long-term vitamin B_6 therapy is essential, PLP was successfully discontinued in about one-third of patients with vitamin B_6-responsive infantile spasms.[7]

In another study, 6 of 13 patients with infantile spasms had a dramatic and sustained improvement after oral treatment with PLP. Of the 6 patients who improved, 4 failed to respond to pyridoxine, presumably because of a defect in their capacity to convert pyridoxine to PLP. The effective dose in the PLP responders was 30–41 mg/kg of body weight per day.[8]

Twenty-eight children (mean age, 9 months) with infantile spasms were treated with oral PLP. The initial dose was 20–30 mg/kg of body weight per day; this was increased after a mean of 6 days to 40–50 mg/kg/day. If the seizures resolved within 2 weeks and no relapse occurred after a total of 4 weeks, treatment with PLP alone was continued. If seizures did not cease completely, low-dose ACTH was added to PLP treatment for a maximum of 8 weeks, after which PLP alone was continued, as long as it was effective. PLP alone produced excellent results in 3 patients (11%). Of the remaining 25 patients, 21 (84%) were symptom-free 1 month after ACTH was discontinued. This response rate was better than that achieved in previous studies with low-dose ACTH alone, and was similar to the results achieved with higher-dose ACTH. These 21 patients were followed for a mean of 35 months, during which time 48% had normal development and 29% had a recurrence of infantile spasms. Fourteen of the 28 patients had transient increases in serum levels of liver enzymes during treatment. The authors of the study concluded that the combination of PLP and low-dose ACTH produced a high response rate, while avoiding some of the adverse effects associated with high-dose ACTH.[9]

The doses of vitamin B_6 used to treat infantile spasms are higher than those reported to cause sensory neuropathy in some patients (chapter 18). While neuropathy has not been reported as a side effect of vitamin B_6 in patients with infantile spasms, patients should be maintained on the lowest dose that controls seizures.

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136 *Migraine*

A migraine is a throbbing, unilateral headache that is often associated with nausea, vomiting, photophobia, or an aura (i.e., a transient disturbance of vision or of various aspects of neurological function). More than 10% of Americans suffer from migraines, with the prevalence in women being about 3 times that in men. The cause of migraine is not well understood, although it is thought to be due in part to vasoconstriction followed by reactive vasodilatation. The use of tobacco, oral contraceptives, or ergotamine (a drug used to treat acute migraine episodes) has been found to increase the frequency of migraines in some patients.[1]

An array of different drugs is available to treat acute migraine episodes (e.g., serotonin [5-HT_1] agonists such as sumatriptan, naratriptan, and zolmitriptan; opioid analgesics; and dihydroergotamine) and to prevent recurrences (e.g., valproic acid, beta blockers, and methysergide). While the acute treatments are often effective, they may cause adverse effects ranging from rebound headache to drug dependence to acute myocardial infarction. With regard to prophylaxis, even the most effective medications reduce mean migraine frequency by no more than 50%, and many of these drugs are associated with significant side effects. Safer and more effective ways of preventing and treating migraines are therefore needed.

In my experience, at least two-thirds of patients who comply with an appropriate regimen of dietary modification and nutritional supplements experience a substantial reduction in, or a complete cessation of, migraine attacks.

Dietary factors

Reactive hypoglycemia/dysinsulinism. Abnormal blood-glucose regulation appears to be a common cause of migraine. In a 1949 report, 11 patients with recurrent migraines associated with functional hyperinsulinism improved or experienced complete relief after consuming a high-protein, low-carbohydrate diet.[2] In a later study, 74 patients who suffered from migraines in the mid-morning or mid-afternoon fasting state underwent a 5-hour glucose-tolerance test. Six patients (8.1%) were classified as diabetic and 56 (76%) had a curve consistent with reactive hypoglycemia (i.e., serum

glucose less than 65 mg/dl or a drop of 75 mg/dl within 1 hour). Following dietary therapy (restriction of refined sugar and consumption of 6 meals per day), all patients with a diabetic glucose curve and 56% of those with reactive hypoglycemia had an improvement of greater than 75% in the frequency and severity of migraines.[3]

Glucose dysregulation should be considered as a potential triggering factor in all migraine patients, particularly those who consume large amounts of refined carbohydrates or whose symptoms begin at a time of the day when blood glucose levels are typically lowest (e.g., late morning or late afternoon). The evaluation and management of reactive hypoglycemia/dysinsulinism is discussed in chapter 6.

Caffeine. Caffeine is recognized in most review articles as a potential migraine trigger, but it is not generally assigned great importance. However, one practitioner observed that avoidance of caffeine frequently improved migraine patients' responses to treatment and sometimes eliminated the need for long-term drug therapy.[4] In my experience, avoiding caffeine is often beneficial and occasionally results in dramatic improvement in migraine sufferers. Caffeine consumption not only impairs blood glucose regulation, it also appears to trigger headaches by a mechanism unrelated to its effect on blood glucose control.

Sodium chloride. One investigator observed that a sudden salt load, particularly if taken on an empty stomach, can cause a migraine 6–12 hours later. Twelve patients with a history of migraines for many years were advised to avoid all salted snack foods (such as pretzels, nuts, and potato chips) before meals. During a 6-month follow-up period, migraines ceased completely in 3 patients and an additional 7 experienced a reduction in the frequency of attacks.[5]

Food allergy. Food allergy appears to be one of the most common causes of migraines. As with many other chronic health conditions, the allergic reactions that provoke migraines are usually masked or hidden. While they cannot be reliably identified from a dietary history or skin tests, they can usually be "unmasked" by an elimination diet followed by individual food challenges.

