Migraine Headaches: Nutritional, Botanical And Other Alternative Approaches

Steven Sinclair, N.D., LAc

Abstract

Migraine headaches are an increasingly common health problem with a wide range of potential etiological factors. Stress, food allergies, neuroendocrine imbalances and nutritional deficiencies all may contribute to migraine attacks. Many nutritional and botanical therapies aim to reduce migraine incidence by decreasing platelet aggregation and preventing the release of vasoactive neurotransmitters, and avoiding triggering foods. This article reviews much of the research on nutritional, botanical, dietary, and other alternative approaches to the treatment and prevention of migraines.
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Introduction

Migraine is a recurrent neurovascular headache disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, and nausea and vomiting. It is apparently a global disorder, occurring in all races, cultures, and geographical locations. Current figures suggest that 18 percent of women and six percent of men suffer from migraine and those numbers are increasing.[1] The Centers for Disease Control reported a 60-percent increase in the disease from 1980 to 1989.[2] The highest incidence of migraine occurs between the ages of 20 and 35, and is often associated with a positive family history of the disease. Remissions are common during pregnancy and menopause; however, migraines may also occur for the first time during pregnancy or with the initiation of oral contraceptive use.[3] Migraine headaches are divided into two diagnostic categories. Migraine without aura, previously classified as a common migraine, consists of unilateral or generalized cephalgia, throbbing or pulsatile in nature, in conjunction with nausea, vomiting, and photophobia. Migraine with aura, by definition, is preceded by a 15-20 minute episode of visual or sensory aura. Auras are most commonly visual alterations, usually experienced as hemianopic field defects and scotomas that enlarge and spread peripherally.[4] Visual auras are associated with spreading cortical depression, and recent studies have confirmed the pathophysiology of migraine strongly affects visual cognitive processing in the brain.[5] Sensory auras are usually experienced as paraesthesias of the arm and face.

This article reviews the clinical research on migraine headaches and focuses on prevention using nutritional, botanical, and dietary approaches.

Steven Sinclair, ND, LAc - Associate Editor, Alternative Medicine Review; Private Practice, Hagerstown, Maryland.
Correspondence address: Green Valley Health, 1305 Pennsylvania Ave, Hagerstown, MD 21742

Pathophysiology

While the exact etiology of migraine headaches is unknown, several theories have been proposed. Current concepts of the pathogenesis of migraine focus on three mechanisms and anatomic regions. The vascular theory, as proposed in 1938 by Graham and Wolff, attributes migraines to an initial intra-cranial arterial vasoconstriction, resulting in reduced blood flow to the visual cortex, followed by a period of extra-cranial vasodilation.[6] Although a long standing theory, research has shown during a common migraine attack there are in fact only minor changes in cerebral blood flow, and the proposed initial vasoconstrictive phase may actually last several hours longer than the aura.[7] It is also hypothesized migraine sufferers have an inherent vasomotor instability and are more susceptible to the vasodilatory effects of certain chemical and physical agents.

Moskowitz's unifying theory involves the trigeminovascular complex, which links the aura and the cephalgia of migraine.[8] It is thought the trigeminovascular neurons release substance P and other inflammatory neurotransmitters in response to various stressors. Substance P is associated with vasodilation, mast cell degranulation, and alterations in vascular permeability. Excessive trigeminal discharge and ensuing release of vasoactive substances is thought to directly affect cerebral blood flow resulting in migraine headache.

