Foods and Supplements in the Management of Migraine Headaches

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Objective: Although a wide range of acute and preventative medications are now available for the treatment of migraine headaches, many patients will not have a significant improvement in the frequency and severity of their headaches unless lifestyle modifications are made. Also, given the myriad side effects of traditional prescription medications, there is an increasing demand for "natural" treatment like vitamins and supplements for common ailments such as headaches. Here, we discuss the role of food triggers in the management of migraines, and review the evidence for supplements in migraine treatment.

Methods: A review of the English language literature on preclinical and clinical studies of any type on food triggers, vitamins, supplements, and migraine headaches was conducted.

Results: A detailed nutritional history is helpful in identifying food triggers. Although the data surrounding the role of certain foods and substances in triggering headaches is controversial, certain subsets of patients may be sensitive to phenylethylamine, tyramine, aspartame, monosodium glutamate, nitrates, nitrites, alcohol, and caffeine. The available evidence for the efficacy of certain vitamins and supplements in preventing migraines supports the use of these agents in the migraine treatment.

Conclusions: The identification of food triggers, with the help of food diaries, is an inexpensive way to reduce migraine headaches. We also recommend the use of the following supplements in the preventative treatment of migraines, in decreasing order of preference: magnesium, Petasites hybridus, feverfew, coenzyme Q10, riboflavin, and alpha lipoic acid.

Key Words: migraine, food triggers, magnesium, feverfew, butterbur, riboflavin, coenzyme Q10, alpha lipoic acid, alternative treatment

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Migraine is a common and disabling disorder that affects over 28 million Americans.[1] Although a wide range of acute and preventative medications are now available for the treatment of headaches, most patients will not have a significant improvement in the frequency and severity of their headaches unless lifestyle modifications are made. These include sleep hygiene, stress management, regular aerobic exercise, and dietary modification. Unfortunately, these lifestyle recommendations are frequently overlooked by physicians. In this review the role of food and nutrients in the treatment and prevention of migraine headaches will be discussed.

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SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified by searches of PubMed from 1966 to February 2008 with the terms "migraine," "food trigger," "alternative treatment," "magnesium," "coenzyme Q10 (CoQ10)," "riboflavin," "feverfew," "alpha lipoic acid," and "butterbur." Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

EPIDEMIOLOGY

Migraine affects 18% of women and 6% of men in the United States,[2] and has an estimated worldwide prevalence of about 10%.[3] For both men and women, the prevalence of migraine rises throughout early adult life and falls after midlife. In girls and women, the rate almost triples between age 10 and 30 years.

Population-based studies have reported that migraine is inherited, with a relative risk of migraine headache in a first-degree family member ranging from 1.4 to 1.9 when the proband has migraine without aura.[4,5] In monozygotic twins the concordance rates for migraine range from 37% to 52%, and 15% to 21% for dizygotic twins.[6,7] These figures indicate that both genetic and environmental factors play a significant role in the migraine.

PATHOPHYSIOLOGY

Although the understanding of migraine pathophysiology has increased dramatically in recent years, the exact etiology remains to be defined. The current prevailing theory is based on a hyperexcitable "trigeminovascular complex" in patients who are genetically predisposed to migraine. In these people, there is a lowered threshold for migraine attacks and a vulnerability to environmental triggers. In susceptible individuals, the trigeminovascular neurons release neurotransmitters, such as calcitonin gene-related peptide and substance P, when headache triggers are encountered. This leads to vasodilation, mast cell degranuation, increased vascular permeability and meningeal edema, resulting in neurogenic inflammation. This nociceptive information is transmitted from the trigeminal nerve to brainstem nuclei, thalamic nuclei, and the cortex, where migraine pain is ultimately perceived.[8] The locus coeruleus, dorsal raphe, and the periaqueductal gray also play modulatory roles in the transmission of pain.[9]

Mitochondrial dysfunction, which leads to impaired oxygen metabolism, has been speculated to play a role in migraine pathophysiology,[10–12] as migraineurs have been shown to have a reduction in mitochondrial phosphorylation potential in between headaches.[13,14] This is the basis

for the use of supplements that enhance mitochondrial function in the treatment of migraine, such as riboflavin, CoQ10, and alpha lipoic acid.

THE ROLE OF FOODS AND SUPPLEMENTS IN MIGRAINE

The importance of eating regularly cannot be overemphasized, as skipping meals can trigger headaches.[15] Skipped meals and fasting were reported migraine triggers in over 56% in a population-based study[16] and 40% to 57% in subspecialty clinic-based studies.[17–19] The mechanism by which fasting and skipping meals triggers headaches may be related to alterations in serotonin and norepinephrine in brainstem pathways,[20] or the release of stress hormones such as cortisol. Hypoglycemia could potentially bring on a headache.[9] In one study[21] 3 quarters of participants with migraine headaches demonstrated 5-hour glucose tolerance tests consistent with reactive hypoglycemia.

Although migraine triggers as a whole can act at central or peripheral sites to precipitate an attack, most food and beverage triggers likely act peripherally at the level of the dural blood vessel or the peripheral trigeminal nerve, as many dietary trigger components cannot cross an intact blood-brain barrier.[9] Caffeine (see below) is one notable exception. Furthermore, the vascular space is the initial site of exposure for dietary triggers.