The importance of food allergy as a cause of migraines has been documented repeatedly in the medical literature for more than 70 years, but most doctors remain unaware of this information. Tyramine and other compounds in food (such as nitrates and monosodium glutamate) are recognized in conventional medicine as precipitating factors (see below), but it is uncommon for migraine patients to become headache-free solely by avoiding these substances.

Balyeat and Rinkel reported in 1930 and 1931 that food allergy is a frequent cause of migraine. Among 202 migraine patients treated by these investigators, avoidance of specific offending foods produced complete or near-complete symptom relief in 21.7% and partial improvement in an additional 66.3% (for a total response rate of 88%).[6,7] Four other studies from the 1930s reported similar results.[8–11] Those studies included a total of 400 patients, and the frequency of partial or complete relief obtained by avoiding allergenic foods ranged from 50.8% to 78%. One of the studies was conducted by Elmer L. DeGowin, coauthor of a classic textbook of physical diagnosis.

Since then, numerous other investigators have reported that food allergy is a major factor in the etiology of migraine.[12–21] One study of adults and another of children provided detailed information and are described below.

Sixty patients with chronic, frequent migraines (mean duration of illness, 18.5 years) consumed an elimination diet for 5 days, consisting only of 2 low-risk foods (usually lamb and pears) and bottled spring water. Migraines disappeared within 5 days in most cases. Each patient then tested 1 to 3 common foods per day, looking for symptoms or acute pulse changes (which are thought by some investigators to indicate allergic reactions). Foods that most frequently caused reactions were wheat (78%); orange (65%); egg (45%); tea and coffee (40% each); chocolate and milk (37% each); beef (35%); corn, cane sugar, and yeast (33% each); mushrooms (30%); and peas (28%). When an average of 10 foods (range, 1–30) were avoided, all patients improved. The number of headaches in the group fell from 402 per month to 6 per month, and 85% of the patients became headache-free.[22]

Eighty-eight children with severe, frequent migraines followed an elimination diet consisting typically of one meat (lamb or chicken), one carbohydrate (rice or potato), one fruit (banana or apple), one vegetable (brassica family), water, and vitamin and calcium supplements for 3–4 weeks. Children who were headache-free or who experienced only 1 headache during the last 2 weeks of the diet reintroduced one additional food per week. If no reaction occurred, the food was added back to the diet, but foods that evoked symptoms were avoided again. Children who did not improve on the diet were offered a second oligoantigenic diet, with no foods in common with the first diet. Seventy-eight children (88.6%) recovered completely on the first or second oligoantigenic diet and 4 improved greatly, for a total improvement rate of 93%. Most patients reacted to several foods. Fifty-five different foods evoked symptoms, the most common of which were cow's milk (31%); egg (27%); chocolate (25%); orange and wheat (24% each); benzoic acid (16%); cheese and tomato (15% each); tartrazine and rye (14% each); pork and fish (10% each); beef and corn (9% each); soy and tea (8% each); oats, goat's milk, and coffee (7% each); and peanuts (6%). Forty of the patients who improved participated in double-blind, placebo-controlled food challenges, which confirmed the etiologic role of food allergy.[23]

That at least some food-induced migraines are mediated by an allergic mechanism (as opposed to a non-immunologically mediated mechanism) is suggested by the fact that cromolyn sodium, a drug that blocks allergic reactions, prevented migraines in patients who ingested a known migraine-provoking food.[24]

Despite this large body of evidence implicating food allergy as a major cause of migraine, the consensus of 290 headache specialists in the United States who participated in a survey was that diet is usually not an important factor. Seventy-four percent of the respondents believed that foods are triggering factors in only 1–20% of migraine patients, whereas only 2% of the doctors estimated the frequency to be as high as 60–80%.[25]

Vasoactive compounds in foods. In contrast to masked allergies, the existence of which most patients are unaware, some patients are aware that ingestion of chocolate, cheese, citrus fruits, or alcohol (particularly red wine) precipitates migraines. The symptoms in these patients appear to be caused by reactions to vasoactive substances in foods or beverages, rather than by an allergic reaction. Compounds in foods and beverages that have been implicated as migraine triggers include tyramine,[26,27] phenylethylamine,[28] and possibly histamine[29] and phenolic compounds.[30]

The increased susceptibility that some people appear to have to these food-derived substances may be related to an inherent weakness in their capacity to metabolize them. Phenol sulfotransferase (PST) is an enzyme that exists in the body in 2 forms; PST-M which acts specifically on monoamines such as tyramine, and PST-P which inactivates certain phenolic compounds. Patients with migraines associated with a known food trigger had significantly lower platelet PST-P activity and nonsignificantly lower PST-M activity, compared with healthy controls and with migraine patients who had no known dietary triggers.[30,31] Patients who developed migraines after eating chocolate also had significantly lower platelet monoamine oxidase activity, compared with controls.[28] Monoamine oxidase metabolizes a number of different amines, including tyramine and phenylethylamine.

In addition, certain types of red wine were found to inhibit PST activity *in vitro*. Even after the wines were diluted 75-fold, they inhibited human platelet PST-P by a mean of 99% and human PST-M by 12%.[32] If such inhibition occurs *in vivo*, then ingestion of these red wines could result in increased concentrations of various phenolic substances and amines, an effect that might explain why some red wines induce migraines.