Lance et al proposed the idea of a "migrainous threshold" which is determined by a dynamic balance between excitation and inhibition at various levels in the central nervous system. Hormonal influences, environmental and physiologic stressors, low blood sugar, and fatigue are all thought to determine this threshold. Once the threshold is exceeded, trigeminovascular discharge is thought to be responsible for inducing a migraine.[9]

Platelets become an important etiological consideration in migraines, as they contain over 90 percent of the serotonin in the blood. Once they aggregate, platelets release serotonin, and other vasoactive chemicals causing a potent vasoconstrictive effect (Figure 1). Platelet aggregation has been shown to be altered in migraine patients, and raises the possibility that platelet activating factor may be involved in the pathogenesis of migraine.[10] Kovac et al demonstrated platelets of migraine patients showed abnormal tendencies toward hyperaggregability and reduced monoamine oxidase activity (MAO). There was a significant correlation in this study between MAO activity and sensitivity to prostacyclins (PGI2).[11] Even during headache-free periods, migraine patients were shown to exhibit greater degrees of platelet sensitivity to serotonin and adenosine diphosphate than healthy controls.[12] Urinary serotonin metabolites have been shown to increase during the acute phase of a migraine attack.[4] Other vasoactive chemical constituents that may play a role in migraines include tyramine,

Figure 1. Platelet aggregation results in release of vasoactive chemicals implicated in migraines.

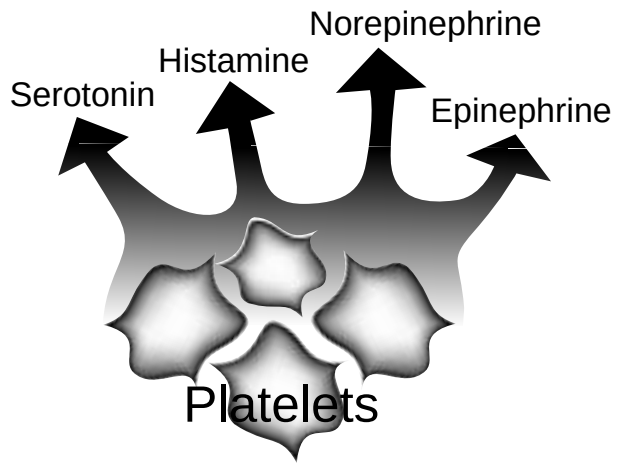
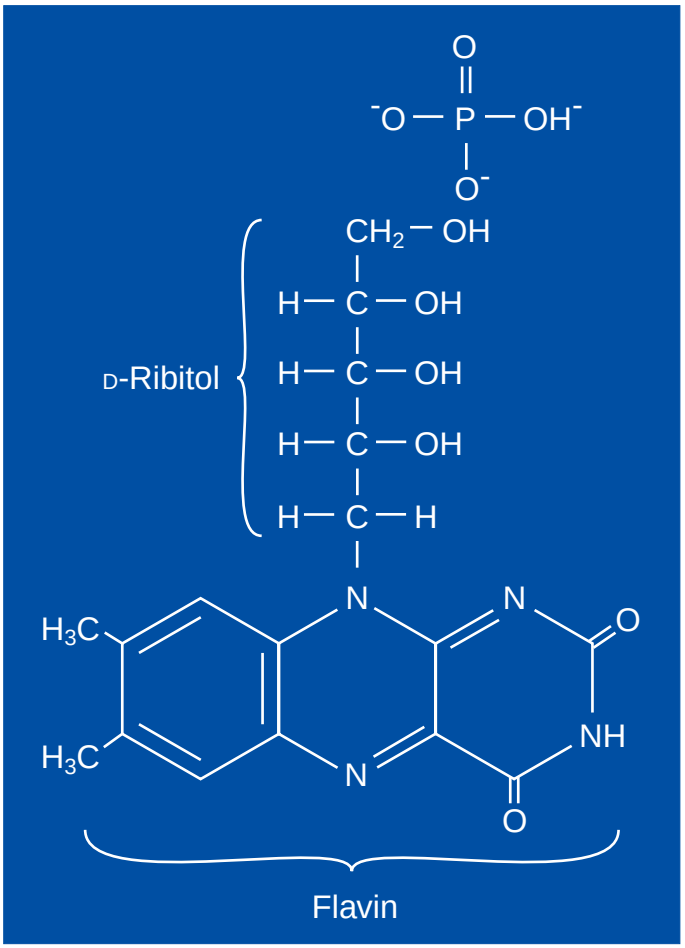


Figure 2. Riboflavin 5'Phosphate: The active form of riboflavin.



histamine, plasmakinin, epinephrine, and norepinephrine.[2,13] Many nutritional and botanical therapies aim to decrease platelet aggregation to inhibit the release of inflammatory neurotransmitters.