Food Triggers

The recognition of dietary migraine triggers is important because it helps not only in reducing the frequency of migraine, but also in giving migraineurs a sense of control over a condition that can render them helpless and debilitated.[9] Two subspecialty clinic-based studies,[18,22] in which participants were asked to report their dietary triggers and rate their level of certainty that the food was a migraine trigger, have shed some light on the prevalence of dietary triggers. Reported dietary triggers included alcohol (29% to 35%), chocolate (19% to 22%), cheese (9% to 18%), caffeine (14%), and monosodium glutamate (MSG) (12%).

Although the foods and substances discussed below are often cited by patients as headache triggers, not all of the foods will trigger a migraine in any one individual. Therefore, migraineurs need not avoid all the potential triggers described below if there is clearly no relationship between their headaches and those substances. Headaches are generally triggered by a combination of substances, during a time of particular vulnerability (eg, menses, stress, sleep deprivation). Food diaries can be helpful in sorting out which ones are problematic for each patient, but this is complicated by the fact that food triggers are not always consistent. Furthermore, headaches triggered by certain foods can occur 24 hours after trigger exposure, making it difficult to pinpoint the offending substance.[9] Nonetheless, keeping a detailed food and headache diary over the course of several months may be useful in detecting relationships between certain foods and headaches. Although the data regarding the role of all the following substances in triggering headaches is controversial (with the exception of alcohol and caffeine), the evidence suggests that subsets of migraineurs may be susceptible to these potential triggers.[9]

Phenylethylamine

Phenylethylamine is a substance found in cacao. In migraineurs, especially those who have reduced monoamine oxidase B activity, phenylethylamine causes the release of vasoactive amines such as serotonin and catecholamine.[23] Although migraine patients commonly cite chocolate as a migraine trigger, the role of phenylethylamine remains inconclusive. Furthermore, in patients with headaches triggered by chocolate, caffeine (see below) may be the offending component.

Tyramine

Tyramine is an amine derived from the amino acid tyrosine, and is found in aged cheese, cured meats, smoked fish, beer, fermented food and yeast extract, among other foods. Tyramine's primary effect is the release of norepinephrine from sympathetic nerve terminals and thus it may trigger headaches by means of the release of norepinephrine and its agonist effect on α-adrenergic receptors.[9] The relationship between tyramine and headache was initially observed when patients on monoamine oxidase inhibitors developed headaches and hypertensive crises after eating aged cheese, which has a high tyramine content.[24]

Aspartame

Aspartame is an artificial sweetener (NutraSweet) that is 180 to 200 times sweeter than sugar.[23] Since its introduction in 1981, there have been many reports of neurologic or behavioral symptoms, especially headache, attributed to its use.[25] Although some studies[26,27] found that aspartame did not cause more headaches than placebo, other evidence suggests that aspartame may be a headache trigger in people who ingest moderate to high doses (900 to 3000 mg/d) over a prolonged period of time.[28,29]

Sucralose is the active component of another common artificial sweetener (Splenda). Although it was not initially considered to be a migraine trigger, some case reports[30–32] have suggested otherwise.

MSG

MSG is a flavor enhancer that is widely used in Chinese food. It is also used in meat tenderizer (Accent) and many canned, prepared, and packaged foods under the guise of various descriptions including "hydrolyzed vegetable protein," "autolyzed yeast," "sodium caseinate," "yeast extract," "hydrolyzed oat flour," "texturized protein," or "calcium casinate." The pathophysiologic mechanism by which MSG might trigger headaches may involve a direct vasoconstrictor effect at high doses,[33] activity as an agonist of stimulatory glutamate receptors[9] or the activation of a neurotransmission pathway in which nitric oxide is released in endothelial cells, ultimately inducing vasodilation.[34]

Nitrates and Nitrites

Sodium nitrite is a preservative that is used for food coloring, prevention of botulism, and to add a cured or smoked flavor. After eating foods with nitrites, such as sausages or other cured meats and fish, some people develop headaches within minutes to hours.[35] This effect is probably due to the release of nitric oxide and subsequent vasodilation,[9,36] though the interaction of nitrites with blood pigment to produce methemoglobinemia may also play a role.[37] Patients who seem to be sensitive to these

substances should avoid foods with sodium nitrite, sodium nitrate, potassium nitrite, or potassium nitrate.