Avoiding cheese, chocolate, citrus fruits, and alcohol can significantly reduce the frequency of migraines in some patients. However, only 13% of patients in one study became headache-free simply by excluding those foods.[22] That finding underscores the importance not only of avoiding obvious triggering agents, but of searching for hidden food allergens and other dietary factors as well.

Aspartame. There are numerous anecdotal reports of aspartame ingestion causing migraines or other types of headaches.[33–36] Some, but not all, controlled trials have confirmed that aspartame can trigger headaches. In a double-blind crossover trial that included 11 migraine patients, more than twice as many migraines occurred while the patients were receiving aspartame (300 mg 4 times a day for 4 weeks) than while they were receiving placebo (mean number per 4 weeks, 3.55 vs. 1.55; $p < 0.02$).[37] In another study, 18 individuals who reported experiencing headaches after using aspartame were randomly assigned to receive aspartame (30 mg/kg of body weight per day) or placebo for 7 days, and then the alternate treatment for an additional 7 days. Headaches occurred on 33% of the days during aspartame treatment, compared with 24% of the days during placebo treatment ($p = 0.04$).[38]

A study funded by the NutraSweet Company (the makers of aspartame) showed that aspartame did not trigger headaches more frequently than placebo in a group of people who had previously reported vascular headaches following aspartame consumption. In that study, the subjects received a single challenge with aspartame (30 mg/kg of body weight, divided into 3 doses at 8 a.m., 10 a.m., and noon) or placebo, and then the alternate treatment 2 days later.[39] A limitation of that study is that a single aspartame challenge may not be sufficient to induce a headache. It is possible that such headaches occur only after repeated aspartame ingestion, or after a certain cumulative dose is reached.

A potential limitation of all of the controlled trials is that aspartame was administered in capsules or in freshly prepared cool solutions, rather than in soft drinks or other aspartame-containing foods or beverages. Aspartame in commercial products is said to undergo chemical changes on exposure to high temperatures or after storage for more than 2 months, and these degradation products may be responsible in part for the reported adverse effects of aspartame.[40] Therefore, symptoms that occur after ingestion of aspartame-containing commercial products or hot drinks to which aspartame has been added may not be reproducible by challenging with aspartame in capsules or in freshly prepared cool solutions.

Based on the available evidence, aspartame should be considered a potential migraine trigger, and should be excluded during an elimination diet.

Sucralose. There is anecdotal evidence that the artificial sweetener, sucralose (Splenda), can trigger migraines in some individuals.[41]

Chewing gum. Excessive gum-chewing may be a cause of migraines and other types of headaches in some people. The mechanism is thought to be overuse of the temporomandibular joint, although in some cases, sensitivity to aspartame in the chewing gum may be involved.

Thirty children and teenagers (aged 6–19 years) with chronic headaches (18 migraine-like, 12 tension type) and excessive gum-chewing were asked to stop chewing gum for 1 month, and then to resume gum-chewing. During the period of no gum-chewing, 26 of the 30 patients reported significant improvement, and headaches disappeared completely in 19. All 20 patients who resumed gum-chewing experienced a return of headaches within days to 1 week.[42]

Nutritional supplements for prophylaxis

Magnesium. Several lines of evidence suggest that magnesium deficiency is involved in the pathogenesis of migraine. Certain factors that trigger migraines, including stress, menstruation, alcohol ingestion, and some diuretics, are known to cause magnesium depletion.[43] Magnesium concentrations in erythrocytes, mononuclear cells, serum, and brain tissue (measured by ^{31}P-magnetic resonance spectroscopy) were significantly lower in both adults and children with migraines than in healthy controls.[44–49] Experimental magnesium deficiency resulted in arterial spasm, spreading cortical

depression, central neurotransmitter release, and increased platelet aggregation, each of which is believed to play a role in the pathogenesis of migraine.[50] Through its effect on ATP synthesis, magnesium is involved in mitochondrial energy production, which appears to be impaired in migraine patients[49,51] In addition, magnesium increased the activity of phenol sulfotransferases *in vitro*;[52] these enzymes play a role in detoxifying migraine-precipitating compounds such as tyramine.

One practitioner administered 200 mg/day of magnesium (from an amino acid chelate) to more than 3,000 migraine patients (mostly women of childbearing age), and reported a success rate of 80%.[53] Since then, several clinical trials have evaluated the effectiveness of magnesium for migraine prophylaxis, and most have produced positive results.

Eighty-one migraine sufferers were randomly assigned to receive, in double-blind fashion, 600 mg/day of magnesium (as trimagnesium dicitrate) or placebo for 12 weeks. In weeks 9–12 the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group compared with baseline ($p < 0.04$ for the difference in the change between groups). The reductions in mean duration of attacks and mean pain intensity were nonsignificantly greater in the magnesium group than in the placebo group. Adverse effects of magnesium were diarrhea in 18.6% of patients and gastric irritation in 4.7%.[54]

Twenty women with perimenstrual migraine were randomly assigned to receive, in double-blind fashion, 360 mg/day of magnesium or placebo, starting on day 15 of each cycle and continuing until menstruation. After 2 cycles, the Pain Total Index, which measures duration and intensity of migraines, was significantly lower in the magnesium group than in the placebo group ($p < 0.03$). The mean number of days with headaches was reduced by 49% compared with baseline in the magnesium group ($p < 0.01$), but there was no significant change in the placebo group.[55]

