Chapter 11
Adjunctive and Integrative Therapy in Migraine Management

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Introduction

According to the 2012 National Health Interview Survey (NHIS), 33.9% of adults and 12% of children have used approaches to medical care that are considered outside of those typically practiced in standard Western medicine [1]. These approaches are often interchangeably referred to as complementary or alternative medicine (CAM). More precisely defined, complementary medicine refers to a therapy used *in addition to* standard Western medicine, while alternative medicine refers to a practice used *instead of* traditional Western medical care [2]. In December of 2014, The National Center for Complementary and Alternative Medicine (NCCAM) suggested the term "integrative health" be used instead of "alternative medicine", changing its own name to the National Center for Complementary and Integrative Health (NCCIH). NCCIH noted that large population based studies had demonstrated that the sole use of practices that have no scientific proof is actually rare. More commonly, patients combine complementary approaches with conventional treatment [3]. The American Board of Integrative Medicine has offered sub-specialty certification for fellows since 2014 [4].

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Of the patients included in the 2009 NHIS, 27.4 million US adults reported suffering from migraine or severe headache within 3 months of the survey date. Approximately one half of these (49.5%) used at least one CAM therapy in the year prior. Overall, it is believed that up to 82% of patients with headaches use integrative therapies, sometimes at the recommendation of allopathic practitioners. Only one half of these patients disclosed this use to their medical providers. Mind/body therapies were the most frequently used, followed by biologically based therapies, including herbs and supplements. Combining herbs, vitamins, and supplements (nutraceuticals) with conventional medications leads to more success than using nutraceuticals alone [5, 6].

The American Academy of Neurology (AAN) and the American Headache Society (AHS) published guidelines for various aspects of migraine prevention using a defined classification scheme for therapeutic questions [7]. Complementary therapies were initially reviewed in 2000 and updated in 2012 [8, 9]. Behavioral and physical treatments were last reviewed in 1998 [10]. Levels of evidence of the therapies from these guidelines are summarized below. The authors have updated it for this chapter to include all therapies discussed herein. Therapies included in the Holland et al. review [9] are in bold.

AAN evidence level A: established as effective, with at least 2 Class I studies:

Petasites
Acupuncture
Relaxation Training
Biofeedback
Cognitive Behavior Therapy

AAN evidence level B: established as probably effective with at least 1 Class I or 2 Class II studies:

Magnesium
MIG-99 (feverfew)
Riboflavin
Exercise

AAN evidence level C: established as possibly effective with at least 1 Class II or 2 Class III studies:

Co-Q10
Phytoestrogens
Chiropractic Therapies
Massage
Hyperbaric Oxygen Therapy
Hypnotherapy

AAN evidence level U: Inadequate or conflicting data:

Melatonin
MVI B6, 9, 12

Omega-3 Fatty Acids
Cannabinoids
Diet
Class I studies: Randomized, controlled trials in representative populations.
Class II studies: Randomized, controlled trials with incomplete data or inadequate controls; or prospective cohort studies.
Class III studies: All other controlled trials, including those in which patients serve as their own controls.

Nutraceuticals

A list of nutraceuticals discussed in this chapter, including dosages, specific brands, and side effects is summarized in Table 11.1.

Petasites *(Butterbur)—Level A Evidence*

Certain plants of the *Petasites* genus have properties that would make them appropriate for management of migraine. There are proven antihistamine, antileukotriene, and calcium channel blocking effects in various *Petasites* species. The sesquiterpenes petasin and isopetasin are thought to be the active ingredients. Because of these properties, *Petasites* would appear to be an ideal product for use in patients with allergy and migraine, or the classic "sinus headache" [11, 12].

A number of clinical trials suggest that the use of 150 mg of *Petasites* for a minimum of 3 months is useful in the prevention of migraine headaches [11, 13, 14, 15]. One small pediatric randomized control trial (RCT) showed efficacy in 19 patients (50–100 mg) only in weeks 40–48 [16]. The AAN and AHS have graded this product as level A evidence, though the German, Austrian, and Swiss headache societies and the German Society of Neurology have reviewed it less favorably. A 2004 review published in Otolaryngology Head and Neck Surgery gives it a moderate rating and suggests that more research is appropriate [17].

While *Petasites* appears to be effective in prevention of migraines, there are safety concerns, specifically regarding hepatotoxicity and carcinogenicity [18]. Many of the RCTs have used the brand Petadolex, produced by a German company. The product is produced utilizing a patented technique to remove toxic pyrrolizidine alkaloids (PA) from the rhizome of the plant. This extraction process utilized a methylene chloride solvent that was subsequently changed to a supercritical carbon dioxide (CO_2) process thought to be superior. Approval for Petadolex was initially granted by the German Health Regulatory Authority with the first solvent and withdrawn when the new extraction process was resubmitted for registration, as it was considered different than the original. In 2012, the

Table 11.1 Nutraceutical dosing information

Nutraceutical	Preferred formulation	Dose/time	Side effects	Precautions, interactions, contraindications
ALA		300–600 mg/d/3 mo	Rare, case reports	Possible hypoglycemia. May interact with antidiabetes, thyroid drugs or chemotherapeutic agents.
B2 Riboflavin		200–400 mg/d	Polyuria, diarrhea	
B3 Niacin	Oral, Sustained release (SR), IV	300–500 mg oral/d SR- 750 mg oral/d IV- 100–300 mg until flushing for 15 min	IV-abdominal cramping, vomiting, skin burning. Oral-flushing, pruritis, nausea, and vomiting.	Hepatotoxicity with sustained release formulations.
B6 Pyridoxine		25 mg/d	Rare—photosensitivity, nausea, asthma exacerbation	Doses over 200 mg have produced reversible neuropathy.
B9 Folic Acid		2 mg/d	Rare—nausea, bloating, depression	Possible interaction with Primidone, Pyrimethamine, Mysoline, Daraprim.
B12 Cobalamin		400 mcg/d	Rare—rash, acne, nausea, dysphagia	
Cannabis	Unclear—vaporized, edible, topical and smoked	≥once daily	Drowsiness	
CoQ10		1–3 mg/kg/d or 150 mg/d	Anorexia, GI, rash	Possible interaction with Anisindione, Dicumarol.
N3 Fatty Acids		2000 mg tid	Eructations	May increase bleeding potential.
Feverfew	MIG-99	6.25 mg tid/3 mo	Arthralgias, oral ulcerations	Uterine contractions in pregnant women. Cross reactivity with daisy allergy.

