

Diagnostic summary 1401**General considerations 1401**

Classification and diagnosis 1402
 Pathophysiology 1402

Therapeutic considerations 1404

Drug reaction 1405
 Diet 1406
 Nutritional supplements 1408
 Physical medicine 1409
 Botanical medicines 1411

Therapeutic approach 1411

Migraine headache

Michael T. Murray, ND

Joseph E. Pizzorno Jr, ND

DIAGNOSTIC SUMMARY

- Recurrent, paroxysmal attacks of headache
- Headache is typically pounding and unilateral, but may become generalized
- Attacks often preceded by psychological or visual disturbances; accompanied by anorexia, nausea, and gastrointestinal upset; and followed by drowsiness.

GENERAL CONSIDERATIONS

Migraine headaches are caused by excessive dilation of a blood vessel in the head. Migraines are a surprisingly common disorder, at some time in their life affecting 15–20% of men and 25–30% of women.¹ More than half of the patients have a family history of the illness.

Although many migraines come without warning, many migraine sufferers have warning symptoms (auras) before the onset of pain. Typical auras last a few minutes and include:

- blurring or bright spots in the vision
- anxiety
- fatigue
- disturbed thinking
- numbness or tingling on one side of the body.

In vascular headaches, like migraine headaches, the pain is characterized by a throbbing or pounding sharp pain. In non-vascular headaches, like tension headaches, the pain is characterized as a steady, constant, dull pain that starts at the back of the head or in the forehead and spreads over the entire head, giving the sensation of pressure or as if a vise grip has been applied to the skull (see Table 172.1 for primary classifications of headaches).

The pain of a headache comes from outside the brain because the brain tissue itself does not have sensory nerves. Pain arises from the meninges and from the scalp and its blood vessels and muscles when these structures are stretched or tensed.

The most common non-vascular headache is the

Table 172.1 Primary classifications of headache*Vascular headache*

- Migraine headache
 - classic migraine
 - common migraine
 - complicated migraine
 - variant migraine
- Cluster headache
 - episodic cluster
 - chronic cluster
 - chronic paroxysmal hemicrania
- Miscellaneous vascular headaches
 - carotidynia
 - hypertension
 - exertional
 - hangover
 - toxins and drugs
 - occlusive vascular disease

Non-vascular

- Tension headache
 - common tension headache
 - temporomandibular joint (TMJ) dysfunction
- Increased or decreased intracranial pressure
- Brain tumors
- Sinus infections
- Dental infections
- Inner or middle ear infections

tension headache. This headache is usually caused by tightening in the muscles of the face, neck, or scalp as a result of stress or poor posture. The tightening of the muscles results in pinching of the nerve or its blood supply which results in the sensation of pain and pressure. Relaxation of the muscle usually brings about immediate relief.

Classification and diagnosis

Migraine headache has been subdivided into several types, based on the presence or absence of preceding or concomitant neurological manifestations and the nature of the manifestations. Although there are several subtypes, the three most common (*common*, *classic*, and *complicated*) comprise the vast majority of patients, and differentiation, while important, does not at this time have any therapeutic significance. The differentiation and diagnosis of these types are summarized in Table 172.2.

Cluster headache was once considered a migraine-type headache, since vasodilation is a key component, but

it is now separately classified. Also referred to as histamine cephalgia, Horton's headache, or atypical facial neuralgia, it is much less common than migraine.

Another headache to be considered in this chapter is chronic daily headache (CDH). Approximately 40% of patients seen in headache clinics suffer from CDH. Other terms used to describe CDH by doctors include:

- chronic tension headache
- migraine with interparoxysmal headache
- transformed migraine
- evolutive migraine
- mixed headache syndrome
- tension-vascular headache.

To simplify matters, CDH has now been divided into four major types (see Table 172.3).

Pathophysiology

Considerable evidence supports an association between migraine headache and vasomotor instability, but the mechanisms are not yet known. Although most clinicians and researchers believe that the sequence of events is excessive intracranial arterial constriction (causing brain ischemia) followed by rebound dilation of the extracranial vessels (the headache phase), sophisticated studies of sequential cerebral blood flow before, during, and after are inconsistent in their support of this hypothesis.^{2,3}

Vasomotor instability

It is a well-known clinical observation that superficial temporal vessels are visibly dilated and local compression of these vessels or the carotid artery temporarily relieves migraine pain.⁴ However, other types of extracranial vasodilation (e.g. heat- or exercise-induced) are not associated with migraine. Despite the extracranial vasodilation, the patient appears pale during the headache, suggesting constriction of the small vessels. This is supported by the observation of lower skin temperature on the affected side.

The clinical manifestations of focal or diffuse cerebral or brain stem dysfunction have been attributed to intracranial vasoconstriction. A majority, but not all, of the studies measuring cerebral blood flow have confirmed

Table 172.2 Migraine classification

	Common	Classic	Complicated
Incidence	80%	10%	10%
Pain	Frontal, uni/bilateral	Unilateral	Unpredictable, may be absent
Aura	Unusual	0.5 hour, striking	Neurological aura, vertigo, syncope, diplopia, hemiparesis
Duration of headache	1–3 days	2–6 hours	Unpredictable
Physical examination	Unhappiness	Pallor, vomiting	Mild neurological signs, speech disorder, hemiparesis, unsteadiness, cranial nerve III palsy

Table 172.3 The four types of chronic daily headache

-
- Transformed migraine
 - drug-induced
 - non-drug-induced
 - Chronic tension-type headache
 - New daily persistent headache
 - Post-traumatic headache
-

a reduction of blood flow, sometimes to very low and critical levels, during the prodromal stage. This is followed by a stage of increased blood flow that can persist for more than 48 hours. There is significant decrease in regional cerebral blood flow in classic, but not common, migraine.⁵ The abnormal blood flow appears confined to the cerebral cortex, while deeper structures are perfused normally.