One hundred eighty-eight children (aged 3–17 years) with at least 1 migraine per week during the previous 4 weeks were randomly assigned to receive, in double-blind fashion, magnesium (9 mg/kg of body weight per day, as magnesium oxide, given in 3 divided doses per day) or placebo for 16 weeks. Compared with baseline, the number of days with at least 1 headache decreased significantly in the magnesium group ($p < 0.004$) and nonsignificantly in the placebo group ($p = 0.086$). The percent decrease in headache frequency was nonsignificantly greater in the magnesium group than in the placebo group (data not shown). Mean headache severity was significantly lower in the magnesium group than in the placebo group ($p < 0.003$).[56]

Sixty-nine patients with a history of migraines for at least 2 years were randomly assigned to receive, in double blind fashion, 243 mg of magnesium (as magnesium aspartate) twice a day or placebo for 12 weeks. A positive response was defined as a reduction of at least 50% in the intensity or duration of migraine attacks. The proportion of responders was 28.6% in the magnesium group and 29.4% in the placebo group. However, 33% of patients receiving magnesium and 11% of patients receiving placebo felt that their treatment was superior to previously used migraine medications.[57] Several weaknesses of this study limit its usefulness. First, the study was underpowered: 146 patients were needed to detect a clinically meaningful difference in response rate between treatment groups, but only 61 patients completed the study. Second, more than half of the patients had apparently failed to respond to migraine-prevention drugs, suggesting that the study included a high proportion of treatment-resistant patients. Third, the criteria for improvement (a reduction of at least 50% in the duration or intensity of migraines) were unusually strict. Only a few studies have used these criteria and most of them (including studies of beta blockers, which are known to be effective) showed no significant benefit from the treatment being tested.

Thus, magnesium supplementation appears to be a simple, safe, and effective way to reduce the frequency or severity of migraines, or both. In addition, there is evidence that intravenous magnesium can abort acute migraine episodes (see below).

Riboflavin. As the precursor of flavin adenine dinucleotide (FAD), a coenzyme involved in the electron-transport chain, riboflavin plays a role in mitochondrial energy production, which appears to be impaired in migraine patients.[49,51]

Riboflavin at a dosage of 5 mg 3 times per day was reported in 1946 to be effective for migraine prophylaxis. Of 15 patients with simple migraine, 10 had a complete cessation of attacks and an additional 3 were markedly improved. Four of 4 patients with ophthalmic migraine had no further attacks after starting riboflavin. A dosage of 5 mg twice a day was found to be insufficient in some cases.[58]

The apparent effectiveness of riboflavin was confirmed in a 1956 report. Of more than 100 migraine patients, the vast majority had a complete cessation of attacks after riboflavin supplementation. The dosage was 10 mg 3 times per day with meals for 6 months, followed by 10 mg/day indefinitely. Marked improvement was usually seen in less than a month. If a patient discontinued treatment, attacks would recur within a few months.[59]

These early observations were forgotten, and more than 40 years passed before a new generation of researchers, apparently unaware of the initial reports, again found riboflavin to be effective.

Forty-nine patients with recurrent migraines received 400 mg of riboflavin once a day for at least 3 months. The mean number of migraine attacks fell by 67% and mean migraine severity improved by 68%. One patient stopped treatment because of gastric intolerance (that person was also taking small amounts of aspirin), but no other side effects were reported.[60]

Twenty-three patients with recurrent migraines received 400 mg/day of riboflavin for 3 months, with an option to extend the treatment for an additional 3 months. Median headache frequency decreased from 4 days per month at baseline to 2 days per month after 3 and 6 months ($p < 0.05$). The median headache duration decreased by 44%, from 50 hours at baseline to 28 hours at 3 and 6 months ($p = 0.1$).[61]

Fifty-five migraine patients were randomly assigned to receive, in double-blind fashion, 400 mg of riboflavin once a day or placebo for 3 months. In intent-to-treat analysis, riboflavin was superior to placebo in reducing attack frequency ($p = 0.005$) and headache days ($p = 0.012$). The proportion of patients who experienced at least a 50% reduction in the number of headache days was 59% with riboflavin and 15% with placebo ($p = 0.002$). Three minor adverse events occurred, 2 in the riboflavin group (diarrhea and polyuria) and 1 in the placebo group.[62]

Fifty-two migraine patients were randomly assigned to receive, in double-blind fashion, daily treatment with 1) a combination of 400 mg of riboflavin, 300 mg of magnesium, and 100 mg of feverfew, or 2) "placebo" (25 mg of riboflavin) for 3 months. The proportion of patients who achieved a 50%-or-greater reduction in migraine frequency was 42% with combination therapy and 44% with low-dose riboflavin ($p = 0.87$). Both treatments reduced the frequency of migraines by approximately one-third. Mean headache severity ($p = 0.04$) and mean number of days with tension headache ($p = 0.01$) decreased with low-dose riboflavin, but not with combination therapy. The effect of low-dose riboflavin was greater than that reported for placebo in previous migraine trials.[63] Each of the 3 compounds present in the combination treatment has been shown, when given alone, to reduce the incidence of migraines. While it is somewhat surprising that low-dose riboflavin was at least as effective as this combination treatment, it is possible that one or more of the substances in the combination product interfered with the effect of the others, or that massive doses of riboflavin are less effective than more moderate doses.