(continued)

Table 11.1 (continued)

Nutraceutical	Preferred formulation	Dose/time	Side effects	Precautions, interactions, contraindications
Ginkgo	Migrasoll Pharmaval Srl	Ginkgolide B 80 mg, coenzyme Q10 20 mg, vitamin B2 1.6 mg, magnesium 300 mg	Atopic dermatitis, muscle weakness	May increase bleeding potential. Severe allergic reactions with crude ginkgo plant parts. Interacts with cytochrome P450 3A4 (CYP3A4) substrates and some HIV drugs.
Magnesium	Oral—varies IV—sulfate	400–1200 mg/d/3–4 months	GI	Caution in pts with renal failure. Decreased absorption of Gabapentin.
Melatonin		3 mg/1 h prior to bedtime/3 months	Lethargy, dry mouth, constipation, weight gain	Hypotension, hypoglycemia, caution in pts on opioids.
Petasites	Petadolex	50–150 mg/d	GI, cholestatic hepatitis, liver cancer	Not for use in children and pregnancy. Must be free of pyrrolizidine alkaloids.

United Kingdom's Medicines and Healthcare Products Regulatory Agency took all *Petasites* products off the market, citing safety concerns [19]. Other European regulatory agencies have similarly removed this product from the market, often for failure to adhere to stringently low levels of PA [11].

While Petadolex continues to be available in the US, patients should be advised of these potential risks [18]. It should not be recommended for use in children, pregnant or nursing women, or patients with kidney or liver disease [19, 20].

Magnesium—Level B Evidence

Intravenous magnesium supplementation is widely used for acute and prophylactic treatment of migraine, while oral administration is often used for prophylaxis. Magnesium is thought to decrease the sensitivity of the brain to external and internal stimuli, and as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, magnesium is essential for synaptic plasticity and memory [19, 21, 22]. Magnesium

also serves to maintain vascular tone, promote propagation of cortical impulses, and regulate levels of inflammatory mediators, serotonin, nitrous oxide, and substance P [6].

Hypomagnesaemia is not uncommon and is seen in up to 15% of the general population [23]. Adult and pediatric migraneurs are often deficient in magnesium, as measured in the blood, saliva, or brain. Such deficiency is more commonly seen in migraine with aura (MA) and migraine during menses (MM) and is known to worsen during attacks [24–28]. Ionized serum magnesium (IMg^{2+}) is thought of as the most accurate reflection of aberrations of magnesium levels in the soft tissue, but the more commercially available red blood cell (RBC) magnesium is considered an acceptable substitute [29].

Acute Management

Mauskoup et al. demonstrated that 50% of subjects (n = 40) with migraine had low levels of IMg^{2+} during an acute migraine attack. 85% of these had a reduction in pain of more than 50% with IV infusion of magnesium sulfate ($MgSO_4$), and treatment response correlated with the level of magnesium deficiency [30]. A 2014 meta-analysis of existing studies looked at acute management 30 min after infusion of IV $MgSO_4$. There was no reduction in pain and no effect on need for rescue medications. Furthermore, an increase in adverse effects was also noted. The authors cited heterogeneity of studies and small sample size as confounding factors [31]. Due to methodological selection criteria, the Mauskoup trial was not included in this review.

Prevention

Most published trials examine magnesium for acute migraine management. Teigen and Boes performed an evidence-based review of 4 RCTs of magnesium supplementation for prophylaxis. While the studies consistently showed a relationship between migraines and lower magnesium status, there was significant variability in the effectiveness of treatment. The authors attribute this to methodological differences and confounding variables, including endpoints and formulations of magnesium used. They propose that magnesium levels should be assessed in migraine patients and that increased dietary magnesium intake could offer a reasonable alternative for prophylaxis [32].

Riboflavin—Level B Evidence

It has long been hypothesized that vitamin B_2 could be utilized in migraine treatment and prophylaxis. There is a known interictal reduction of phosphorylation

potential (OXPHOS) in migraine without aura (MO), MA, and MM which impacts mitochondrial energy production [33]. This results in hyper-excitability in both neurons and muscle fibers of migraneurs. Vitamin B_2 plays a role in OXPHOS reactions that can prevent this hyper-excitability and benefit mitochondrial energy production [30, 34]. Figure 11.1 outlines the possible roles for riboflavin in the prevention of headache.

The clinical trials of riboflavin in prevention of migraine attacks are mixed. While some show a significant improvement, others show no or minimal effects. The studies vary widely in terms of type of migraine, sex, age, dosages, length of time the product is used, placebo control and therapeutic end points. Sample sizes are generally small [34].

One of the most frequently cited RCTs noted a 50% reduction in attacks in 59% of adult patients taking 400 mg of riboflavin daily for 3 months [35]. A combination product of 400 mg of riboflavin, 300 mg magnesium and 100 mg of feverfew was compared to a "placebo" of 25 mg of riboflavin. There was a difference in both groups in the number of days with migraine and the frequency of attacks [36]. One recent study suggests that riboflavin is most effective in patients with the non-H mitochondrial DNA haplotype, which is more prevalent in Europeans and associated with lower mitochondrial function [37]. Vitamin B_2 has also shown usefulness when added to other pharmaceutical preventative therapies [38].