There is some evidence that migraine patients have an inherited abnormality of vasomotor control. Migraine patients suffer from orthostatic symptoms more often than normal people, and they seem to be abnormally sensitive to the vasodilatory effects of physical and chemical agents.

Platelet disorder

The migraine platelet shows significant differences from the normal platelet both during and between headaches.⁶ These differences include a significant increase in spontaneous aggregation, highly significant differences in the manner of serotonin release, and significant differences in platelet composition.

The major proponent of the platelet hypothesis is Hanington,⁶ who starts with the observation that the most common precipitant of migraine is some type of stressor. This results in a rise in plasma catecholamine levels which triggers the release of serotonin and resultant platelet aggregation and vasoconstriction.

The platelets of migraine sufferers aggregate more readily than normal platelets, both spontaneously and when exposed to serotonin (and to adenosine diphosphate and catecholamines). The increase in spontaneous aggregation is similar to that reported in patients suffering from transient cerebral ischemic attacks (TIAs). This is significant, considering the close resemblance of the symptomatology of TIAs and the prodromal phase of the migraine headache.

The onset of an attack is accompanied by a significant rise in plasma serotonin levels, followed by an increase in urinary 5-hydroxyindoleacetic acid, the breakdown product of serotonin metabolism. All of the serotonin normally in the blood is stored in the platelets and is released by platelet aggregation and in response to various stimuli, such as catecholamines. There is no difference in total serotonin content between normal platelets and the platelets of migraine patients. However,

the quantity of serotonin released by the platelets of the migraine patient in response to serotonin stimulation, while normal (or even subnormal) immediately after an attack, becomes progressively higher as the next attack approaches.⁶

The platelet hypothesis is strengthened by the observation that patients with classic migraine have a twofold increase in incidence of mitral valve prolapse.⁷ Using careful clinical and echocardiographic criteria and matched controls, the researchers found in the migraine patients definite mitral prolapse in 16% and possible prolapse in 15%. The controls had 7 and 8%, respectively. This is of significance, since the prolapsing mitral valve is known to damage platelets and increase their aggregation. This work has been confirmed in several studies.^{8,9}

Neuronal disorder

A third major hypothesis is that the nervous system plays a role in initiating the vascular events in migraine.¹ It has been suggested that the trigeminovascular neurons, which innervate the pial arteries, release peptide substance P either in direct response to the various initiators or secondarily to changes in the central nervous system.¹⁰ Substance P is an important mediator of pain, and its release into the arteries is associated with vasodilation, mast cell degranulation, and increased vascular permeability. It is thought that the endothelial cells of the arteries respond to substance P by releasing vasoactive substances, such as arachidonic acid metabolites, purine compounds, or molecules containing carbonyl groups.

This theory suggests that functional changes within the noradrenergic system constitute the threshold for migraine activation, and it is through modulation of sympathetic activity that potentiators exert their effect.¹⁰ Chronic stress is thought to be an important potentiator in this model.

Migraine as a "serotonin deficiency" syndrome

The final hypothesis is that migraine headache represents a serotonin deficiency state. The story of serotonin and headaches began in the 1960s when researchers found that there was an increase in the serotonin breakdown product 5-hydroxyindoleacetic acid (5-HIAA) in the urine during a migraine.¹¹ Initially it was thought that serotonin excess was the culprit; however, newer information indicates that the factor responsible for the increase in 5-HIAA is more likely the increased breakdown of serotonin as a result of increased activity of monoamine oxidase (MAO).^{12,13} Because migraine sufferers actually have low levels of serotonin in their tissues, it led researchers to refer to migraine as a "low serotonin syndrome".¹⁴

Low serotonin levels are thought to lead to a decrease

in the pain threshold in patients with chronic headaches. This contention is strongly supported by over 35 years of research, including positive clinical results in double-blind studies with the serotonin precursor 5-hydroxytryptophan (5-HTP). For more information on the clinical studies with 5-HTP in migraine headaches, see Chapter 92.

The link between low serotonin levels and headache is the basis of many prescription drugs for the treatment and prevention of migraine headaches. For example, the serotonin agonist drug sumatriptan (Imitrex) is now among the most popular migraine prescriptions. In addition to sumatriptan, monoamine oxidase inhibitors (which increase serotonin levels) have also been shown to prevent headaches. The bottom line is that there is considerable evidence that increasing serotonin levels leads to relief from chronic migraine headaches.