Conventional Treatment

Conventional treatments include the symptomatic use of NSAIDs, beta-blockers, tricyclics such as amitriptyline, ergotamine derivatives, and selective-serotonin receptor agonists such as sumatriptan.[14] Sumatriptan acts on a particular 5-HT-1 subtype and works by selectively constricting intracranial arteries.[15] Sumatriptan is contraindicated in coronary artery disease,[16] and an FDA report cited cases of coronary vasospasm, myocardial ischemia, and myocardial infarction occurring after sumatriptan use. Eight serious cases of ischemic colitis have also been reported in patients with migraine treated with sumatriptan.[17]

Specific Nutrient Therapy

Riboflavin: Several studies have shown high-dose riboflavin, a co-enzyme in the electron-transport chain, to be effective in migraine prophylaxis (Figure 2). Altered mitochondrial energy metabolism may play a role in migraine pathogenesis, and patients with migraines have demonstrated a reduction in mitochondrial phosphorylation potential in between attacks.[18] Theoretically, riboflavin may work by increasing mitochondrial energy efficiency. Recently, Schoenen et al compared 400 mg riboflavin to placebo in 55 patients with migraine in a randomized trial of three months duration. Riboflavin proved superior to placebo in reducing both attack frequency (p=.005) and headache days (p=.012). The number of patients in the study who improved by at least 50 percent was 15 percent in placebo and 59 percent in the riboflavin group (p=.02). Three minor adverse reactions were reported. Two occurred in the riboflavin group (diarrhea and polyuria) and one in the placebo group (abdominal cramping).[19]

In a previous pilot study, 49 patients with migraine (45 without aura, 4 with) were treated with a daily dose of 400 mg riboflavin for at least three months. There was a mean global improvement of 68.2 percent. With the exception of one subject who withdrew due to gastric intolerance (this person was also taking small amounts of aspirin), no other side effects were reported.[18]

The tricyclic anti-depressant amitriptyline is sometimes prescribed for migraines. It should be noted, however, this medication appears to interfere with riboflavin metabolism, increasing its renal excretion.[20] Although supported by only a few clinical

reports, prophylactic migraine therapy using high-dose riboflavin may prove to be part of a safe, low-cost and effective treatment program.

Magnesium: Several researchers have suggested magnesium plays an integral role in establishing a threshold for migraine attacks. The activities of magnesium in the body include counteracting vasospasm, inhibiting platelet aggregation, and stabilizing cell membranes, all of which are involved in migraine pathogenesis (Table 1).[21] Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, inflammatory mediators, and a variety of other migraine related receptors and neurotransmitters. Magnesium has also been shown to inhibit platelet aggregation and adhesion *in vitro*, and reduce the formation of inflammatory eicosanoids. Intravenous magnesium inhibits platelet function *in vivo*, when given in conjunction with aspirin.[22] Current evidence suggests up to 50 percent of migraine patients have lowered levels of ionized magnesium during an acute migraine attack.[23] Researchers determined migraine patients, both with and without aura, had significantly lower red blood cell magnesium levels than normal controls.[24,25] One study found brain magnesium concentrations were 19-percent lower in patients during migraine attack compared to healthy controls.[25]

Eighty-one patients ages 18-65 with migraine, with a mean attack frequency of 3.6 per month, were given 600 mg oral magnesium (trimagnesium citrate) for twelve weeks or placebo. During the ninth through the twelfth week of the study, migraine attack frequency was reduced 41.6 percent in the magnesium group versus 15.8 percent in the placebo group ($p<0.05$). The number of days with migraine also decreased significantly in the magnesium group. Duration and intensity of attacks, and drug consumption per attack also decreased in the magnesium group but failed to be significant. Adverse reactions included diarrhea (18.6%) and gastric irritation (4.7%).[26]