Alcohol

Alcohol, in particular red wine, is frequently cited as a migraine trigger. It can have an immediate (within 3 h) or delayed (hangover) effect. Some patients even report that alcohol can trigger a headache within minutes. Whether red wine is more likely than white wine to trigger headaches is controversial.[38–40] Wine contains tyramine, sulfites, histamine, and the phenolic flavonoids, all of which can theoretically precipitate migraines.[9,41,42]

Alcohol hangover headache (AHH) is a common occurrence that generally occurs after the ingestion of large amounts of alcohol. In addition to headache, AHH comprises a constellation of symptoms including anorexia, tremulousness, dizziness, nausea, tachycardia, irritability, and depressed concentration.[43] The headache usually occurs the morning after alcohol consumption, when the blood alcohol concentration is falling[44] and can continue for 24 hours after the blood alcohol concentration reaches zero. AHH is not always dose-related and in fact occurs more commonly in light or moderate drinkers than regular heavy drinkers.[45,46]

Darker colored alcoholic beverages, such as red wine, whiskey, and bourbon, contain congeners, which are the natural byproducts of alcohol fermentation.[47] These drinks are more likely to induce AHH as compared with clear alcoholic beverages such as gin or vodka. The exact mechanism by which AHH occurs is unknown, but may involve a vasodilatory effect on the intracranial vasculature, alteration of sleep patterns, or an inflammatory mechanism through an alteration of cytokine pathways and prostaglandin release.[48–50] Magnesium depletion is known to be caused by alcohol and is a possible cause of this headache.

Patients who are prone to AHH should drink in moderation, and stay well hydrated. Anecdotal information suggests that eating fatty food before alcohol consumption may help to slow or delay alcohol absorption, and consuming foods rich in fructose (ie, honey, tomato juice) may allow for more effective alcohol metabolism. Certain nonsteroidal anti-inflammatory drugs, in particular, the anthranilic acids (such as mefenamic acid) may also be effective in the treatment of AHH.[43]

Caffeine

Caffeine is a common dietary substance found in coffee, tea, soda, and chocolate. It is also included in various prescription (Fioricet, Fiorinal, Esgic) and over-the-counter headache medications (Excedrin, Anacin). Caffeine works by means of the blockade of inhibitory and excitatory adenosine receptors in the brain and vasculature, resulting in vasoconstriction and the release of excitatory neurotransmitters. Some of the involved pathways are important in the modulation of pain perception.[51,52]

Caffeine's effect on the central nervous system varies with the dose and frequency of use. In general, one serving of brewed coffee has 115 mg caffeine, whereas a serving of Pepsi has 38 mg. Excedrin contains 65 mg caffeine per tablet. At low-to-moderate doses (50 to 300 mg), caffeine causes increased alertness, concentration, and energy. At doses greater than 300 mg anxiety, restlessness, insomnia, and irritability can occur.[9,53]

Caffeine's effect on headaches is paradoxical in that it can serve to either worsen or alleviate headaches, depending on dosage and frequency. When used infrequently, caffeine is effective in the treatment of headaches because it has a mild analgesic effect and also assists in the absorption of other analgesics. It also crosses the blood-brain barrier quickly. These characteristics make caffeine a useful component of combination analgesics. High doses (> 300 mg/d) consumed on a regular basis are associated with headache. Regular use of caffeine-containing analgesics is associated with medication-overuse headaches (formerly referred to as "rebound headaches").[54–57]

Headaches also occur with abrupt withdrawal of caffeine, usually in people who regularly consume at least 200 mg daily. The higher the level of baseline caffeine ingestion, the greater the likelihood of caffeine withdrawal headache, although headaches can occur even when patients consuming 100 mg caffeine daily stop abruptly.[58] Caffeine withdrawal is also associated with depression, drowsiness, and impaired concentration.

Patients with headaches who wish to continue drinking caffeinated beverages should limit their daily intake to less than 200 mg. Patients who use caffeine-containing analgesics should limit intake to 2 d/wk to avoid medication-overuse headache. Those who wish to cease caffeine consumption should gradually taper their intake over several weeks.[9]

Vitamins and Other Supplements in the Prevention of Migraine

Magnesium

Magnesium is an essential cation that plays a vital role in multiple physiologic processes. Deficits in magnesium can be seen in any chronic medical illness, including cardiovascular disease, diabetes, preeclampsia, eclampsia, sickle cell disease, and chronic alcoholism.[59] Symptoms of magnesium deficiency include premenstrual syndrome, leg muscle cramps, coldness of extremities, weakness, anorexia, nausea, digestive disorders, lack of coordination, and confusion. Magnesium may be involved in migraine pathogenesis by counteracting vasospasm, inhibiting platelet aggregation, and the stabilization of cell membranes.[60] Its concentration influences serotonin receptors, nitric oxide synthesis and release, inflammatory mediators, and various other migraine-related receptors and neurotransmitters.[61] Magnesium also plays a role in the control of vascular tone and reactivity to endogenous hormones and neurotransmitters, through its relationship with the NMDA receptor.[62]

Studies have shown that migraineurs have low brain magnesium during migraine attacks[63] and may also have a systemic magnesium deficiency.[64,65] Furthermore, a deficiency of magnesium may play a particularly important role in menstrual migraine.[66] Two double-blind, placebo-controlled trials have shown that oral magnesium supplementation is effective in headache prevention.[67,68] A third study[69] was negative, but this result has been attributed to the use of a poorly absorbed magnesium salt, as diarrhea occurred in almost half of patients in the treatment group. Intravenous magnesium has been shown to be an effective migraine abortive agent in patients with low ionized magnesium levels, but not in those with normal levels.[70] The most commonly reported adverse effect of magnesium supplementation is diarrhea.