The effects that 5-HTP, sumatriptan, and other drugs exert on the serotonin system are extremely complex because of the multiple types of serotonin receptors. The manner in which many substances produce their effects on cells is by first binding to receptor sites on the cell membrane. Some serotonin receptors are involved in triggering migraines and others prevent them. This situation is quite clear by looking at the different effects that various drugs exert when binding to these different serotonin receptors. Drugs which bind to serotonin receptors designated as 5-HT_{1c} trigger migraines, while drugs like methysergide that inhibit 5-HT_{1c} are used to prevent migraines.¹⁵ In addition, the serotonin receptor 5-HT_{1d} may prevent migraine headaches since drugs like sumatriptan which bind to these receptors and mimic the effects of serotonin are quite effective in the acute treatment of migraine.¹⁶

5-HTP supplementation affects these different receptors in several ways. For example, some serotonin receptors appear to undergo desensitization when exposed to higher levels of serotonin. It is thought that by increasing serotonin levels, 5-HT_{1c} lose their ability or affinity to bind serotonin, resulting in more serotonin binding to the 5-HT_{1d} receptor. In other words, it is thought that what is occurring with 5-HTP in the preventive treatment of migraine headache is that the higher levels of serotonin produced over time result in a decrease in the sensitivity of the 5-HT_{1c} receptors and an increased sensitivity for 5-HT_{1d} receptors.¹⁷ As a result, there would be a lowered tendency to experience headache. One of the key pieces of evidence to support this concept is the fact that 5-HTP is more effective over time (better results are seen after 60 days of use than after 30).

Unified hypothesis

The mechanism of migraine can be described as a three-stage process: initiation, prodrome, and headache.

Table 172.4 Factors that trigger migraine headaches

-
- Low serotonin levels
 - genetics
 - shunting of tryptophan into other pathways
 - Foods
 - food allergies
 - histamine-releasing foods
 - histamine-containing foods
 - Alcohol, especially red wine
 - Chemicals
 - nitrates
 - MSG (monosodium glutamate)
 - nitroglycerin
 - Withdrawal from caffeine or other drugs which constrict blood vessels
 - Stress
 - Emotional changes, especially let-down after stress, and intense emotions, such as anger
 - Hormonal changes, e.g. menstruation, ovulation, birth control pills
 - Too little or too much sleep
 - Exhaustion
 - Poor posture
 - Muscle tension
 - Weather changes, e.g. barometric pressure changes, exposure to sun
 - Glare or eyestrain
-

Although a particular stressor may be associated with the onset of a specific attack, it appears that initiation is dependent on the accumulation over time of several stressors. These stressors ultimately affect serotonin metabolism (see Table 172.4). Once a critical point of susceptibility (or threshold) is reached, a cascade event is initiated. This susceptibility is probably a combination of decreased tissue serotonin levels, changes in the platelet, alteration in the responsiveness of key cerebrovascular end-organs, increased sensitivity of the intrinsic noradrenergic system of the brain, and the build-up of histamine, arachidonic acid metabolites, or other mediators of inflammation. The platelet changes include increased adhesiveness, enhanced tendency to release serotonin, and increased levels of arachidonic acid in the membranes. Once the platelet is stimulated to secrete serotonin, platelet aggregation, vasospasm, and inflammatory processes result in local cerebral ischemia. This is followed by rebound vasodilation and the release of peptide substance P and other mediators of pain. These events are summarized in Figure 172.1.

THERAPEUTIC CONSIDERATIONS

Modern pharmacological treatment of headache, whether migraine or tension, is ultimately doomed because it fails to address the underlying cause. The first step in treating migraine headache is identifying the precipitating factor. Although food intolerance/allergy is the most important, many other factors must be considered as either primary causes or contributors to the migraine process. In particular, it is very important to assess the

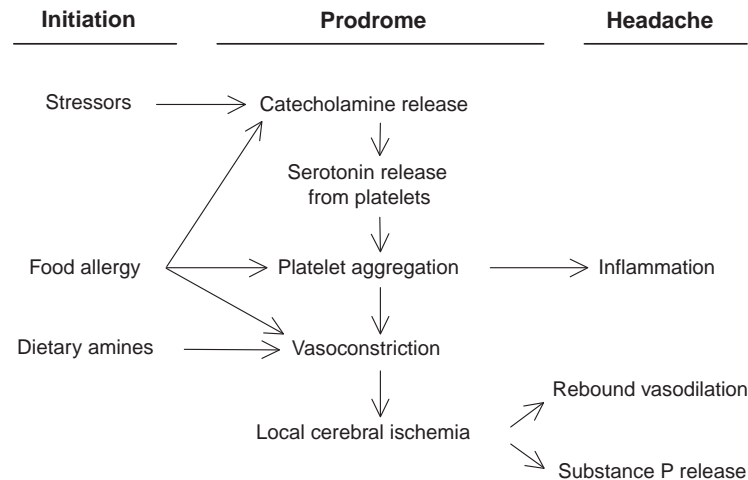


Figure 172.1 The pathogenesis of migraine.

role that headache medications may be playing, especially in chronic headaches.

Drug reaction

Several clinical studies have estimated that approximately 70% of patients with chronic daily headaches suffer from drug-induced headaches.¹⁸ There are two main forms of drug-induced chronic daily headaches: analgesic rebound headache and ergotamine rebound headache.¹⁹

Withdrawal of medication results in prompt clinical improvement in most cases. In one study (summarized in Table 172.5) of 200 patients suffering from analgesic-rebound headache, discontinuation of these symptomatic medications resulted in 52% improvement in the total headache index, improvements in headache frequency and severity, general well-being, sleep patterns, and a reduction in irritability, depression, and lethargy.¹⁹

These 200 patients were typical in that they sought relief from a variety of drugs. Table 172.6 lists the types