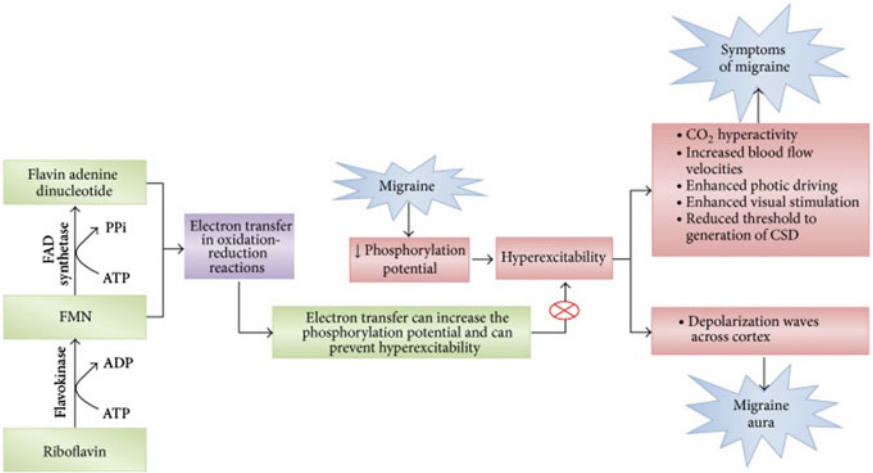

Fig. 11.1 Possible roles of riboflavin in ameliorating migraine. Schematic diagram depicting the possible roles of riboflavin in ameliorating migraine. *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *FAD* flavin adenine dinucleotide, *PPi* pyrophosphate (anion $P_2O_7^{4-}$), *CO_2* carbon dioxide, and *CSD* cortical spreading depression. *Red circled* times symbol: inhibition of the pathway (Reproduced from Shaik, M. M. and S. H. Gan (2015). "Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine." Biomed Res Int 2015: 469529 [34] under the Creative Commons Attribution License. http://www.hindawi.com/journals/bmri/2015/469529/)

Overall, because of the favorable risk benefit ratio, most would recommend including riboflavin in the treatment plan of adult migraneurs [19]. A recent systematic review of use in children has not shown efficacy, and therefore its use is not recommended for pediatric use at this time [39].

Feverfew—Level B Evidence

The plant *Tanacetum parthenium L* has a long history of traditional use in the prevention of migraine. It is unclear how feverfew works. Parthenolide, a sesquiterpene lactone found in the aerial portion of the plant, is widely held to be the most important active ingredient. Parthenolides most likely exert their effect by inhibiting prostaglandin production, interfering with both contraction and relaxation of intracerebral blood vessels. They may also affect the secretion of serotonin [40]. A Cochrane review of this herb was published in 2004 and updated in 2015. While many studies suggested benefit, they failed to show efficacy due to poor trial design with low numbers of patients and unstable extracts of the product [40–42].

MIG-99 is considered a superior formulation of feverfew. This supercritical CO_2 extraction enriches the parthenolide content and produces a chemically stable product. Clinical trials performed with its predecessor product are susceptible to variance in both concentration and stability of the parthenolides and clinical results are variable.

One of two studies utilizing MIG-99 demonstrated no benefit over placebo in 147 subjects over 3 different dosages of the product. It was, however, noted that a smaller subgroup of the most severely affected patients had a response to MIG-99 [43]. Therefore, a second RCT on a larger pool of subjects ($n = 170$) was performed. Here, a significant reduction in both frequency and severity of attacks was noted (30.3% vs. 17.3%). The effect of MIG-99 begins as early as one month and reaches maximal benefit in two months. Once usage is stopped, the effect is sustained for at least four months [44]. In both studies, adverse effects of MIG-99 were similar to placebo.

Coenzyme Q10 (CoQ10)—Level C Evidence

CoQ10 is an enzyme cofactor critical for maintenance of mitochondrial energy stores [19]. It has been shown to be deficient in approximately one-third of children and adolescents with migraine. This deficiency is potentially due to oxygen free radical formation during migraine attacks that could deplete stores of CoQ10. Supplementation in deficient children has shown a statistically significant reduction in both frequency and disability associated with attacks [45, 46].

In a group of patients treated with standard multidisciplinary treatments for migraine, addition of CoQ10 in a crossover RCT showed a difference in frequency of attacks only early on in therapy [46]. In adults, a small open label study showed

lowered migraine frequency with 3 months of 150 mg daily [47]. In another RCT ($n = 42$), 300 mg daily was noted to improve frequency of attacks, days with headache, and headache-associated nausea [48]. Side effects are minimal and noted in less than 1% of the subjects [47].

Melatonin—Level U Evidence

Melatonin acts as an anti-inflammatory by scavenging free radicals and down regulating pro-inflammatory cytokines. It is also involved in neurovascular regulation by affecting maintenance of nitric oxide, dopamine, and serotonin. Melatonin could also affect the circadian predilection for migraines noted in some patients. Altered melatonin levels are seen in various forms of migraine [49, 50]. *Petasites* and feverfew have substantial amounts of melatonin and are used in the treatment of migraine [11, 51].

The first study of use of melatonin for prevention of migraine showed efficacy, but was underpowered and open label [50]. A subsequent study using a prolonged release product did not show improvement in attack frequency when compared to placebo [52]. In a randomized, multicenter group design melatonin was slightly superior to 25 mg of amitriptyline in days per month with headache. Side effects were minimal and less than in the amitriptyline group [53].

Vitamins B6, 9, 12—Level U Evidence

Elevated homocysteine levels have been implicated in MA. It is thought that this deficiency produces an inflammatory reaction in the meninges and endothelial injury within cerebral blood vessels. Trigeminal fibers are activated and nitric oxide becomes less bioavailable [54]. A schematic of the role of vitamins B6, 9 and 12, in migraine pathophysiology is outlined in Fig. 11.2.