The studies cited above were conducted in adults. In contrast to the beneficial effects observed in these studies, the results in children are less clear. In an uncontrolled trial, of 41 children and adolescents with migraines who received 200 or 400 mg/day of riboflavin for up to 6 months, 68% had at least a 50% reduction in attack frequency.[64] However, in 2 double-blind studies in children and adolescents, supplementation with 50 or 200 mg/day of riboflavin for 12–16 weeks did not decrease the frequency or severity of migraines compared with placebo.[65,66]

While some of the more recent trials used a very large dose of riboflavin (400 mg/day), moderate doses (15–30 mg/day) also seem to be effective. Although high-dose riboflavin has not been associated with significant toxicity in short-term studies, it has the potential to act as a photosensitizer (chapter 14) or to cause imbalances of other nutrients. Therefore, it would seem prudent to reserve high-dose riboflavin for patients who do not respond to moderate doses.

Coenzyme Q_{10}. As a component of the electron-transport chain, coenzyme Q_{10} (CoQ_{10}) plays a role in mitochondrial energy production, which appears to be impaired in migraine patients[49,51] In a study of 1,550 children and young adults with migraine, the serum concentration of CoQ_{10} was below the reference range in 32.9% of the patients.[67] Two open-label trials[67,68] and one double-blind trial[69] found CoQ_{10} to be effective for migraine prophylaxis.

Thirty-two patients with a history of episodic migraines received 150 mg/day of CoQ_{10} for 3 months. During the last 2 months of treatment, compared with baseline, 61.3% of the patients had a greater-than-50% reduction in the number of days per month with migraines. The mean number of days per month with migraines decreased by 59.8% (2.95 vs. 7.34; $p < 0.0001$) and the mean attack frequency decreased by 42% (2.81 vs. 4.85 per month; $p < 0.001$). CoQ_{10} had no significant effect on headache intensity.[68]

Forty-two migraine patients were randomly assigned to receive, in double-blind fashion, 100 mg of CoQ_{10} 3 times per day or placebo for 4 months. The proportion of patients who had a 50%-or-greater reduction in attack frequency during the fourth month compared with baseline was 47.6% in the CoQ_{10} group and 14.3% in the placebo group ($p = 0.02$). The mean reduction in attack frequency was 27.1% in the CoQ_{10} group and 2.1% in the placebo group ($p < 0.05$ for the difference in the change between groups). The mean duration and severity of migraines did not differ between groups.[69]

However, in another double-blind trial, CoQ_{10} did not decrease the frequency, duration, or severity of migraines compared with placebo. It is not clear why the results of this study differed from those of the positive studies.[70]

Niacinamide/Niacin. As the precursor of nicotinamide adenine dinucleotide (NAD), a coenzyme involved in the electron-transport chain, niacinamide plays a role in mitochondrial energy production, which appears to be impaired in migraine patients.[49,51] While niacinamide has not been studied for migraine prophylaxis, 3 other nutrients that play a role in mitochondrial energy production (magnesium, riboflavin, and coenzyme Q_{10}) have each been found to be beneficial (see above). It is therefore possible that niacinamide (perhaps in doses of 500–1,000 mg/day) would reduce the frequency or severity of migraines.

In a case report, niacin supplementation successfully prevented attacks in a chronic migraine sufferer. However, that improvement may have been mediated by niacin's vasodilatory effect, an action that is not shared by niacinamide. The dose of niacin was 375 mg of a sustained-release preparation twice a day, subsequently reduced to once a day.[71]

Folic acid. Of 22 children (aged 8–18 years) with recurrent migraines without aura, 16 were found to have hyperhomocysteinemia and one or more polymorphisms of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene (mainly homozygosity for 677C→T) that are associated with reduced enzyme activity and moderate hyperhomocysteinemia. Those 16 children received 5 mg/day of folic acid for 6 months. Ten of the 16 children had a complete cessation of migraine attacks, 5 had a 75% reduction in attack frequency, and 1 had a 50% reduction in attack frequency. Of 3 patients who had been having daily migraines, all had a complete cessation of attacks.[72] Plasma homocysteine levels became normal in all 16 patients. The mechanism by which hyperhomocysteinemia might promote the development of migraines is not known.

In a double-blind trial conducted in Australia, supplementation with folic acid in combination with vitamin B_6 and vitamin B_{12} reduced the frequency and severity of migraines in adults with migraines accompanied by an aura.

Fifty-two patients (mean age, 52 years) with migraines accompanied by an aura were randomly assigned to receive, in double-blind fashion, daily B vitamins (2 mg of folic acid, 25 mg of vitamin B_6, and 400 μg of vitamin B_{12}) or placebo for 6 months. At baseline, the mean plasma homocysteine concentration was 10.8 μmol/L, which was 21% higher than the mean value for the general population. The mean plasma homocysteine level decreased by 39% in the active-treatment group ($p = 0.001$ compared with the change in the placebo group). The proportion of patients suffering from severe migraine disability fell from 61% to 30% in the active-treatment group

(p = 0.01), but did not change in the placebo group. Median headache frequency fell by 75% (p = 0.04) and median headache severity decreased by 25% (p = 0.002) in the active-treatment group; these values did not change in the placebo group. The reduction in migraine disability was most pronounced in the 31 patients with the CC and CT MTHFR 677C→T genotypes. In that subgroup, the proportion of patients suffering from severe migraine disability fell from 76% to 28% (p = 0.002). In contrast, the reduction in severe migraine disability in patients with the TT genotype was not statistically significant. It was suggested that patients with the TT genotype may have needed a higher dose of folic acid, since patients with that genotype have an increased folate requirement.[73]

In a follow-up study by the same Australian research group, the beneficial effect of the same B-vitamin regimen on migraines and on homocysteine levels was less pronounced than in the original study. The authors suggested that this difference may have been due to the implementation of folic acid fortification of wheat flour in Australia in the interim.[74]