Table 172.5 Profile of 200 patients with chronic daily headache

Medications	Average no. of tablets/week	Range of no. of tablets/week	No. of patients	Percentage of patients
Butalbital/aspirin, acetaminophen/caffeine with or without codeine	30	14–86	84	42
Codeine	28	10–84	80	40
Aspirin or acetaminophen with caffeine	42	14–108	50	25
Ergotamine	15 mg	6–42 mg	44	22
Acetaminophen	52	15–105	34	17
Propoxyphene	26	14–56	32	16
Nasal decongestants and antihistamines	14	6–30	24	12
Aspirin	28	10–64	8	4

Table 172.6 Commonly used drugs to prevent migraine headaches

Drug	Adult daily dosage	Common side-effects
Aspirin	650–1950 mg	Gastric irritation, ulcer formation
Propranolol	80–240 mg	Fatigue, lassitude, depression, insomnia, nausea, vomiting, constipation
Amitriptyline and imipramine	10–150 mg	Drowsiness, dry mouth, constipation, weight gain, blurred vision, water retention
Sertraline	50–200 mg	Anxiety, insomnia, sweating, tremor, gastrointestinal disturbances
Fluoxetine	20–60 mg	Similar to those of sertraline
Ergonovine maleate	0.6–2 mg	Nausea, vomiting, abdominal pain, diarrhea
Cyproheptadine	12–20 mg	Sedation, dry mouth, gastrointestinal disturbances
Clonidine	0.2–0.6 mg	Dry mouth, drowsiness, sedation, headache, constipation
Methysergide	4–8 mg	Nausea, vomiting, diarrhea, abdominal pain, cramps, weight gain, insomnia, edema, decreased blood flow to extremities, heart and lung fibrosis
Calcium-channel blockers (verapamil, nifedipine, diltiazem, etc.)	80–160 mg	Headache, low blood pressure, flushing, water retention, constipation

of drugs used for symptomatic relief. Most of these patients took at least three of these preparations at the same time.

Analgesic-rebound headache

In the early 1980s, it began to be quite apparent in the medical literature that headache medications increase the tendency for headache and perpetuate chronic headache. Early reports were labeled “paradoxical” in that heavy analgesic users experienced headaches of much greater frequency and intensity. For example, in one study it was found that sufferers of migraine headaches who took more than 30 analgesic tablets per month had twice as many headache days per month as those who took fewer than 30 tablets.²⁰ This finding led to the recommendation that analgesic use should be restricted in patients with chronic daily headaches.

In another study, 70 patients with daily headaches who were consuming 14 or more analgesic tablets per week were told to discontinue their use.²¹ One month later, 66% of the patients were improved. At the end of the second month, this percentage had grown to 81%.

Analgesic-rebound headaches should be suspected in any patient with chronic headaches who is taking large quantities of analgesics and who is experiencing daily predictable headache. The critical dosage which can lead to analgesic-rebound headache is estimated to be 1,000 mg of either acetaminophen or aspirin.

Analgesic medications typically contain substances in addition to the analgesic such as caffeine or a sedative like butabarbital. These substances further contribute to the problem and may lead to withdrawal headache and related symptoms such as nausea, abdominal cramps, diarrhea, restlessness, sleeplessness, and anxiety. Withdrawal symptoms typically start at 24–48 hours, and in most cases subside in 5–7 days.

Ergotamine-rebound headache

Ergotamine is the most widely used drug in the treatment of severe acute migraine and cluster headaches. Ergotamine works by constricting the blood vessels of the head, thereby preventing or relieving the excessive dilation of the blood vessels that is responsible for the pain of migraine and cluster headaches. Ergotamine is administered intramuscularly, by inhalation or by suppository since it is poorly absorbed when given orally.

Although usually quite effective, ergotamine is also associated with some significant side-effects. Symptoms of acute poisoning include:

- vomiting
- diarrhea
- dizziness

- rise or fall of blood pressure
- slow, weak pulse
- dyspnea
- convulsions
- loss of consciousness.

Symptoms of chronic poisoning include two types of manifestations: those resulting from blood vessel contraction and reduced circulation – numbness and coldness of the extremities, tingling, pain in the chest, heart valve lesions, hair loss, decreased urination, and gangrene of the fingers and toes – and those resulting from nervous system disturbances – vomiting, diarrhea, headache, tremors, contractions of the facial muscles, and convulsions.

Regular use of ergotamine in migraine headaches is also associated with a dependency syndrome characterized by severe chronic headache with an increase in headache intensity upon cessation of medication. Because most migraine headaches rarely occur more than once or twice a week, the presence of an almost daily migraine-type headache in individuals taking ergotamine is a good clue for ergotamine-rebound headache. Dosage of ergotamine can also be a clue. In most cases of ergotamine-rebound headache, individuals take weekly dosages in excess of 10 mg. In some cases, patients may be taking dosages as high as 10–15 mg daily.

Stopping ergotamine causes predictable, protracted, and extremely debilitating headache usually accompanied by nausea and vomiting. These symptoms usually appear within 72 hours and may last for another 72 hours. Improvement after stopping the medication is very common. Ginger (discussed below) may lessen ergotamine withdrawal symptoms.