The enzyme methylenetetrahydrofolate reductase (MTHFR) is essential to re-methylation of methionine and elimination of homocysteine. This reaction requires vitamins B6 (pyridoxine), B12 (cobalamin) and B9 (folic acid). Hyperhomocysteinemia has been observed in deficiencies of these vitamins [34]. The MTHFR C677T genetic variant has been associated with increased levels of homocysteine and risk of MA [55].

Menon et al. demonstrated an inverse relationship between dietary intake of B9 and MA frequency in patients homozygous for MTHFR C677T [54]. Lea and colleagues demonstrated a reduction in migraine frequency, disability, and pain severity with a reduction in homocysteine achieved with a 6-month protocol of folic acid (2 mg), B6 (25 mg) and B12 (400 mcg) [56].

The selected vitamin content of foods is included in Table 11.2

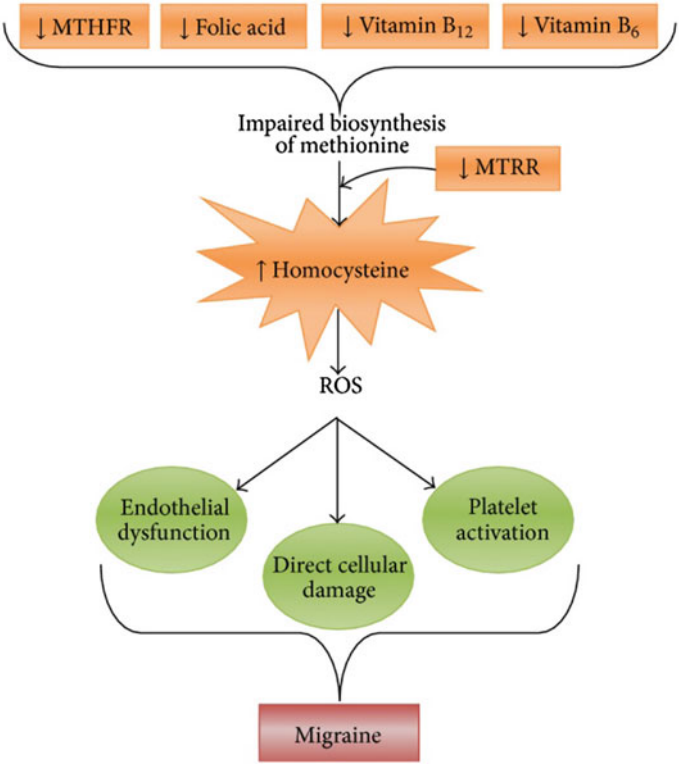

Fig. 11.2 The role of vitamins B6, B12, and folic acid in migraine pathophysiology. Schematic representation depicting the role of vitamins B6, B12, and folic acid in migraine pathophysiology. *MTRR* (or *MSR*) methionine synthase reductase, *MTHFR* methylene tetrahydrofolate reductase, and *ROS* reactive oxygen species (Reproduced from Shaik, M. M. and S. H. Gan (2015). "Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine." Biomed Res Int 2015: 469529 [34] under the Creative Commons Attribution License. http://www.hindawi.com/journals/bmri/2015/469529/)

Alpha Lipoic Acid (ALA)—Level U Evidence

Thioctic (alpha lipoic) acid is a water and fat soluble antioxidant, which like riboflavin and CoQ10 enhances mitochondrial metabolism and ATP production. It does so by removing reactive oxygen species and chelating transition metal ion byproducts of oxidative stress [57, 58].

In a RCT of 26 study patients, ALA (600 mg daily for 3 months) showed a reduced monthly attack frequency that was not statistically significant when compared to placebo. Within-group analyses showed a significant reduction in attack frequency, headache days, and headache severity in patients treated with ALA. These benefits were not seen in the placebo group. The authors conclude that the study group was underpowered, but that a clear trend toward less frequent attacks

Table 11.2 Selected vitamin content of foods

Vitamin or supplement	Foods containing
Omega 3 fatty acids	Salmon, tuna, mackerel, anchovies, sardines, herring
Magnesium	Legumes, almonds and other nuts, spinach, sweet potatoes, white potatoes, swiss chard, sunflower seeds, brown rice, whole grains, and dairy products
Alpha lipoic acid	Meat products, heart, liver and kidneys, broccoli, spinach, brewer's yeast, brussel sprouts, peas, tomatoes
Riboflavin	Milk, eggs, cheese, yogurt, broccoli, almonds, soy, fortified cereal
B9	Fortified foods, spinach, broccoli, lettuce, okra, asparagus, bananas, melons, lemons, legumes, yeast, mushrooms, organ meat, beef liver, kidney, orange and tomato juice
B12	Meat, fish, poultry, eggs, dairy
B6	Whole grain products, liver, bananas, green beans, carrots, chicken, eggs, meat, fish, spinach, walnuts and sunflower seeds

was noted. They also note that like riboflavin and CoQ10 results accrue over time. No side effects were noted [59].

In a randomized, uncontrolled study adolescent girls were given Topiramate or ALA alone or both combined, for one month. All three groups showed improvement in migraine frequency. Reduction in mean monthly migraine days was significantly greater in the group receiving combined Topiramate ALA therapy (from 12.32 ± 1.85 to 5.74 ± 1.1). Side effects were noted solely in the Topiramate monotherapy group [58].

Essential Fatty Acids—Level U Evidence

Omega-3 polyunsaturated fatty acids (n-3 FA) are known to affect production of inflammatory cytokines. N-3 fatty acids can also be converted to lipid mediators that have antinociceptive properties, such as endovanilloids, eicosanoids, endocannabinoids, and resolvins. In addition, these compounds have anti-coagulant and vaso-relaxant properties, all of which suggest their usefulness in the treatment of migraine [60, 61].