Alpha-lipoic acid. Alpha-lipoic acid plays a role in mitochondrial energy production, which appears to be impaired in migraine patients.[51] In a small double-blind trial, supplementation with 600 mg of alpha-lipoic acid once a day for 3 months significantly reduced the frequency of migraine attacks (comparing the third month with baseline). However, when compared with the change in the placebo group, the reduction in attack frequency in the ALA group did not reach statistical significance (p = 0.06).[75]

Vitamin C. A 32-year-old man with a 6-year history of migraines found that attacks could be prevented by supplementing with 6 g/day of vitamin C. He then participated in a double-blind trial. Each day for 15 days he was randomly assigned to receive vitamin C or placebo. He experienced severe headaches on all of the placebo days and either no headaches or very minor ones on the vitamin C days.[76] The mechanism of action of vitamin C and the frequency with which it might help other migraine patients are not known.

L-Tryptophan. Migraines appear to be caused in part by abnormalities of the serotonergic system, and serotonin receptor agonists (triptans) are effective in the treatment of acute migraines. L-Tryptophan is a naturally occurring precursor to serotonin. There is evidence that chronic migraine sufferers have a deficiency of serotonin in the brain,[77] an abnormality that might be reversible with L-tryptophan supplementation. Two studies suggest that L-tryptophan may be an effective prophylactic agent for some migraine patients.

Eight migraine patients who had been refractory to conventional therapy received, in double-blind fashion, 500 mg of L-tryptophan every 6 hours or placebo (L-leucine) for 3 months, and then the alternate treatment for an additional 3 months. The mean headache index (the number of attacks multiplied by the intensity) was nonsignificantly lower by 32.8% with L-tryptophan than with placebo. In 4 of the 8 patients, headache indices were markedly lower with L-tryptophan than with placebo.[78]

In a study published in Italian for which an English abstract is available, patients with migraines received, in double-blind fashion, 3 g/day of L-tryptophan or placebo for one month. Those receiving L-tryptophan had significantly fewer migraines of significantly shorter duration than did those receiving placebo.[79]

While there are no clear guidelines regarding when to use L-tryptophan, a therapeutic trial might be worthwhile for migraine patients with a history of depression, insomnia, or premenstrual syndrome.

L-5-Hydroxytryptophan (5-HTP), a metabolite of L-tryptophan and a direct precursor to serotonin, has also been evaluated for migraine prophylaxis. In 2 studies, 5-HTP at doses of 200 and 600 mg/day, respectively, appeared to be as effective as methysergide.[80,81] However, 5-HTP was ineffective in children.[82] For reasons explained in chapter 48, L-tryptophan seems to be preferable to 5-HTP as a therapeutic agent in most circumstances.

Co-administration of L-tryptophan or 5-HTP and drugs that increase serotonergic activity (such as serotonin receptor agonists [triptans], selective serotonin-reuptake inhibitors, amitriptyline, and monoamine oxidase inhibitors) may increase both the efficacy and the toxicity of the drugs. If a patient is taking one of these medications, L-tryptophan should either be avoided completely (particularly in the case of triptans) or used with caution and in low doses (perhaps 500–1,000 mg/day), while monitoring for signs of serotonin excess (serotonin syndrome).

Fish oil. In 2 double-blind crossover trials (published as abstracts) that included a total of 23 patients with severe recurrent migraines, treatment with approximately 15 g/day of fish oil for 6 weeks appeared to reduce the severity and possibly the frequency of headaches.[83,84]

In 2 other studies, fish oil reduced headache frequency compared with baseline, but not compared with the placebo, which was olive oil or olive oil/lactose. In one of these studies, which included 196 migraine patients, administration of 6 g/day of fish oil for 16 weeks reduced mean headache frequency by 55%, as compared with a 45% reduction in the olive oil/lactose group (p = 0.058 for the difference in the change between groups).[85] In the other trial, which included 27 adolescents with frequent migraines, treatment with fish oil (providing 756 mg/day of eicosapentaenoic acid [EPA] and 498 mg/day of docosahexaenoic acid [DHA]) for 2 months reduced mean headache frequency by 87%; however, the same 87% reduction was seen with olive oil.[86] The improvements seen in these studies may have been due to a placebo effect, but they are also consistent with the possibility that both fish oil and olive oil are effective for migraine prophylaxis. Each of these oils has anti-inflammatory activity, and inflammation has been implicated as a factor in the pathogenesis of migraine.

A significant reduction in the number of migraine days per month was also achieved in one study by following a diet for 12 weeks that was low in omega-6 fatty acids and high in EPA and DHA (as compared with a diet low in omega-6 fatty acids and containing the low amount of EPA and DHA present in a typical U.S. diet).[87]

Vitamin B_{12}. Twenty patients with a history of 2–8 migraine attacks per month for more than one year received 1 mg/day of hydroxocobalamin intranasally for 3 months. Half of the patients experienced at least a 50% reduction in migraine frequency. The mean attack frequency decreased from 4.7 per month prior to the study to 2.7 per month during treatment (43% reduction; $p < 0.001$). Adverse reactions included nasal irritation ($n = 6$) and wheezing ($n = 3$).[88] Vitamin B_{12} is believed to work by scavenging nitric oxide, which plays a role in the pathogenesis of migraines.

Concerns have been raised that long-term intranasal administration of vitamin B_{12} might damage pulmonary tissue.[89] However, orally administered vitamin B_{12} raises serum cobalamin concentrations far less than does intranasal treatment. Periodic intramuscular injections of vitamin B_{12} might provide the best balance of efficacy and safety. A reasonable regimen would be 1,000 μg intramuscularly once a week for 4–6 weeks, continuing as needed if it appears to be effective.