Diet

Food allergy/intolerance

There is little doubt that food allergy/intolerance plays a role in many cases of migraine headache. Many double-blind, placebo-controlled studies have demonstrated that the detection and removal of allergic/intolerant foods will eliminate or greatly reduce migraine symptoms in the majority of patients. What is unclear is the percentage of migraine patients for whom food control is the most important factor. Table 172.7 summarizes the results of several clinical studies. As can be seen, success ranges from 30 to 93%, with the majority of studies showing a remarkably high degree of success.^{21–27}

A possible explanation for the large difference between the results of Mansfield et al²¹ and the others is that the Mansfield design was carefully selected for food allergy only, while the others included food intolerance. These studies found the incidence of food allergy to be similar for the three major types of migraine. The foods most

Table 172.7 Food allergy/intolerance and migraine headache

Study	Percentage responding	Method
Mansfield et al ²¹	30	Elimination
Carter et al ²²	93	Oligoantigenic diet
Hughes et al ²³	80	Fasting, rotation, elimination
Egger et al ²⁴	93	Elimination
Monro et al ²⁵	70	RAST, elimination, sodium cromoglycate
Grant ECG ²⁶	85	Elimination

commonly found to induce migraine headaches are listed in Table 172.8.

The mechanism by which food allergy/intolerance induces a migraine attack is still unknown. Several theories have been proposed:

- idiopathic response to a pharmacologically active substance, such as tyramine
- monoamine oxidase deficiency
- platelet phenolsulfotransferase deficiency; immunologically mediated food allergy
- platelet abnormalities, etc.

Table 172.8 Foods which most commonly induce migraine headaches

Food	Egger et al ²⁴	Hughes et al ²³	Monro et al ²⁵
Cow's milk	67%	57%	65%
Wheat	52	43	57
Chocolate	55	57	26
Egg	60	24	22
Orange	52	—	13
Benzoic acid	35	—	—
Cheese	32	—	—
Tomato	32	14	—
Tartrazine	30	—	—
Rye	30	—	—
Rice	—	—	30
Fish	22	29 (shell)	17
Grapes	12	33	—
Onion	—	24	—
Soy	17	24	—
Pork	22	—	17
Peanuts	12	29	—
Alcohol	—	29	9
MSG	—	19	—
Walnuts	—	19	—
Beef	20	14	—
Tea	17	—	17
Coffee	15	19	17
Nuts	12	19 (cashew)	17
Goat's milk	15	14	—
Corn	20	9	—
Oats	15	—	—
Cane sugar	7	19	—
Yeast	12	14	—
Apple	12	—	—
Peach	12	—	—
Potato	12	—	—
Chicken	7	14	—
Banana	7	—	—
Strawberry	7	—	—
Melon	7	—	—
Carrot	7	—	—

Egger et al²⁴ suggested that migraine headache may result from chronic alteration of the non-specific responsiveness of cerebral vascular end-organ as a result of long-term antigenic stimulation. This mechanism would be analogous to the response in asthma of the bronchioles to exercise or cold after antigen contact. Allergic reactions to foods are known to cause platelet degranulation, with resultant serotonin release.²⁷

There are several methods which can be used to detect food allergies, most of which are described in Chapter 15. Although laboratory procedures are probably the most convenient for the patient, challenge testing is thought to be the most reliable. Unfortunately, challenge testing has limitations: some foods evoke a delayed response, which may require several days of repeated challenge to elicit recognizable symptoms; also, ingestion of large amounts of several foods may be necessary to detect those that are marginally reactive. The recommended procedure for the diagnosis and management of food allergy/intolerance is described in the section on "Therapeutic approach" (p. 1411).

Dietary amines

Foods such as chocolate, cheese, beer and wine precipitate migraine attacks in many people because they contain histamine and/or other vasoactive compounds which can trigger migraines in sensitive individuals by causing blood vessels to expand (see Table 172.9).²⁸⁻³⁰ Red wine is much more likely than white wine to cause a headache because it contains 20–200 times the amount of histamine and also stimulates the release of vasoactive compounds by platelets.^{6,29,31} It is also much higher in flavonoids – the antioxidant components shown to help prevent heart disease. These compounds can also inhibit the enzyme (phenolsulfotransferase) which normally breaks down

Table 172.9 Factors involved with histamine-induced headaches

Histamine levels increased by:

- Histamine in alcoholic beverages (particularly red wine)
- Histamine in food
- Histamine-releasing foods
- Food allergy
- Vitamin B₆ deficiency

Histamine breakdown inhibited by:

- Vitamin B₆ antagonists
 - alcohol
 - drugs
 - food additives (e.g. yellow dye #5, monosodium glutamate)
- Vitamin C deficiency

Histamine release prevented by:

- Di-sodium chromoglycate
- Quercetin
- Antioxidants (e.g. vitamin C, vitamin E, selenium, etc.)

Histamine breakdown promoted by:

- Vitamin B₆
- Vitamin C

serotonin and other vasoactive amines in platelets. Many migraine sufferers have been found to have significantly lower levels of this enzyme.³² Since red wine contains substances which are potent inhibitors of this enzyme, it often triggers migraines in these individuals, especially if consumed along with high vasoactive amine foods like cheese or chocolate. The standard treatment of histamine-induced headache is the histamine-free diet along with vitamin B₆ supplementation.^{29,30}

The activity of the enzyme diamine oxidase, which breaks down histamine in the lining of the small intestine before it is absorbed into the circulation, appears to play a major role in determining whether or not a person is going to react to dietary histamine. Individuals sensitive to dietary histamine have lower levels (about half) of this enzyme in their tissues compared with control subjects.²⁹ Diamine oxidase is a vitamin B₆-dependent enzyme. Not surprisingly, compounds which inhibit vitamin B₆ also inhibit diamine oxidase.²⁹ These inhibiting factors include food coloring agents (specifically the hydrazine dyes like FD&C yellow #5), some drugs (isoniazid, hydralazine, dopamine, and penicillamine), birth control pills, alcohol, and excessive protein intake. Yellow dye #5 (tartrazine) is often consumed in greater quantities (per capita intake of 15 g/day) than the RDA for vitamin B₆ of 2.0 mg for males and 1.6 mg for females.