Riboflavin

Riboflavin, also known as vitamin B2, is a precursor for flavin mononucleotides that are cofactors in the Krebs cycle. It is essential for membrane stability and the maintenance of energy-related cellular functions.[71] There has been one well-designed randomized controlled trials evaluating the use of riboflavin as a migraine prophylactic agent. Daily use of 400 mg riboflavin for 3 months resulted in a 50% reduction in attacks in 59% of patients, as compared with 15% for placebo. Two minor adverse reactions, diarrhea and polyuria, were reported in the treatment group.[72]

CoQ10

CoQ10 is an endogenous enzyme cofactor made by all cells in the body, functioning to promote mitochondrial proton-electron translocation. In an open label study[73] in which 31 patients with migraine used 150 mg daily of CoQ10 for 3 months, 61% had at least a 50% reduction in migraine days without significant adverse events. Supplementation was effective within the first month of therapy. Later, a small randomized controlled trial[74] was conducted in which the treatment group received 100 mg of CoQ10 3 times daily. Although a soluble form of CoQ10 that is not currently available in the United States was used in the study, results showed that CoQ10 significantly decreased attack frequency, headache days, and days with nausea. Gastrointestinal disturbances and "cutaneous allergy" were reported, but at a low rate.

CoQ10 supplementation may be particularly effective in the treatment of pediatric migraine. CoQ10 levels were measured in a study[75] of 1550 patients (mean age 13.3 ± 3.5 y) with frequent headaches, and found to be below the reference range in 32.9%. Supplementation with 1 to 3 mg/kg/d of CoQ10 in liquid gel capsule formulation resulted in an improvement in total CoQ10 levels, headache frequency and degree of headache disability.

Alpha Lipoic Acid

Like riboflavin and CoQ10, alpha lipoic acid (also known as thioctic acid) enhances mitochondrial oxygen metabolism and ATP production.[76] Its use in migraine prevention has been evaluated in one open pilot study (unpublished data, discussed in Ref. 77) and one randomized placebo-controlled trial[77] to date. Fifty-four patients were recruited into the randomized, placebo-controlled study, in which participants received either 600 mg alpha lipoic acid or placebo daily for 3 months. Although there was a clear trend for reduction of migraine frequency after treatment with alpha lipoic acid, the result was not significant. This result was attributed to the fact that the study was underpowered. However, within-group analyses did show a significant reduction in attack frequency, headache days, and headache severity in the treatment group.

Herbal Preparations

Feverfew (Tanacetum Pathenium)

Feverfew is an herbal preparation that is available as the dried leaves of the weed plant tanacetum pathenium. It was used to treat headache, inflammation, and fever several centuries ago, and rediscovered in the late 20th century. The mechanism by which it works in migraine prophylaxis may be related to the parthenolides within the leaves. These may inhibit serotonin release from platelets and white blood cells, and inhibit platelet aggregation. Feverfew may also have anti-inflammatory action through the inhibition of prostaglandin synthesis and phospholipase A.[78–81]

Several randomized controlled studies have been conducted over the past decades with conflicting results,[82–87] including a meta-analysis[87] that did not recommend its use for headaches due to the paucity and low average quality of the existing randomized controlled trials on the subject. Inconsistencies in the results of those studies were probably related to wide variations in the strength of the active ingredient (parthenolide), and differences in the stability of feverfew preparations. Taking these differences into account, a new, more stable feverfew extract (MIG-99) was evaluated in a placebo-controlled trial involving 147 patients.[88] Although none of the doses were significant for the primary endpoint (number of migraine attacks in the last month of the 3-month study compared with baseline) relative to placebo, a subset of patients with high frequency of migraine attacks did seem to benefit. In a follow-up multicenter, double-blind, placebo-controlled study with 170 participants,[89] those investigators evaluated 6.25 mg 3 times a day of MIG-99 versus placebo, and reported a statistically significant and clinically relevant reduction in migraine frequency in the MIG-99 group compared with placebo. Side effects reported in clinical trials include gastrointestinal disturbances, mouth ulcers, and a "post-feverfew syndrome" of joint aches.

Butterbur (Petasites Hybridus)

In recent years, Petasites hybridus root extract, also known as butterbur, has emerged as a potential new treatment in the prevention of migraine. The butterbur plant is a perennial shrub that was used in ancient times for its medicinal properties. Petasites is thought to act through calcium channel regulation and inhibition of peptide-leukotriene biosynthesis. Leukotrienes and other inflammatory mediators may have a role in the inflammatory cascade associated with migraine.[90,91] Although the butterbur plant itself contains pyrrolizidine alkaloids which are hepatotoxic and carcinogenic, these compounds are removed in the commercially available preparations.

A randomized, double-blind, placebo-controlled trial[92] using 50 mg of butterbur twice daily, showed a significantly reduced number of migraine attacks and migraine days per month. Later, Lipton et al[93] compared Petasites extract 75 mg twice daily, Petasites extract 50 mg twice daily, and placebo twice daily in a 3-arm, parallel-group, randomized trial of 245 patients and found that the higher dose of Petasites extract was more effective than placebo in decreasing the number of monthly migraine attacks. A multicenter prospective open-label study[94] of butterbur in 109 children and adolescents with migraine resulted in 77% of all patients reporting a reduction in migraine frequency of at least 50%. In all 3 studies, butterbur was well tolerated and no serious adverse events occurred. The most frequently reported adverse reactions were mild gastrointestinal events, predominantly eructation (burping).