In a Japanese study, Mishima et al compared platelet-ionized magnesium and cyclic AMP levels in patients with tension-type headaches and migraines. While subjects with tension-type headaches had significantly lower platelet ionized magnesium, the migraine group demonstrated increased platelet levels of cyclic AMP, suggesting possible alterations of neurotransmitters within the platelet.[27]

In light of its potential deficiency in many migraine sufferers, its ability to inhibit platelet aggregation, and its clinically documented efficacy, the prophylactic use of magnesium in migraine seems well indicated.

Table 1. Therapeutic actions of magnesium.

Inhibit platelet aggregation
Counteract vasospasm
Stabilize cell membranes
Reduce formation of inflammatory eicosanoids

5-Hydroxytryptophan: Much of the research on the pathogenesis of migraine has demonstrated alterations in the serotonergic system.[28] One study evaluated serotonin and platelet MAO activity in women with migraine versus healthy female controls. Urinary metabolites of serotonin (5HIAA) were higher in the migraine group than those of controls. The migraine group also demonstrated significantly lower levels of serotonin during the luteal phase, suggesting an increased catabolism and/or reduced synthesis of serotonin in menstrual migraine.[29]

Beta-blockers such as propranolol are used in conventional migraine treatment, yet are often accompanied by undesirable side

Figure 3. *Tanacetum parthenium.*

effects in some patients. Thirty-nine migraine patients participated in a double-blind trial, receiving 5-hydroxytryptophan (5-HTP) or propranolol for four months. Both substances resulted in a statistically significant reduction in the frequency of migraine attacks suggesting 5-HTP may be a possible alternative for many migraine patients.[30]

In a double-blind, crossover trial, eight patients were given 500 mg L-tryptophan or placebo (L-leucine) every six hours. At the end of three months, the mean headache index, defined as number of attacks multiplied by the intensity, was 32.8 percent lower in the L-tryptophan group.[31]

Melatonin: Preliminary research has discovered melatonin abnormalities in migraine patients. Claustrat et al found four of six female migraine patients had significantly disturbed plasma melatonin profiles compared to healthy controls. The maximum melatonin level in migraine patients occurred much later during the night than in controls. When melatonin was administered to correct the phase-delay, many of the subjects experienced relief of migraine symptoms.[32]

Thirty patients with delayed sleep phase syndrome were given 5 mg of melatonin in this preliminary study and evaluated for its effect on both chronic tension-type headaches and migraine. It was observed in one 54-year-old man, who had suffered from severe migraine attacks twice a week, that after beginning melatonin treatment he reported only three migraines over the next twelve months.[33] Despite the lack of larger, more migraine specific trials with melatonin, these preliminary studies suggest melatonin may be helpful to migraine sufferers with delayed sleep phase syndrome in reducing and preventing headaches.

Botanical Considerations

Feverfew: *Tanacetum parthenium* (feverfew) has a long history of medicinal use for the treatment of fever, arthritis, and migraines (Figure 3). It is a member of the Asteraceae family and is rich in sesquiterpene lactones. Parthenolide was found to be the main constituent of the lactones and is believed to be responsible for feverfew's anti-migraine effects.[34]

Feverfew inhibits the release of serotonin and histamine from platelets, and decreases the smooth muscle response to endogenous vasoactive substances, such as norepinephrine, acetylcholine, prostaglandins, bradykinin, histamine, and serotonin. It has also been shown to produce dose-dependent inhibition of inflammatory leukotrienes and thromboxane B2.[35,36]

In one double-blind crossover study, 72 patients were randomly given either one capsule of dried feverfew leaf or placebo for four months, then switched to the other treatment for an additional four months. Fifty-nine patients finished the study which found treatment with feverfew was associated with

a reduction in the mean number and severity of attacks, and in the degree of vomiting. The duration of individual attacks was unaltered and no serious side-effects were reported.[37]