Vitamin B₆ supplementation (usually 1 mg/kg body weight) has been shown to improve histamine tolerance, presumably by increasing diamine oxidase activity.^{29,32} Women have lower levels of diamine oxidase which may explain their higher incidence of histamine-induced headaches. Women are also much more frequently unable to tolerate red wine.²⁹ Interestingly, the level of diamine oxidase in a woman increases by over 500 times during pregnancy.^{33,34} It is very common for women with histamine-induced headaches to experience complete remission of their headaches during pregnancy.

Nutritional supplements

5-HTP

The role of 5-HTP in preventing migraine headaches by increasing serotonin levels was discussed above. In addition to this mechanism of action, 5-HTP also increases endorphin levels. The use of 5-HTP in the prevention of migraine headache offers considerable advantages over drug therapy. Although a number of drugs have been shown to be useful in the prevention of migraine headaches, all of these currently used drugs carry with them significant side-effects. 5-HTP is at least as effective as other pharmacological agents used in the prevention of migraine headaches and is certainly much safer and better tolerated. While some studies have used a dosage of 600 mg/day, equally impressive results have been achieved at a dosage as low as 200 mg/day. The clinical

studies with 5-HTP in migraine headaches are discussed in Chapter 92.

EFAs and arachidonic acid

The role of essential fatty acids in the pathogenesis of migraine may be quite important but does not appear to have received much research attention. Considering the significance of platelet aggregation and arachidonic acid metabolites in the mediation of the events leading to the prodromal cerebral ischemia of migraine, manipulation of dietary EFAs may be very useful. It has been well demonstrated that reducing the consumption of animal fats and increasing the consumption of fish will significantly change platelet and membrane EFA ratios and decrease platelet aggregation.³⁵⁻³⁷

Riboflavin

Another hypothesis for explaining migraine headaches is that they are caused by a reduction of energy production within the mitochondria of cerebral blood vessels. If this hypothesis is true, riboflavin, which has the potential of increasing mitochondrial energy efficiency, might have preventive effects against migraine. To test this hypothesis, 49 patients suffering from migraine were treated with a very large dose (400 mg daily) of riboflavin for at least 3 months.³⁸ Overall improvement after therapy was 68.2% in the riboflavin group as determined by the migraine severity score used in the study. No side-effects were reported. The results from this preliminary study suggest high-dose riboflavin could be an effective, low-cost preventive treatment of migraine.

Magnesium

Low magnesium levels may also play a significant role in many cases of headaches as several researchers have provided substantial links between low magnesium levels and both migraine and tension headaches based on both theory and clinical observations.³⁹⁻⁴¹ A magnesium deficiency is known to set the stage for the events that can cause a migraine attack as well as a tension headache. Low brain and tissue magnesium concentrations have been found in patients with migraines, indicating a need for supplementation since one of magnesium's key functions is to maintain the tone of the blood vessels as well as preventing overexcitability of nerve cells.³⁹⁻⁴²

Unfortunately, two recent double-blind studies have given conflicting results in the prevention of migraines in people prone to recurrent migraine headaches. In the first study, 250 mg of magnesium or placebo was given twice daily to 69 patients (35 received magnesium, 34 the placebo) for 12 weeks.⁴³ The number of responders was

10 in each group (28.6% under magnesium and 29.4% under placebo). There was no benefit with magnesium compared with placebo in the number of migraine days or migraine attacks.

In the other double-blind study, 81 patients suffering from recurrent migraines were given either 600 mg of oral magnesium daily for 12 weeks or placebo.⁴⁴ By the ninth week, the attack frequency was reduced by 41.6% in the magnesium group compared with only 15.8% in the placebo group. The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Side-effects with magnesium supplementation included diarrhea (18.6%) and gastric irritation (4.7%).

It appears that magnesium supplementation may only be effective in those individuals with low tissue or low ionized levels of magnesium. Low tissue levels of magnesium are common in patients with migraine, but most cases go unnoticed because most physicians rely on serum magnesium levels to indicate magnesium levels, a very unreliable indicator as most of the body's store of magnesium lies within cells, not in the serum. A low magnesium level in the serum reflects end-stage deficiency. More sensitive tests of magnesium status are the level of magnesium within the red blood cell (erythrocyte magnesium level) and the level of ionized magnesium (the most biologically active form) in serum.

Another possible benefit of magnesium in migraine sufferers may be its ability to improve mitral valve prolapse. Mitral valve prolapse is linked to migraines because it leads to damage to blood platelets, causing them to release vasoactive substances like histamine, platelet-activating factor, and serotonin.⁷⁻⁹ Since research has shown that 85% of patients with mitral valve prolapse have chronic magnesium deficiency, magnesium supplementation is indicated.⁴⁵ This recommendation is further supported by several studies showing that oral magnesium supplementation improves mitral valve prolapse.