Other Supplements

Ginger has been used for its medicinal qualities in China for centuries, in the treatment of pain, inflammation, and musculoskeletal symptoms. It has anti-inflammatory qualities that could be related to the reduction of platelet

aggregation and the inhibition of prostaglandin and leukotriene biosynthesis.[95] There are anecdotal and folkloric descriptions of its efficacy in relieving headache and nausea.

Valerian root is a perennial herb that is used for its sedative and hypnotic qualities, especially in insomniacs. The effective dose for insomnia is 300 to 600 mg, which is equivalent to 2 to 3 g of dried herbal valerian root soaked in 1 cup of hot water.[96] In migraine patients with anxiety, it may be preferable to benzodiazepines as it is not associated with sleepiness on awakening. At doses higher than recommended, it is associated with headaches and muscle spasm.

Eicosapentaenoic acid (EPA), one of the body's natural omega-3 fatty acids, may also be useful in the prevention of headaches. Small studies[97] have suggested that headache severity and frequency can be reduced by adding EPA to the diet, possibly by lowering prostaglandin levels and serotonin activity. Omega-3 fatty acid supplementation has also been associated with a positive outcome in the treatment of mood disorders.[98] Although the FDA has not established a recommended daily allowance for EPA, a dose of 600 mg/d in 3 divided doses has been suggested for headache prevention.[99] Foods richest in EPA are fish that inhabit cold deep water, such as salmon, tuna, mackerel, and herring. EPA should not be taken in by diabetic patients or people at risk of stroke, nosebleeds, or bleeding disorders.

SPECIAL CONSIDERATIONS

Pregnancy and Lactation

Pregnancy and lactation are situations that also warrant special consideration in the treatment of the migraineur. Although migraines generally improve during pregnancy, headaches may worsen or remain the same in some women.[2] An increase in headaches during the first trimester is not uncommon, due to wide fluctuations in estrogen levels.

Women of reproductive age should be counseled about the relevant teratogenic risks of acute and preventative migraine medications. Owing to the limitations on pharmacologic treatment of migraine during pregnancy and lactation, nondrug approaches such as biofeedback, regular exercise, and lifestyle modification are emphasized in this population.[100] Food triggers should be identified through the use of food diaries and elimination diets, preferably before pregnancy. Maintaining hydration and electrolye balance is also crucial, especially for those in whom nausea and vomiting are prominent. These women should also avoid herbal remedies, including feverfew and butterbur, as they may be teratogenic.[100]

For patients who continue to have frequent headaches during pregnancy and lactation, magnesium supplementation is an option for both acute and preventative treatment. High-dose (4 to 6 g) intravenous magnesium sulfate is used for the prevention of recurrent seizures in eclamptic women, and also for seizure prophylaxis in women with hypertensive disorders of pregnancy.[101] For acute migraine treatment, the dose is much lower. One gram of magnesium sulfate in 10 mL normal saline given by slow push or dripped in slowly in a larger volume is used for both pregnant and nonpregnant patients. For preventative treatment, magnesium oxide, chelated magnesium, or slow release magnesium is recommended. Supplementation is unlikely to be associated with adverse effects,[102] and may even be effective in the prevention of premature labor and sudden infant death syndrome.[103]

TREATMENT RECOMMENDATIONS

Given the data discussed we recommend the following oral supplements, in decreasing order of preference.

- Magnesium: Chelated magnesium, magnesium oxide, and slow-release magnesium are likely to be the best absorbed. The daily dose is 400 mg. Diarrhea may be a limiting adverse effect in some patients.
- Petasites hybridus (Petadolex): 75 mg twice daily for 1 month, then 50 mg twice daily.
- Feverfew: 100 mg daily.
- CoQ10: 300 mg daily.
- Riboflavin (vitamin B2): 400 mg daily.
- Alpha lipoic acid: 600 mg daily.

To our knowledge, there are no significant interactions between these supplements and traditional pharmacologic treatments. Intravenous magnesium given within 1 week of menstruation, is an option for women with menstrual migraines who do not respond to oral supplementation. Patients with nonmenstrual migraines can also be given magnesium infusions on an as needed basis if they do not respond to oral magnesium or have gastrointestinal side effects from oral dosing.

CONCLUSIONS

Although a wide range of acute and preventative treatments for migraine are available, nutritional guidance plays an integral role in the care of the migraineur. In the evaluation of the migraine patient, a detailed nutritional history should be taken, with special attention to skipped meals, caffeine consumption, and the presence of perceived food triggers. Food diaries are essential in determining the relationship between certain foods and headaches. The identification of food triggers and the use of supplements are inexpensive ways in which the primary care physician or neurologist can break a cycle of frequent migraines. Although changing one's diet may require a great deal of motivation from the patient, the results are likely to be lasting and rewarding.