Seventeen migraine sufferers who had been using feverfew prophylactically were selected for a double-blind study. They were given either a 50 mg capsule of feverfew or placebo. The mean frequency of attacks in the placebo group increased from 1.22 monthly prior to the study to 3.43 attacks during the final three months of the six-month study. Patients remaining on feverfew continued to experience migraine relief and reported a far lower incidence of nausea and vomiting than the placebo group.[38]

The minimum recommended dosage is 125 mg of dried feverfew leaf standardized to 0.2-percent parthenolide content. It is recommended feverfew be used continuously for at least four to six weeks to determine efficacy. No long-term toxicity studies have been performed on feverfew; however, the only reported side-effect was mouth ulcerations, and this occurred mainly in individuals chewing the leaves. Feverfew is contraindicated during pregnancy, lactation, and in children less than two years of age.[36]

Ginger: *Zingiber officinale* (ginger) has been used in Ayurvedic and Chinese medicine for centuries as a carminative and intestinal spasmolytic.[34] Recent studies have found the active ingredients – gingerols and shogaols – are capable of inhibiting platelet aggregation.[39] In an *in vitro* study, platelet rich plasma was incubated with an ethanol extract of ground ginger. The ginger extract completely inhibited arachidonate-induced platelet aggregation.[40] Kiuchi et al determined gingerols are potent inhibitors of prostaglandin synthetase and are also effective at inhibiting leukotriene biosynthesis.[41] By inhibiting these inflammatory neurotransmitters, ginger, much like feverfew, may play an important role in migraine prevention.

While specific clinical evaluations of ginger and migraine have yet to be conducted, there was an observational report published in the *Journal of Ethnopharmacology*. A 42-year-old woman with a long history of migraines discontinued all medications for 2-3 months and began taking 500-600 mg dried ginger at the onset of the visual aura. This dose was repeated every four hours for four days. The authors reported improvement within thirty minutes of administering the ginger. It was also noted as ginger was subsequently added to her daily diet migraines decreased in frequency and severity.[42]

There does not appear to be any associated toxicity with ginger. A recommended dosage is one gram daily of dried ginger.[34]

Ginkgo : Kovac's study on platelet aggregation in migraine patients also determined abnormalities in platelet-activating factor (PAF) and proposed the idea of using PAF antagonists in migraine patients.[10] *Ginkgo biloba* extract has been shown to contain three specific PAF antagonists.[43] Two clinical trials using Ginkgo extract were conducted in France and, although these studies were small, they suggest Ginkgo may be beneficial in migraine patients.[44] The recommended dosage of Ginkgo, standardized to 24-percent ginkgo heterosides, is 40 mg three times per day.[34]

Dietary factors

It is estimated that 20 percent of migraines are caused by food sensitivities.[45] Certain foods containing vasoactive amines, such as tyramine and phenylalanine, can cause migraines in sensitive patients. Examples include aged cheeses, red wine, beer, chocolate, and yogurt.[46] Food additives such as monosodium glutamate, aspartame, and sodium nitrate are also recognized migraine triggers.[47] Littlewood et al found migraine sufferers have significantly lower levels of platelet phenolsulphotransferase than normal controls.

Table 2. Treatment considerations for migraines

Nutritional Deficiencies
Riboflavin
Magnesium
Botanicals
Feverfew
Ginger
Ginkgo
5-HTP / Melatonin
Lifestyle / Dietary Factors
Stress reduction
Food allergies / sensitivities
Hypoglycemia
Elimination diet
Other Alternatives
Acupuncture
Spinal manipulation

This enzyme and its variants inactivate monoamines; and the author suggests low gut activity of this enzyme may allow large amounts of these potentially toxic substances to pass into the bloodstream.[48]

Several studies support the idea migraines may be caused or exacerbated by food allergies. Sixty patients with migraines were studied – mean duration of migraines was 18 years for women and 22 years for men. When patients were put on an exclusion diet for five days, migraines disappeared by the fifth day in most cases. The mean number of foods causing symptoms was ten per patient, the most frequent offenders being 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 offending foods were avoided all patients improved. In fact, the number of headaches fell from 402 to 6 per month, with 85 percent of the subjects becoming headache free.[49]