There is only one existing RCT of n-3 FAs for migraine. After a four week single blind placebo run in period, patients were assigned to 16 weeks of either 6 g of n-3 FA daily or placebo. There were no differences noted in the mean number of attacks during the last four weeks of the study but the overall number of attacks was reduced in the treatment group. A greater level of eructation was noted in the n-3 related group without other side effects [61].

Omega 6 polyunsaturated fatty acids (n-6 FA) are prevalent in the western diet. These are thought to potentially contribute to headache pathogenesis by hyperactive

metabolism of n-6 linoleic (n-6 LA) and arachidonic (n-6 AA) acids, and insufficient metabolism of n-3 eicosapentaenoic (n-3 EPA) and docosahexaenoic (n-3 DHA) acids [62]. Although not specific to migraine, Ramsden and colleagues treated a cohort of patients (n = 56) with chronic daily headaches with targeted dietary fatty acid alterations. The study was a randomized, single-blinded, parallel-group clinical trial with a four week pre-intervention phase. Patients were randomized to 12 weeks of dietary interventions: a high n-3 plus low n-6 (H3-L6) diet, or a low n-6 (L6) one. Clinical outcomes were tracked by a headache diary (HIT-6) during both phases of the study. Biochemical outcomes included assessments of bioactive n-3 and n-6 derivatives and erythrocyte n-6 in highly unsaturated fatty acids (HUFA) score. Results showed that both groups achieved targeted intakes of n-3 and n-6 fatty acids, but the H3-L6 intervention produced a significantly greater improvement in the HIT-6 score, number of headache days/month and number of headache hours/day.

In contrast to the negative results noted with supplementation of n-3 fatty acids alone, the authors conjecture that while n-3 ingestion is known to increase circulating EPA + DHA and to reduce AA and bioactive AA derivatives, the dietary n-6 lowering component may be necessary to produce maximal clinical benefit. By lowering n-6 fatty acids, n-3 fatty acids have less competition for hepatic desaturation and are thus more readily incorporated into tissue and converted to bioactive derivatives [60].

Ginkgolide B—Level U Evidence

Ginkgolide B, extracted from *ginkgo biloba* tree leaves, is a natural modulator of the action of glutamate in the CNS. Glutamate plays a role in initiating and propagating spreading depression seen in MA, through stimulation of glutamate receptors linked to NMDA channels [63]. It also is a potent inhibitor of platelet-activating factor (PAF), which is pro-inflammatory and nociceptive. Thus there has been interest in the use of Ginkgo for treatment of MA [63].

None of the existing clinical trials examining the use of Ginkgolide B for migraine are placebo controlled, and all utilize a combination product, Migrasoll (Pharmaval Srl) which contains Ginkgolide B 80 mg, CoQ10 20 mg, vitamin B_2 1.6 mg, and magnesium 300 mg. When administered twice daily for four months to 50 women suffering from MA, decreased frequency and duration of attacks was noted [63]. Similar results were produced in a more recent study of both men and women, and further substantiated in a larger group (n = 119) of pediatric migraine patients [64, 65]. While none of the studies found serious side effects, gingko should be used with caution in patients on blood thinners, as spontaneous bleeding is potentially a concern, though a meta-analysis of patients on ginkgo did not note any increase in bleeding potential over placebo [66].

Phytoestrogens—Level U Evidence

Phytoestrogens found in soy, such as genistein and daidzein have been reported to be helpful with menopausal symptoms. They are heterocyclic phenols and are structurally related to estradiol-17-beta and selective estrogen receptor modulators (SERMS). They exhibit weak mixed agonist/antagonist SERM activity. Black cohosh (*Cimicifuga racemosa*) is derived from the roots of a perennial plant from the buttercup family and has been found to contain several compounds with estrogen receptor activity similar to soy isoflavones. Dong quai (*Angelica polymorpha*) is a member of the plant family that includes parsley, celery, and carrots. Dong quai has been used for centuries in traditional Chinese, Korean, and Japanese medicine for relief of menopausal symptoms. Animal studies have shown it to have effects similar to estrogen [67].

In a group of 49 patients with MM, subjects were randomized to receive either placebo, or 60 mg soy isoflavones 100 mg dong quai, and 50 mg black cohosh daily for 24 weeks. Each component was standardized to its primary alkaloid. Average frequency of migraine attacks was reduced from 10.3 in placebo-treated patients to 4.7 ($P < 0.01$) in the treatment group. Migraine severity was also significantly diminished. The effect began after one month of treatment [67].

Cannabis—Level U Evidence

Cannabis is composed of more than 400 compounds, 60 of which are naturally occurring cannabinoids (CBs). These include psychoactive Δ^9-tetrahydrocannabinol (THC), and cannabidiol (CBD). The latter makes up 40% of the plant's extract and is one of the primary constituents of medical marijuana [68]. CBs have serotonergic, dopaminergic, and anti-inflammatory effects. They stimulate the endocannabinoid system found throughout the body comprised of specific cannabinoid receptors and endogenous cannabinoids. This system includes cannabinoid 1 (CB1) and 2 (CB2) receptors, and cannabinoid ligands such as Anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

One of the most documented uses of medicinal marijuana is in the treatment of chronic pain, and it has long been argued that cannabis is ideally suited for use in treatment of migraine [69]. CBs are active through CB1 receptors in various areas of the brain and brainstem involved with migraine pathophysiology including the trigeminal nucleus and ganglia [70]. When these receptors are activated they can inhibit dural trigeminovascular nociceptive responses [68]. THC inhibits serotonin release from platelets during migraine, stimulates 5-HT synthesis, and modulates dopamine production [71]. The endocannabinoid AEA modulates pain signaling in the central nervous system in various ways by inhibiting dural blood vessel dilation and via indirect effects on NMDA, opiate, and γ-aminobutyric acid (GABA) receptors [71].