REFERENCES

1. Lipton RB, Diamond S, Reed ML, et al. Migraine diagnosis and treatment: results of the American Migraine Study II. *Headache*. 2001;41:638–645.
2. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41:646–657.
3. Sheffield RE. Migraine prevalence: a literature review. *Headache*. 1998;38:595–601.
4. Russel MB, Iselius L, Olesen J. Migraine without and migraine with aura are inherited disorders. *Cephalalgia*. 1997; 16:305–309.
5. Stewart WF, Staffa J, Lipton RB, et al. Familial risk of migraine: a population-based study. *Ann Neurol*. 1997;41: 166–172.
6. Larsson B, Billie B, Pedersen NL. Genetic influence in headache: a Swedish twin study. *Headache*. 1995;3:513–519.
7. Merikangas K, Tierney C, Martin N, et al. Genetics of migraine in the Australian twin registry. In: Rose C, ed. *New Advances in Headache Research 4*. London: Smith-Gordon & Company; 1994:27–28.
8. Moskowitz MA. The neurobiology of vascular head pain. *Ann Neurol*. 1984;16:157–168.

9. Martin VT, Behbehani MM. Toward a rational understanding of migraine trigger factors. *Med Clin North Am*. 2001;85:911–941.
10. Lanteri-Minet M, Desnuelle C. Migraine and mitochondrial dysfunction. *Rev Neurol*. 1996;152:234–238.
11. Koo B, Becker LE, Chuang S, et al. Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS): clinical, radiological, pathological, and genetic observations. *Ann Neurol*. 1993;34:25–32.
12. Bresolin N, Martineeli P, Barbiroli B, et al. Muscle mitochondrial DNA deletion and 31P-NMR spectroscopy alterations in a migraine patient. *J Neurol*. 1991;104:182–189.
13. Montagna P, Cortell P, Barbiroli B. Magnetic resonance spectroscopy studies in migraine. *Cephalalgia*. 1994;14: 184–193.
14. Schoenen J, Lenaerts M, Bastings E. High dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia*. 1994;14:328–329.
15. Tfelt-Hansen P, Mathew NT. General approach to treatment. In: Olesen J, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1999:367–369.
16. Turner LC, Molgaard CA, Gardner CH, et al. Migraine trigger factors in non-clinical Mexican-American population in San Diego county: implications for etiology. *Cephalalgia*. 1995;15:523–530.
17. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27:394–402.
18. Scharff L, Turk DC, Marcus DA. Triggers of headache episodes and coping response of headache diagnostic groups. *Headache*. 1995;35:397–403.
19. Robbins L. Precipitating factors in migraine: a retrospective review of 494 patients. *Headache*. 1994;34:214–216.
20. Fuenmayor LD, Garcia S. The effect of fasting on 5-hydroxytryptamine metabolism in brain regions of the albino rat. *Br J Pharmacol*. 1984;83:357–62.
21. Dexter JD, Roberts J, Byer JA. The five-hour glucose tolerance test and effect of low sucrose diet in migraine. *Headache*. 1978;18:91–94.
22. Peatfield RC, Glover V, Littlewood JT, et al. The prevalence of diet-induced migraine. *Cephalalgia*. 1984;4:179–183.
23. Pereira Monteiro JM, Dahlof CG. Single use of substances. In: Olesen J, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1999:861–869.
24. Blackwell B. Hypertensive crisis due to monamine-oxidase inhibitors. *Lancet*. 1963;2:849.
25. Council of Scientific Affairs. Aspartame: review of safety issues. *JAMA*. 1985;254:400–402.
26. Schiffmann SS, Buckley CE, Sapson HA, et al. Aspartame and susceptibility to headache. *N Engl J Med*. 1987;317: 1181–1185.
27. Leon AS, Hunninghake DB, Bell C, et al. Safety of long-term doses of aspartame. *Arch Intern Med*. 1989;1989:2318–2324.
28. Van den Eeden SK, Koepsell TD, Longstreth WT Jr, et al. Aspartame ingestion and headaches: a randomized crossover trial. *Neurology*. 1994;44:1787–1793.
29. Loehler SM, Glaros A. The effect of aspartame on migraine headache. *Headache*. 1988;28:10–14.
30. Bigal ME, Krymchantowski AV. Migraine triggered by sucralose—a case report. *Headache*. 2006;46:515–517.
31. Hirsch AR. Migraine triggered by sucralose—a case report. *Headache*. 2007;47:447.