Vitamin D and calcium. Two postmenopausal women with frequent and severe migraines and 2 premenopausal women with a history of migraines related to the menstrual cycle experienced a marked reduction in migraine frequency after treatment with a combination of vitamin D_2 (50,000 IU once a week for an unspecified period of time) and calcium (1,000–2,000 mg/day). One patient initially received 1,600 IU/day of vitamin D_3 for 2 months and showed marked improvement before being switched to 50,000 IU/week of vitamin D_2. In all cases, pretreatment 25-hydroxyvitamin D levels were below normal or near the lower end of the normal range.[90,91] Potential adverse effects of high-dose vitamin D are discussed in chapter 23.

Melatonin. Plasma levels and urinary excretion of melatonin were significantly lower in migraine patients than in controls.[92] In an uncontrolled trial, administration of 3 mg/day of melatonin 30 minutes before bedtime for 3 months significantly decreased the frequency, intensity, and duration of headaches in patients with recurrent migraines.[93] However, in a double-blind trial, the reduction in migraine frequency did not differ between patients who received 2 mg/day of melatonin before bedtime for 8 weeks and patients who received placebo.[94]

Nutritional supplements for acute treatment

Intravenous magnesium. Parenteral magnesium was mentioned in the 1930s and 1940s as an effective treatment for migraine.[95] More recently, numerous trials have examined the effect of intravenous magnesium in patients with acute migraine. Most,[96–101] but not all,[102–104] of the results have been positive.

Forty patients with an acute migraine received 1 g of magnesium sulfate in a 10% solution intravenously over 5 minutes. Fifteen minutes after the infusion, 35 patients (87.5%) had at least a 50% reduction of pain, and 9 (22.5%) had complete relief. In 21 of the 35 patients who improved, the improvement persisted for 24 hours or more. Pain relief lasting at least 24 hours was seen in 18 of 21 patients (86%) whose pretreatment serum ionized magnesium level was below 0.54 mmol/L, and in 3 of 19 patients (16%) whose level was at or above 0.54 mmol/L ($p < 0.001$). Twelve patients felt lightheaded for a few minutes upon sitting up after the infusion, but no other side effects were noted.[96]

Forty patients with an acute headache (of which 27 were migraines) received 1 g of magnesium sulfate in a 10% solution intravenously over 5 minutes. Pain resolved completely within 15 minutes in 32 patients (80%); in most of these cases the headache began to improve before the end of the infusion. Gastrointestinal symptoms, nausea, and photophobia were also completely eliminated in patients whose headaches were relieved. Of the 32 patients who improved, 18 were relieved of their headache for more than 24 hours. Of the 18 patients who had sustained relief, 16 (89%) had a low pretreatment serum ionized magnesium level. Of the 8 patients who had no relief, only 37.5% had a low ionized magnesium level.[97]

Sixty patients with migraine with aura and 60 patients with migraine without aura were randomly assigned to receive, in double-blind fashion, intravenous magnesium sulfate (1 g diluted to 10 ml with 0.9% sodium chloride, given over 20 minutes) or placebo (0.9% sodium chloride). In the group with aura, at 60 minutes, 36.7% of those receiving magnesium and 6.7% of those receiving placebo were pain-free ($p < 0.05$). At 24 hours, the respective percentages were 83.3% and 73.3% (difference not significant). The severity of photophobia, phonophobia, and nausea were significantly less in the magnesium group than in the placebo group. In the group without aura, at 60 minutes, 23.3% of those receiving magnesium and 10% of those receiving placebo were pain-free (difference not significant). At 24 hours, 66.7% of those receiving magnesium and 46.7% of those receiving placebo were pain-free ($p < 0.05$). The severity of photophobia and phonophobia were significantly less and the severity of nausea was nonsignificantly less in the magnesium group than in the placebo group. Thus, intravenous magnesium sulfate relieved pain and associated symptoms in some patients with migraine with aura, but was somewhat less effective in patients with migraine without aura.[98]

Thirty patients with moderate or severe migraine attacks were studied. The first 15 patients received, in single-blind fashion, magnesium sulfate intravenously (1 g diluted to 10 ml with 0.9% sodium chloride, given over 15 minutes), and the next 15 patients received placebo (0.9% sodium chloride). Patients in the latter group who did not improve after 30 minutes were treated with magnesium in the same fashion. Immediately after treatment and at 30 minutes and 2 hours, 86.6% of the patients in the magnesium group were pain-free, and the remaining 13.4% reported a reduction in pain severity. At all 3 time periods, accompanying symptoms (such as nausea, vomiting, photophobia, and irritability) had disappeared in each of the 14 patients who had experienced them. None of the patients given magnesium had a recurrence of pain within 24 hours. In the placebo group, no patient became pain-free ($p < 0.001$ for the difference between groups) and only 1 (6.7%) experienced a reduction in pain. Accompanying symptoms disappeared in 3 patients (20%) 30 minutes after placebo administration ($p < 0.0001$ for the difference between groups). When patients in the placebo group were given magnesium, the response was similar to that in the magnesium group. Mild side effects occurred in 86.6% of the patients given magnesium; these included a burning sensation in the face and neck, flushing, and/or a decrease in systolic blood pressure of 5–10 mm Hg.[99]