There are five case reports in the literature of patients who used illicit marijuana products for treatment of their vascular or migraine headaches and who experienced an overall decrease in migraine headache [72]. There is also one retrospective observational chart review of patients treated at a medical marijuana clinic. Of 121 patients with a primary diagnosis of migraine, 85% reported decreased headache frequency with the use of medical marijuana. Most patients used more than one form of marijuana and used it daily for prevention and acute treatment. Formulations included vaporized, topical, edible, and smoked. Approximately one half of patients used prescribed migraine medications concomitantly. Somnolence was the most common side effect. Unfortunately, there were no standardized methods of evaluating efficacy since the treatment responses were based upon the medical record and subjective reports [68].

As medical marijuana becomes more readily available it is possible that we will see further research that supports or refutes its use in the treatment of migraine.

Niacin-Level U Evidence

When taken intravenously or orally, niacin produces cutaneous flushing that might produce intracranial vasodilation and prevent the vasoconstriction associated with MA. The scientific evidence is stronger for niacin's peripheral vasodilatory effects, and the central mechanisms of niacin in acute MA remain unclear. Prophylactically, niacin helps maintain mitochondrial energy metabolism by increasing substrate availability to complex I [73]. While the literature suggests oral, sustained release (SR) or IV niacin could be helpful for prevention and acute treatment, all of the existing trials are small case series and none have placebo controls [73, 74].

Diet and Exercise

Diet–Level U Evidence

Food allergies, metabolic abnormalities and specific "trigger" foods such as chocolate, red wine, cheese, and processed meats have been examined for their potential to precipitate migraine. Some commonly reported food and chemical triggers are included in Table 11.3. Overall, there are no studies that clearly show an unequivocal relationship between specific dietary intake and migraine [75]. Caffeine, while utilized in a number of migraine medications, has been suspected as causing headaches in both adults and children with overuse (>200 mg/d). It is generally recommended to keep consumption less than this level, and not to stop abruptly as withdrawal has been clearly shown to precipitate headaches, and is potentially also a precipitant of migraine [76]. Low fat, vegan, and elimination diets

Table 11.3 Potential trigger foods [76]

Food or chemical	Present in	Strength of evidence	Possible mechanism
Aspartame	Sugar substituted foods	Moderate	Increased phenylalanine.
Caffeine/theobromine consumption	Coffee, tea, chocolate, colas	Moderate	Modulation of noradrenergic and nocioceptive pathways. Enhanced sympathetic tone, serotonin and dopamine.
Caffeine withdrawal		Strong	Increased blood flow in posterior cerebellar and basilar artery.
Chocolate		Weak	Based on components phenylethylamine, theobromine and caffeine.
Histamine	Cheese, fish, sausage, vegetables, and alcoholic beverages	Moderate	NO_2 release.
MSG	Frozen, canned or dried foods, processed meats, international and snack foods, tomato or barbecue sauces	Moderate	Vasoconstriction. NMDA receptor agonist. Release of NO_2.
Nitrates	Cured meats, cabbage, carrots, celery, lettuce, radishes, beets, spinach	Moderate	NO_2 release.
Polyphenols	Red wine, some vegetables and spices	Weak	Serotonin release.
Phenylethylamine	Chocolate, some mood and weight loss supplements	Weak	Alterations in cerebral blood flow. Release of norepinephrine.
Sulfites	Beer, wine, vinegar, dried fruit, grape juice	Weak	Release of histamine. Production of sulfur dioxide causing irritation of cholinergic neurons.
Tyramine	Cheese, wine, beer, preserved fish and meats, sauerkraut, yeasts	Weak	Release of norepinephrine. Dopamine synthesis.
Wine		Moderate	Based on components: tyramine, sulfites, histamine, polyphenols.

Table 11.4 Elimination diet as per Bunner 2014 [77]

	Avoid these foods	Favor these foods
Grains	Wheat, rye, barley, corn	Oats, rice, quinoa, buckwheat, amaranth, sorghum, millet, teff
Fruits	Citrus, bananas, apples	Pears, apricots, blueberries, plums
Vegetables	Night shades (tomatoes, eggplant, peppers, potatoes), onions, garlic, sweet potatoes, yams, celery	Artichokes, asparagus, broccoli, cauliflower, brussel sprouts, cabbage, bok choy, carrots, chard, kale, collard and mustard greens, spinach, lettuce, zucchini
Legumes	Soybeans, chickpeas, peanuts	Lentils
Other	Animal products, nuts, seeds, chocolate, sugar, coffee, tea, alcohol	Olive oil, vanilla extract, brown rice syrup, maple syrup, salt

have been associated with improvement in headache pain [77–80]. An elimination diet used by Bunner et al. is outlined in Table 11.4 [77].

There is good data to suggest that for some patients, fasting can precipitate an attack [81]. There are many potential mechanisms for this, including alterations in levels of serotonin and norepinephrine, release of stress hormones that could induce headache; induction of hypoglycemia and withdrawal of caffeine or nicotine. It is suggested that all migraineurs avoid prolonged periods of fasting [76].

In a population-based retrospective of a 326 migraine-patient database, no dietary factors were identified as causing an increase in risk of migraine attacks. However, when the same database was examined at the individual level, dietary factors were significantly associated with attacks in some patients although individual dietary triggers were seen in less than 10% of patients [82, 83]. Overall, the data suggests that although many foods and substances are often cited as headache triggers by patients, not all of the foods will trigger a migraine in any one individual.