32. Patel RM, Sarma R, Grimsley E. Popular sweetener sucralose as a migraine trigger. *Headache*. 2006;46:1303–1304.
33. Merrit JE, Williams PB. Vasospasm contributes to monosodium glutamate-induced headache. *Headache*. 1990;30: 575–580.
34. Scher W, Scher BM. A possible role for nitric oxide in glutamate (MSG)-induced Chinese restaurant syndrome, glutamate induced asthma, ''hot-dog headache,'' pugilistic Alzheimer's disease, and other disorders. *Med Hypotheses*. 1992;38:185–188.
35. Henderson WR, Raskin NH. Hot-dog headache: individual susceptibility to nitrite. *Lancet*. 1972;2:1162–1163.
36. Mauskop A, Fox B. *What Your Doctor May not tell you About Migraines. The Breakthrough Program That can Help end Your Pain*. New York: Warner Books, Inc; 2001.
37. Askew GI, Finelli L, Genese CA, et al. Bouillabaisse: an outbreak of methemoglobinemia in New Jersey in 1992. *Pediatrics*. 1994;94:381–384.
38. Peatfield RC. Relationships between food, wine, and beer-precipitated migrainous headaches. *Headache*. 1995;35: 355–357.
39. Relja J, Nider G, Chiodo-Grandi F, et al. Is red or white wine an important inducing factor in migraine attacks?. *Cephalalgia*. 1993;13:129.
40. Chabriat H, Danchot J, Michel P, et al. Precipitating factors of headache. A Prospective Study in a National Control-Matched Survey in Migraineurs and Nonmigraineurs. *Headache*. 1999;39:335–338.
41. Lassen LH, Thomsen LL, Olesen J. Histamine induces migraine via the H1-receptor: support for the NO hypothesis of migraine. *Neuroreport*. 1995;6:1475–1479.
42. Pattichis K, Louca LL, Jarman J, et al. 5-Hydroxytryptamine release from platelets by different red wines: implications for migraine. *Eur J Pharmacol*. 1995;292:173–177.
43. Evans RW, Sun C, Lay C. Expert opinion: alcohol hangover headache. *Headache*. 2007;47:277–279.
44. Swift R, Davidson D. Alcohol hangover: mechanisms and mediators. *Alcohol Health Res World*. 1998;22:54–60.
45. Harburg E, David D, Cummings KM, et al. Negative affect, alcohol consumption and hangover symptoms among normal drinkers in a small community. *J Stud Alcohol*. 1981;42: 998–1012.
46. Gunn R. Hangovers and attitudes towards drinking. *Q J Stud Alcohol*. 1973;34:194–198.
47. Greenberg LA. Studies of congeners in alcoholic beverages. *Q J Stud Alcohol*. 1970;5(suppl 5):1–5.
48. Wiese JG, Shlipak MG, Browner WS. The alcohol hangover. *Ann Intern Med*. 2000;132:897–902.
49. Kangasaho M, Hillbom M, Kaste M, et al. Effects of ethanol intoxication and hangover on plasma levels of thromboxane B2 and 6-ketoprostaglandin F1 alpha and on thromboxane B2 formation by platelets in man. *Thromb Haemost*. 1982; 48:232–234.
50. Calder I. Hangovers. *BMJ*. 1997;314:2–3.
51. Mathew RJ, Barr DL, Weinman ML. Caffeine and cerebral blood flow. *Br J Psychiatry*. 1983;143:604–608.
52. Sawynok J. Adenosine receptor activation and nociception. *Cur J Pharmacol*. 1998;347:1–11.
53. Nehlig A. Are we dependent upon coffee and caffeine? A review on human and animal data. *Neurosci Biobehav Rev*. 1999;23:563–576.
54. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. *Headache*. 1987;27:102–106.
55. Mathew NT, Stubits E, Higam MP. Transformation of episodic migraine into daily headache: analysis of factors. *Headache*. 1982;22:66–68.
56. Rapoport A, Stang P, Gutterman DL, et al. Analgesic rebound headache in clinical practice: data from a physician survey. *Headache*. 1996;36:14–19.
57. Kudrow L. Paradoxical effects of frequent analgesic use. *Adv Neurol*. 1982;33:335–341.
58. Evans SM, Griffiths RR. Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. *J Pharmacol Exp Ther*. 1999;289:285–294.
59. Laires MJ, Monteiro CP, Bicho M. Role of cellular magnesium in health and human disease. *Front Biosci*. 2004; 1:262–276.
60. McCarty MF. Magnesium taurate and fish oil for prevention of migraine. *Med Hypotheses*. 1996;47:461–466.