Magnesium bound to citrate, malate, aspartate, or some other Krebs cycle compound is better absorbed and better tolerated than inorganic forms, such as magnesium sulfate, hydroxide, or oxide, which tend to produce a laxative effect.⁴⁶ If magnesium produces a loose stool or diarrhea, advise the patient to cut back to a level that is tolerable. Also, it is a good idea to prescribe at least 50 mg of vitamin B₆ daily as this B vitamin has been shown to increase the intracellular accumulation of magnesium.⁴⁷

Intravenous magnesium for acute migraine headaches

Intravenous magnesium has been shown to be an extremely effective treatment in some cases of acute migraine, tension, and cluster headaches in three studies. A dosage of 1–3 g of intravenous magnesium (over a 10 minute

period) typically resulted in a nearly 90% success rate in patients with low ionized magnesium levels.⁴⁸⁻⁵⁰

In the first study, the efficacy of intravenous infusion of 1 g of magnesium sulfate (MgSO₄) was evaluated in 40 patients (16 patients had migraines without aura, nine had cluster headaches, four had chronic tension-type headaches, and 11 had chronic migraine headaches).⁴⁸ Complete elimination of pain was observed in 32 (80%) patients within 15 minutes of infusion of MgSO₄. No recurrence or worsening of pain was observed within 24 hours in 56% of the patients. Patients treated with MgSO₄ observed complete elimination of migraine-associated symptoms such as sensitivity to light and sound as well as nausea. No side-effects were observed, except for a brief flushed feeling. The eight non-responders exhibited significantly elevated serum ionized magnesium levels compared with responders prior to the infusion of MgSO₄.

In a study of migraine sufferers only, the hypothesis that patients with an acute attack of migraine headache and low serum levels (< 0.54 mmol/L) of ionized magnesium are more likely to respond to an intravenous infusion of magnesium sulfate (MgSO₄) than patients with higher serum ionized magnesium levels was tested.⁴⁹ Serum ionized magnesium levels were drawn immediately before infusion of 1 g of MgSO₄ in 40 consecutive patients with an acute migraine headache. Pain reduction of 50% or more, as measured on a headache intensity verbal scale of 1–10, occurred within 15 min of infusion in 35 patients. In 21 patients, at least this degree of improvement or complete relief persisted for 24 hours or more. Pain relief lasted at least 24 hours in 18 of 21 patients (86%) with serum ionized magnesium levels below 0.54 mmol/L, and in three of 19 patients (16%) with ionized magnesium levels at or above 0.54 mmol/L. The average ionized magnesium level in patients with relief lasting for at least 24 hours was significantly lower than that in patients with no relief or brief relief.

The final study involved patients with cluster headaches.⁵⁰ Because previous studies reported that low serum ionized magnesium levels are common in patients with cluster headaches, researchers examined the possibility that patients with cluster headaches and low ionized magnesium levels may respond to an intravenous infusion of magnesium sulfate. Infusions of magnesium sulfate given to 22 patients with cluster headaches produced meaningful improvement in nine (41%) of them – not great numbers, but certainly worth the effort and certainly much safer than the drugs used in the treatment of acute cluster headaches such as ergotamine.

Physical medicine

Many forms of physical medicine have been used in the treatment of migraine headache. Although most have

been shown to be effective in shortening the duration and decreasing the intensity of an attack, they appear relatively ineffective in actually curing this disorder. Although very effective for headaches which have a significant muscular contraction component, these methods appear to have more limited success in reducing the frequency of attacks of true migraine.

Cervical manipulation

In a 6 month trial in Australia, 85 patients were studied to determine the efficacy of manipulation of the cervical spine by a chiropractor in the treatment of migraine headache. The study was controlled by comparing chiropractic manipulation with manipulation by a medical practitioner or physiotherapist and with simple cervical mobilization. Although the study found no difference in frequency of recurrence, duration, or disability, the chiropractic patients reported greater reduction in the pain associated with the attacks.⁵¹

Temporomandibular joint dysfunction syndrome

Some researchers and clinicians have claimed that a substantial portion of headaches diagnosed as classic or common migraine are in reality the symptoms of temporomandibular joint dysfunction syndrome (TMJ). However, a careful investigation found that the incidence of migraine in patients with TMJ is similar to that in the general population, while the incidence of headache due to muscle tension is much higher.⁵² These results suggest that, while correction of TMJ dysfunction may be of use in the treatment of migraine headaches, it is far more important in muscle tension headaches.

Transcutaneous electrical stimulation

Transcutaneous electrical stimulation (TENS) has been shown in a placebo-controlled trial to be effective in the treatment of patients with migraine and muscle tension headaches (55% responded to treatment vs. an 18% placebo response).⁵³ However, the study also found that inappropriately applied TENS, i.e. TENS applied below perception threshold, was ineffective.

Acupuncture

The use of acupuncture in the treatment of migraine headache has received considerable research attention. However, assessing its efficacy is difficult since the studies have not been blind, migraine patients were seldom studied separately, and most of the research has been reported in foreign languages, with only summaries available in English.

Despite these limitations, sufficient evidence exists to support use of acupuncture to relieve migraine pain.⁵⁴⁻⁵⁶

It is interesting to note that the mechanism of relief is apparently not endorphin-mediated. One study found that the injection of saline or naloxone did not affect the efficacy of the therapy,⁵⁷ and another found that, while acupuncture increased endorphin levels in controls, the low levels of serum endorphins found in migraine patients did not increase with treatment.⁵⁸ The mechanism of action may instead be through normalization of serotonin levels. One study found that acupuncture was effective in relieving pain when it normalized serotonin levels, but was ineffective in relieving pain and in raising serotonin levels in those patients with very low levels of serotonin.⁵⁹