These findings are not surprising. Specific dietary triggers first need to be absorbed through the GI tract, undergo appropriate degradation in order to enter the vascular space, and cross the blood–brain barrier to be able to access appropriate cerebrovascular or neuronal receptors and have an effect. The trigger must be of sufficient quantity and have appropriate affinity for the receptor. Other cofactors may be required for the trigger to precipitate migraine, or multiple triggers may need to be present. Any of these dynamics could vary from person to person and from exposure to exposure [76, 78]. Therefore dietary approaches must be specifically individualized for the patient.

Multiple studies show a relationship between migraine and obesity. The reasons for this are not well understood, but one possible explanation is shared inflammatory processes. It is possible that obesity promotes a low-grade chronic inflammatory state, which may exacerbate the already existent neurovascular inflammatory response in migraine. There could also be common behavioral risk factors that promote further inflammation, one being poor dietary habits [75]. In addition, obesity has also been linked to sleep apnea, snoring, and insulin resistance, which are also associated with migraine [84].

Exercise–Level B Evidence

The exact mechanism by which exercise affects headache is unclear, although various hypotheses have been suggested. These include improved cardiovascular, cerebrovascular, and psychological states, as well as neurochemical changes such as sustained higher serotonin levels, and activation of endogenous endorphins, opioids, and cannabinoids. Both hyper and hypo-functioning of the sympathetic and parasympathetic nervous systems have been reported as well as improved responses to stress, anxiety, and depression [85, 86].

There have been recent randomized trials that provide level 1 evidence that exercise can help prevent migraine occurrence. Most existing studies utilize aerobic exercise performed at the submaximal level (50–85% VO_2 max or 50–85% of maximal heart rate or 11–16 on the Borg Ratio Scale of perceived exertion) for the purpose of cardiorespiratory fitness [86]. Reasons for choosing this form of exercise include less risk of precipitating cardiovascular events and exercise induced migraine. Warm up and cool down should be incorporated for similar reasons [87]. This level of activity also coincides with the American College of Sports Medicine recommendations for regular aerobic exercise, and would be appropriate at the lower levels for more unfit patients. In a cross-sectional study of medical students with migraine, there was no difference between aerobic exercise and strength training with regards to impact on migraine [86, 88], Kiko exercises, similar to Chinese Qi Gong, have also shown efficacy [86].

Neck pain is a common accompaniment of migraines, and is reported more frequently than nausea [89]. Isometric neck strengthening exercises can be useful in these cases, as they eliminate muscle spasm and strengthen the musculature. Mauskopf recommended a simple exercise repeated 10–15 times throughout the day for 2 weeks for improvement. See Table 11.5 for an outline of recommended exercises [90].

Manual Therapy

Manual therapy is a broad category of alternative medicine that includes acupuncture, chiropractic therapy, physiotherapy, massage, and trigger point injections and release. It may also involve correction of posture, stretching,

Table 11.5 Neck exercises [90]

1	Place hand on one side of head
2	Keep head stationary and in a neutral position
3	Apply sustained pressure for 10–15 s
4	Repeat on the other side of head, forehead and then occiput
5	Do this exercise 10–15 times daily for 2 weeks

mobilization, and manipulation techniques. Given the frequency with which these therapies are used, the AAN published a guideline incorporating a robust review of the literature regarding the use and efficacy of non-pharmacologic therapy, although it has not been updated since 2000 [10]. According to the AAN, patients who may benefit the most from behavioral treatments include those who have a preference for non-pharmacologic treatments; have an intolerance or medical contraindication to pharmacologic treatments; have had minimal or no response to pharmacologic treatments; are pregnant or nursing; have used or are currently using analgesics or other medications that may aggravate headache or reduce the effectiveness of headache medications; have life stressors or have inadequate coping mechanisms for stress. In addition to the AAN, various other reviews that have been conducted on these treatments in more recent years have provided a substantial body of literature supporting the use of non-pharmacologic therapy in migraine prophylaxis.

Acupuncture—Level A Evidence

Among the multiple forms of manual therapy, acupuncture is very frequently cited in the treatment of migraine. It typically involves insertion of thin needles into specific points in the body, known as meridians. Acupuncture has been shown to be effective for various types of pain relief, including headache and osteoarthritis, according to several Cochrane reviews [91–95].

The most recent Cochrane review studying the use of acupuncture in migraine prophylaxis was published in 2009 [93]. This review included 22 trials and showed that acupuncture is at least as effective as prophylactic pharmacologic treatment. Interestingly, the 14 trials that compared "true" acupuncture with sham interventions showed no significant difference in efficacy. A systematic review of studies on the effectiveness of placebos in migraine prophylaxis has even shown that compared to their respective interventions, sham acupuncture was associated with higher responder rates compared to responder rates for oral pharmacological placebos [96].

As such, it is still unclear how acupuncture alleviates migraine symptoms. In a study comparing 12 patients with MO and 12 control patients without migraines, acupuncture was associated with normalizing effects on functional MRI (fMRI) [97]. Patients with migraines had fMRIs completed both before and after they received 4 weeks of acupuncture treatment. Pretreatment fMRIs showed that functional connectivity in the right frontoparietal network, the left precentral gyrus, the left supramarginal gyrus, the left inferior parietal lobule, and the left postcentral gyrus was significantly decreased compared to the fMRIs of control patients.

In an era in which the price of health care is under great scrutiny and debate, exploration of cost effective non-pharmacological interventions is even more relevant. In fact, a study of 401 patients with chronic headache, primarily migraine, in England and Wales showed that acupuncture was a cost-effective treatment [98]. While multiple studies comparing acupuncture with pharmacologic therapy have not systematically shown that acupuncture was more effective in decreasing such

measures as frequency of migraine attacks and pain intensity, they have found that acupuncture is equally as effective as pharmacologic therapy with fewer side effects and complications, and higher compliance rates [99–102].