Seventy-six adults with an acute migraine were randomly assigned to receive, in double-blind fashion, intravenous magnesium sulfate (2 g over 10 minutes) or placebo. At 30 minutes, the magnesium group had improved by about 10 points more than the placebo group on a 100-point visual analogue scale for pain, but this difference was not statistically significant. The proportion of patients who needed rescue medication at 30 minutes was lower in the magnesium group than in the placebo group (44% vs. 65%; p = 0.04). However, the recurrence rate at 24 hours was similar in the 2 groups (approximately 50%).[102] Although the authors concluded that intravenous magnesium was not effective, there was a trend suggesting a modest beneficial effect. The relatively unimpressive results seen in this study may be explained in part by the fact that only 18% of the subjects had an aura. As mentioned previously, intravenous magnesium appears to be less effective in patients with migraine without aura than in those with aura.[98]

These studies suggest that intravenous magnesium can in some cases provide rapid and sustained relief from an acute migraine and its associated symptoms. The treatment is effective most often in patients whose migraine is accompanied by an aura, and in those with evidence of magnesium deficiency (i.e., a low serum ionized magnesium concentration).

The Myers cocktail. I have administered the "Myers cocktail" (a combination of magnesium, calcium, B vitamins, and vitamin C) intravenously to half a dozen or more patients who presented on one or more occasions with an acute migraine. In most cases, complete symptom relief or marked improvement occurred within 2 minutes and did not return over the ensuing 24 hours. One patient with frequent migraines associated with multiple food and chemical sensitivities was treated for acute migraines more than 70 times over a 6-year period, and she responded well on all but a few occasions. It has been my clinical impression that this combination of nutrients is more effective than magnesium alone in the treatment of migraines. The Myers cocktail is described in chapter 340.

Niacin. One practitioner successfully used oral niacin to relieve his own migraines. At the onset of the aura, 300–500 mg of niacin was chewed slightly and allowed to dissolve in the mouth.[105]

Recommendations for migraine

Note: These recommendations are classified as "primary" or "other," based on various factors including safety, efficacy, strength of the evidence, clinical experience, and cost.

Primary recommendations

1. Dietary modifications should be individualized. Potentially beneficial interventions include avoiding refined sugar, caffeine, and alcohol; avoiding excessive salt intake; identifying and avoiding allergenic foods; eliminating foods that contain tyramine, phenylethylamine, and other triggering agents (such as chocolate, citrus fruits, some wines, and aged cheeses); avoiding symptom-evoking compounds such as aspartame, monosodium glutamate, and sucralose; and eating oily fish 1–3 times a week (as a source of fish oil).
2. Magnesium: 100–300 mg twice a day for prophylaxis. For acute treatment, intravenous magnesium (combined with calcium, B vitamins, and vitamin C) frequently provides rapid relief.
3. Riboflavin: 15–400 mg/day (may be more effective for adults than children).
4. Coenzyme Q_{10}: 60–300 mg/day.
5. Folic acid: 5 mg/day for patients with hyperhomocysteinemia.

Other recommendations

6. A comprehensive nutritional program may include moderate amounts of vitamin C, vitamin D, niacinamide, vitamin B_{12}, calcium, and fish oil. Higher doses of one or more of these nutrients, or supplementation with L-tryptophan, may be considered for prophylaxis in patients who do not respond adequately to the primary recommendations.
7. Niacin: For acute treatment, 300–500 mg chewed slightly and dissolved in the mouth.
8. Alpha-lipoic acid: 100–600 mg/day.

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137 *Multiple sclerosis*

Multiple sclerosis (MS) is a chronic progressive demyelinating disease of the central nervous system. Common manifestations include paresthesias, diplopia, loss of vision, numbness or weakness of the limbs, bowel or bladder dysfunction, spasticity, ataxia, fatigue, and mental changes. Four main patterns of MS are recognized: relapsing-remitting, primary progressive, secondary progressive, and progressive relapsing. The cause of MS is unknown, although it appears to be an autoimmune disease. Much of what is known about MS has been learned from an animal model of the disease, experimental allergic encephalomyelitis.

Conventional therapy may include immunomodulating drugs (such as certain types of beta interferon) to reduce the frequency of relapses, glucocorticoids to treat acute exacerbations, and amantadine to treat fatigue. Other medications are used for specific MS-related symptoms.

Environmental factors

A meta-analysis of 13 studies showed that exposure to organic solvents was associated with an increased risk of developing MS. The estimated relative risk in individuals exposed to solvents was 1.7–2.6.[1] In patients with a history of exposure to solvents or other toxic chemicals, a detoxification (depuration) program aimed at reducing the body burden of xenobiotic chemicals might help retard or reverse the disease process.[2] One such program is described in chapter 339.

Dietary factors

Low-fat diet. Beginning in 1949, Swank treated 150 MS patients (mean age, 34 years) with a low-fat diet. After adjustments in the protocol during the first 3 years, the recommended diet was as follows: intake of saturated fat was restricted to 20 g/day. Whole milk, cheese, margarine, other sources of hydrogenated oils, and shortenings were prohibited. Patients were encouraged to eat fish 3 or more times a week. The diet was supplemented with 5 g/day of cod liver oil and 10–40 g/day of vegetable oils high in polyunsaturated fatty acids. During the first 7 years, the frequency and severity of disease exacerbations appeared to be reduced. Patients who began treatment early in the course of the disease and before severe disability had developed had the best outcomes, with only 8% of patients deteriorating during an average follow-up period of 3.6 years. In contrast, about 65% of late cases deteriorated during the same period.[3] Relapses became