61. Bianchi A, Salomone S, Caraci F, et al. Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. *Vitam Horm*. 2004;69:297–312.
62. Altura BM, Altura BT, Carella A, et al. $Mg2^{+}$-$Ca2^{+}$ interaction in contractility of vascular smooth muscle: $Mg2^{+}$ versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can J Physiol Pharmacol*. 1987;65:729–745.
63. Ramadan NM, Halvorson H, Vande-Linde A. Low brain magnesium in migraine. *Headache*. 1989;29:590–593.
64. Trauinger A, Pfund Z, Koszegi T, et al. Oral magnesium load test in patients with migraine. *Headache*. 2002;42: 114–119.
65. Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraine. *Clin Neurosci*. 1998; 5:24–27.
66. Mauskop A, Altura BT, Altura BM. Serum ionized magnesium in serum ionized calcium/ionized magnesium ratios in women with menstrual migraine. *Headache*. 2001;42:242–248.
67. Facchinetti F, Sances G, Borella P, et al. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache*. 1991;31:298–301.
68. Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multicenter, placebo-controlled and double-blind randomized study. *Cephalalgia*. 1996;16:257–263.
69. Pfaffenrath V, Wessely P, Meyer C, et al. Magnesium in the prophylaxis of migraine—a double-blind placebo-controlled study. *Cephalalgia*. 1996;16:436–440.
70. Mauskop A, Altura BT, Cracco RQ, et al. Intravenous magnesium sulfate relieves migraine attacks in patients with low serum ionized magnesium levels; a pilot study. *Clin Sci*. 1995;89:633–636.
71. Evans RW, Taylor FR. Expert opinion: "Natural" or alternative medications for migraine prevention. *Headache*. 2006;46:1012–1018.
72. Schoenen J, Jacquy J, Lanaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. *Neurology*. 1998;50: 466–470.
73. Rozen TD, Oshinsky ML, Gebeline CA, et al. Open label trial of Coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002;22:137–141.
74. Sandor PS, DiClemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*. 2005;64:713–715.
75. Hershey AD, Powers SW, Vockell AB, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache*. 2007;47:73–80.
76. Matalon R, Tumpf DA, Kimberlee M, et al. Lipoamide dehydrogenase deficiency with primary lactic acidosis: favorable response to treatment with oral lipoic acid. *J Pediatr*. 1984;104:65–69.
77. Magis D, Ambrosini A, Sandor P, et al. A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis. *Headache*. 2007;47:52–57.
78. Heptinstall S, White A, Williamson L, et al. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leukocytes. *Lancet*. 1985;1:1071–1074.
79. Heptinstall S, Goenewegen WA, Spangenberg P, et al. Extracts of feverfew may inhibit platelet behaviour via neutralisation of suphydryl groups. *J Pharm Pharmacol*. 1987;39:459–465.
80. Pugh WH, Sambo K. Prostaglandin synthetase inhibitors in feverfew. *J Pharm Pharmacol*. 1988;40:743–745.
81. Makheja AM, Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew (Tanacetum parthenium). *Prostaglandins Leukotrienes Med*. 1982;8:653–660.
82. Johnson ES, Kadam NP, Hylands DM, et al. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J*. 1985;291:569–573.
83. Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet*. 1988;2:189–192.
84. Kuritzky A, Elhacham Y, Yerushalmi Z, et al. Feverfew in the treatment of migraine: its effect on serotonin uptake and platelet activity. *Neurology*. 1994;44(suppl):293P.
85. De Weerdt CJ, Bootsma HPR, Hendricks H. Herbal medicines in migraine prevention: randomized double-blind placebo-controlled crossover trial of feverfew preparation. *Phytomoedicine*. 1996;3:225–230.
86. Palevitch D, Earon G, Carasso R. Feverfew (Tanacetum parthenium) as a prophylactic treatment for migraine: a placebo-controlled double-blind study. *Phytother Res*. 1997; 11:508–511.
87. Vogler BK, Pittler BK, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia*. 1998;18:704–708.
88. Pfaffentreath V, Diener HC, Fisher M, et al. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis—a double-blind, multicentre, randomized placebo-controlled dose-response study. *Cephalalgia*. 2002;22: 523–532.
89. Diener HC, Pfaffenrath V, Schnitker J, et al. Efficacy and safety of 6.25 mg tid feverfew CO_2 extract (MIG-99) in migrane prevention—a randomized, double-blind, multicenter, placebo-controlled study. *Cephalalgia*. 2005;25: 1031–1041.
90. Sheftell F, Rapoport A, Weeks R, et al. Montelukast in the prophylaxis of migraine: a potential role for leukotriene modifiers. *Headache*. 2000;40:158–163.
91. Pearlman EM, Fisher S. Preventive treatment for childhood and adolescent headache: role of once-daily montelukast sodium. *Cephalalgia*. 2001;21:461.
92. Grossman M, Schmidrams H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. *Int J Clin Pharmacol Ther*. 2000;38:430–435.
93. Lipton RB, Gobel H, Einhaupl KM, et al. Petsites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology*. 2004;63:2240–2244.
94. Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache*. 2005;45:196–203.
95. Srivastava KC, Mustafa T. Ginger (Zingziber officinale) in rheumatism and musculoskeletal disorder. *Med Hypotheses*. 1992;33:342–348.
96. Schulz V, Hansel R, Tyler VE. *Rational Phytotherapy: A Physician's Guide to Herbal Medicine*. Berlin: Springer; 1998:81.
97. Werbach M. *Nutritional Influence on Illness: A Sourcebook of Clinical Research*. Tarzana, CA: Third Line Press, Inc; 1988.
98. Stahl LA, Begg DP, Weisinger RS, et al. The role of omega-3 fatty acids in mood disorders. *Curr Opin Investig Drugs*. 2008;1:57–64.
99. Dupois S. A comprehensive approach to treatment of intractable headaches. *Townsend Lett Doctors*. 1990;88:740–744.
100. Loder E. Migraine in pregnancy. *Semin Neurol*. 2007;27: 425–433.
101. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia-eclampsia. *Am J Obstet Gynecol*. 1990;162: 1141–1145.
102. National Research Council. *Magnesium (Chapt 6). In: Dietary Reference Intake for Ca, P, Mg, vitamin D, Fluoride*. Washington DC: National Academy Press; 1997.
103. Durlach J. New data on the importance of gestational Mg deficiency. *J Am Coll Nutr*. 2004;23:694S–700S.