Chiropractic Therapies and Massage—Level C Evidence

Chiropractic therapies, including spinal manipulation, have also been used widely for the treatment of various disorders and very commonly for pain. Chiropractic spinal manipulation is a treatment utilizing high-velocity, low-amplitude movements directed at a specific joint. Several studies on chiropractic spinal manipulation showed improvement in migraine patients based on migraine attack duration, migraine frequency, and use of rescue medications [103–105]. However, some studies did not have adequate control groups. Likewise, studies on the use of massage therapy showed significant improvement after treatment compared to controls but had low sample size and lacked data such as duration of migraines [106, 107].

Trigger Point Injections and Release—Level C Evidence

Headaches have also been associated with trigger points, which are areas of sustained muscular contractions causing pain [108]. Various methods have been utilized to release these muscular contractions and alleviate pain, including massage, injections of local anesthetic such as ropivacaine, and greater occipital nerve blocks using local anesthetic with or without corticosteroids. While studies have shown these therapies to be useful in tension-type headache, there is less evidence in the literature supporting their use in migraines. There has been one recent prospective study of trigger point injection showing up to 59% improvement in migraine [109]. However, RCTs are lacking. Furthermore, multiple RCTs of greater occipital nerve block have had conflicting results regarding the efficacy of this therapy in migraine headache [110, 111]. Given that this therapy is often used for headache disorders, more research into its efficacy would provide further insight into its use.

Mind/Body Techniques

Relaxation Training—Level A Evidence

A review of the literature published in 2007 found multiple studies to support the use of mind–body therapies, including relaxation, to be efficacious for migraine treatment [112]. In addition, the AAN found 10 trials comparing relaxation techniques, principally including progressive muscle relaxation, autogenic training, and

meditation or passive relaxation [10]. Averaging the results of these studies showed a 32% improvement in headache index or frequency of headaches.

Biofeedback—Level A Evidence

Biofeedback is also a commonly used therapy for migraine and provides methods by which a patient receives physiologic data in order to consciously control a function or symptoms that are typically automatically regulated. The most common biofeedback therapies used for migraine are thermal feedback, blood-volume-pulse feedback, and electromyographic feedback. Based on the review by the AAN, effective non-pharmacologic treatments recommended for migraine prevention include relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy [10]. Multiple subsequent reviews have found that biofeedback was an efficacious treatment option for migraine prophylaxis [113, 114].

Cognitive-Behavioral Therapy (CBT)—Level A Evidence

CBT, or stress-management therapy, is also used in migraine management. In the analysis performed by the AAN, an average of the results of 5 trials found that CBT had an average effect size of 0.54 [10]. Additionally, there has been one RCT on hypnotherapy [115]. Migraine frequency was significantly lower in the group receiving hypnotherapy, but this study had a small sample size of 47 patients and compared hypnotherapy to prochlorperazine, a drug infrequently used today. No confirmatory studies of hypnotherapy have been conducted since.

Other Modalities

Hyperbaric Oxygen Therapy—Level C Evidence

A less commonly used non-pharmacological therapy used for migraine treatment is hyperbaric oxygen therapy. Mechanisms for this treatment option include vasoconstriction and facilitating certain metabolic reactions in the brain that require oxygen. A Cochrane review recently included 3 trials with a total of 58 patients comparing hyperbaric oxygen therapy to sham for acute migraine [116]. This study showed that hyperbaric oxygen therapy was effective in relieving migraine headaches in the acute period but had no effect in preventing further attacks or for reducing the need for rescue medication. Furthermore, the level of evidence was low with missing data and small crossover studies. Although there was some

evidence for the effectiveness of hyperbaric oxygen therapy, further studies are needed, especially as it is costly and not widely available.

Summary

The widespread incidence of migraine headache has led to a plethora of potential therapies for relief from acute symptoms and for prevention. Allopathic medical management consists of conventional medications and control of concomitant illnesses. For many patients this does not decrease the burden of disease. A treatment plan that incorporates evidence based alternative therapies within an integrative framework can offer relief not found with conventional treatments alone.

Recommendations

The importance of performing a good medical history and physical exam cannot be overemphasized. Specific attention should be paid to circumstances surrounding occurrence of headaches, including frequency, triggers, related stress, and musculoskeletal factors. Success or failure of previous treatments should be taken into account. It may be necessary to screen for specific nutrient abnormalities such as magnesium, B12, and homocysteine, and to consider genetic typing for mitochondrial DNA and single nucleotide polymorphisms. The therapeutic approach to migraine needs to be individualized to each patient's needs.

Acupuncture, exercise, relaxation training, biofeedback and cognitive-behavioral therapy offer patients alternatives to conventional treatments and have good evidence of efficacy with a low profile of side effects. Consider supplementing with magnesium, MIG-99, riboflavin, or CoQ10, or minimally increasing their dietary sources, along with B6, 9, 12 and possibly n-3 FAs and ALA. Including a vegetarian diet low in n-6 FA's and avoiding identified patient-specific trigger foods can be useful for some. If a patient is peri or post menopausal, phytoestrogens might be helpful. If there is a nocturnal predilection for headache, melatonin or melatonin-rich nutraceuticals should be considered. In subjects who have a musculoskeletal component to their pain, perhaps refer for a trial of massage, trigger point therapy, and possible chiropractic intervention. Patients should be encouraged to incorporate neck exercises if neck pain is a commonly encountered symptom or prodrome.

If all treatment options have been exhausted, use of Petadolex or hyperbaric oxygen therapy should be discussed in detail with patients, as both have good evidence of efficacy. Patients should be guided through the risk benefit analysis of the use of these or any other integrative therapies chosen. Carefully monitoring patients through any elected treatment is prudent and will lead to the best patient care with the least untoward effects. When in doubt, consult reputable individuals in your area who have advanced training in integrative medicine, or in the specific therapies chosen.

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