quality-adjusted life years taken into account, the value becomes apparent. Even so, the amount of money spent on CAM is tremendous, with an estimated $33.9 billion in out-of-pocket costs spent by US adults [89].

Despite the significant amount of research discussed in this chapter, there are still many unanswered questions about most CAM therapies for chronic daily headache [90]. Uncertainty persists as to optimal dosages (frequency, duration, length of treatment), which types of patients and headaches are most responsive to these interventions, and mechanisms of action [90].

Despite all these limitations and persistent questions, CAM therapies may be a viable treatment option for adults with chronic daily headache. Given the significant risks associated with many pharmacologic treatments, especially opioids and the potential for medication-overuse headache, CAM treatments may be especially helpful. The study assessing mindfulness therapy vs. pharmacologic treatments after medication-overuse headache withdrawal is especially encouraging, suggesting that non-pharmacologic treatments may be comparable to pharmacologic treatments for medication-overuse headache.

One of the most important aspects of many CAM therapies is the opportunity for patients to be active in their own treatment plans and to learn techniques that improve their own sense of self-efficacy. Many CAM therapies may not be most effective as individual treatments but, as an approach to care, with patients encouraged to use many CAM therapies discussed in this chapter together, using an "integrative" approach. One study even retrospectively assessed for this possibility through chart reviews comparing a multimodal approach that included osteopathic manipulative treatments, mindfulness, and qigong to standard pharmacologic treatments in 83 adolescents with chronic tension-type headache [91]. Although both were effective, multimodal treatment was statistically more beneficial than the pharmacologic option in headache outcomes.

CAM in the "real world" takes into account patient preference and considers CAM as an integral part of every treatment plan, as first line rather than last resort [92]. Understanding CAM therapies is critical for providers to advocate for their patients' health care, as Dr. Rob Cowan points out, because "we don't need to embrace every alternative medical system to serve our patients, but there exists a wide variety of modalities which, whether we incorporate them into our practices or not, need to be on our radar, and which with we need more than a passing familiarity. Moreover, we need to provide some guidance to our patients in these areas if we are truly able to be their advocate in healthcare" [92, 93]. The goal of these chapters is to equip providers with the knowledge to appropriately counsel patients on these treatment options and to make patients and providers aware of the possibilities that CAM therapies may offer to those who need additional treatment options.

Chronic daily headache is a challenging condition to treat, with high associated disability and psychological comorbidities. One patient describes her experience with integrative medicine in an eloquent letter published in *Headache* and concludes by stating "Since I have begun to incorporate Integrative Medicine, I have started telling myself to stop waiting until I am 100% healthy to live my life. If all I have is 40%, then I make sure it is the best 40%" [94]. Hopefully, a better understanding of CAM therapies and an integrative medicine approach will give all chronic daily headache patients and providers hope to achieve that goal [90].

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