Elimination diets have been shown to be valuable in treating migraine. When 88 children with severe migraines were put on an oligoantigenic diet, 93 percent improved.[50] In another study of 17 patients who completed an elimination diet, migraine attacks were found to be most frequently caused by cow's milk (10 out of the 17). Other culprits included flour, eggs, cheese, pork, and artificial colors and preservatives.[51] In addition to food allergies, other gastrointestinal abnormalities have been detected in migraine patients. When 225 migraine patients were assessed for *Helicobacter pylori* with a 13C-urea breath test, 40 percent tested positive. After eradicating the *H. pylori*, intensity, duration, and frequency of migraine attacks were significantly reduced.[52]

In addition to the avoidance of tyramine-containing foods and identification of potential food allergies, blood sugar abnormalities should also be considered. When a five-hour glucose tolerance test was performed on 74 migraine patients who commonly had headaches in the mid-morning or mid-afternoon, not only were eight percent found to be diabetic, but 76 percent were classified as having reactive hypoglycemia. After initiating dietary therapy to regulate blood sugar, 56 percent with reactive hypoglycemia experienced a 75-percent improvement in both the frequency and severity of migraine attacks.[53]

Physical Treatments

A variety of physical approaches can be beneficial to migraine patients, including biofeedback, physical therapy, stress management, acupuncture, and spinal manipulation. It is believed migraine sufferers do not encounter more stress than headache-free individuals; rather, over-responsiveness to stress appears to be the issue. Thus, lessening response to stress with the use of techniques such as biofeedback, meditation, yoga, and hypnosis may be effective.

Acupuncture has been shown to modulate serotonin and substance P levels within the platelet and may be effective in treating migraines.[54] Twenty-five patients with an average migraine history of 22 years were treated with acupuncture. The study consisted of three 12-week periods – a pre-treatment baseline period, treatment, and follow-up. Patients experienced a 39.5 percent average reduction in migraine severity during both the treatment and follow-up periods. The number of days with migraine was reduced by 34.5 percent on average, during treatment and through the follow-up period (p=.05).[55]

Spinal manipulation was compared to amitriptyline alone or in combination over an eight-week period for the prophylaxis of migraines. After a four-week baseline period, subjects (n=218) were assigned to eight weeks of treatment, followed by a four-week follow-up period. Results were based on headache index scores derived from daily headache pain diaries. Clinically significant improvements were seen in all three groups compared to baseline: 49-percent reduction in the amitriptyline group, 40-percent reduction in the spinal manipulation group, and 41 percent in the combined group (p=0.66). During post-treatment follow-up, the differences were more significant with 24-percent reduction in pain scores in the group who had been receiving amitriptyline, 42 percent for spinal manipulation, and 25 percent for the combined group.[56]

Certain pharmaceuticals and botanical medicines are contraindicated during pregnancy and lactation. Schaff et al investigated alternative approaches in 30 pregnant women suffering from migraines who were treated with physical therapy, relaxation training, and biofeedback. Eighty percent of these women experienced significant headache relief following treatment. Furthermore, 67.5 percent experienced a significant decrease in migraines up to one year after giving birth.[57]

Summary

After reviewing the literature, it is clear there are effective nutritional, botanical, dietary, and other alternative approaches to treating and preventing migraines (Table 2). Migraine is a multi-factorial disease with a variety of potential underlying causes. Stress, food allergies, neuroendocrine imbalances, and nutritional deficiencies all may contribute. Many nutritional and botanical therapies aim to reduce migraine incidence by decreasing platelet aggregation and preventing the release of vasoactive inflammatory neurotransmitters. A comprehensive approach involving specific nutrients and botanicals, in conjunction with appropriate dietary and lifestyle modifications, may prove to be the most efficacious way to approach migraine headaches.

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