Acupuncture appears to have some success in reducing the frequency of migraine attacks, although, as mentioned above, limitations in experimental design make interpretation difficult. One study found that 40% of the subjects experienced a 50-100% reduction in severity and frequency.⁵⁷ Although the authors used a double-blind, cross-over design, the patients were only followed for 2 months. Another (uncontrolled) study found that five treatments (over a period of 1 month) decreased recurrence in 45% of the patients over a period of 6 months.⁶⁰

Biofeedback and relaxation therapy

The most widely used non-drug therapy for migraine headaches is thermal biofeedback and relaxation training. Thermal biofeedback utilizes a feedback gauge to monitor the temperature of the hands. The patient is then taught how to raise (or lower) the temperature of the hand by the device providing feedback as to what is affecting the temperature. Relaxation training involves teaching patients techniques designed to produce the "relaxation response" – a term used to describe the physiological state that is the opposite of the stress response. This term was originally coined by Harvard professor and cardiologist Herbert Benson MD in his best-selling book, *The relaxation response* (William Morrow 1975).

The effectiveness in reducing the frequency and severity of recurrent migraine headaches with biofeedback and relaxation training has been the subject of over 35 clinical studies.⁶¹ When the results from these studies were compared with studies using the beta-blocking drug Inderal (propranolol), it was apparent that the non-drug approach was as effective as the drug approach, but was without side-effect (see Table 172.10).

Table 172.10 Biofeedback/relaxation compared with propranolol – average percentage improvement per patient

Biofeedback/relaxation	56.4%
Propranolol	55.2%
Placebo	14.3%
Untreated	3.2%

Botanical medicines

Botanical medicines have a long history of use as folk cures for migraine headache. Although many botanicals have been used, few have received careful evaluation. Feverfew (*Tanacetum parthenium*) and ginger (*Zingiber officinalis*) are discussed here, as they have the most scientific documentation.

Tanacetum parthenium

Perhaps the most popular preventive treatment of migraine headaches is the herb feverfew. Scientific interest in feverfew began when a 1983 survey found that 70% of 270 migraine sufferers who had eaten feverfew daily for prolonged periods claimed that the herb decreased the frequency and/or intensity of their attacks.⁶² Many of these patients had been unresponsive to orthodox medicines. This survey prompted several clinical investigations of the therapeutic and preventive effects of feverfew in the treatment of migraine.^{62–65}

The first double-blind study was done at the London Migraine Clinic, using patients who reported being helped by feverfew.⁶² Those patients who received the placebo (and as a result stopped using feverfew) had a significant increase in the frequency and severity of headache, nausea, and vomiting during the 6 months of the study, while patients taking feverfew showed no change in the frequency or severity of their symptoms. Two patients in the placebo group who had been in complete remission during self-treatment with feverfew leaves developed a recurrence of incapacitating migraine and had to withdraw from the study. The resumption of self-treatment led to renewed remission of symptoms in both patients. The second double-blind study, performed at the University of Nottingham, demonstrated that feverfew was effective in reducing the number and severity of migraine attacks.⁶³

Follow-up studies to the clinical results have shown that feverfew works in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel-dilating substances from platelets, inhibiting the production of inflammatory substances, and re-establishing proper blood vessel tone.⁶⁴ The effectiveness of feverfew is dependent upon adequate levels of parthenolide, the active principle.⁶⁵

Zingiber officinalis

The common ginger root has been shown to exert significant effects against inflammation and platelet aggregation.^{66,67} Unfortunately, in relation to migraine headache, there is much anecdotal information but little clinical evidence. For example, a 1990 article described a 42-year-old woman with a long history of recurrent

migraines who discontinued all medications for a 3-month period prior to a trial of ginger.⁶⁸ For the trial, 500–600 mg of dried ginger was taken mixed with water at the onset of the migraine and repeated every 4 hours for 4 days. Improvement was evident within 30 minutes and there were no side-effects. The woman subsequently began to use uncooked fresh ginger in her daily diet. Migraines became less frequent and, when they did occur, they were at a “much lower intensity” than previously.

There remain many questions concerning the best form of ginger and the proper dosage. The most active anti-inflammatory components of ginger are found in fresh preparations and the oil.

THERAPEUTIC APPROACH

Migraine headache is a multifaceted disease, and indeed could be accurately described as a symptom rather than as a disease. The challenge for the clinician is to determine which of the several factors discussed here are responsible for each patient’s migraine process. Identification of the precipitating factors, and their avoidance, is important in reducing the frequency of headaches. Avoidance of initiators is particularly significant, considering that they are cumulative in effect.

Due to the high incidence (80–90%) of food allergy/intolerance in patients with migraine headache, diagnosis and management begins with 1 week of careful avoidance of all foods to which the patient may be allergic or intolerant. This can be accomplished through either a pure water fast or the use of an elemental diet (an oligoantigenic diet may be used but is less desirable, since significant allergens may be inadvertently included). All other possible allergens, e.g. vitamins, unnecessary drugs, herbs, etc., should also be avoided. During this procedure, food-sensitive patients will exhibit a strong exacerbation of symptoms early in the week, followed by almost total relief by the end of the fast/modified diet. This sequence is due to the addictive characteristic of the reactive foods. Once the patient is symptom-free, one new food is reintroduced (and eaten several times) each day while symptoms are carefully recorded. Some authors recommend reintroduction on a 4 day cycle. Suspected foods (symptom onset ranges from 20 minutes to 2 weeks) are eliminated, and apparently safe foods are rotated through a 4 day cycle (see Ch. 58). Once a symptom-free period of at least 6 months has been established, the 4 day rotation diet should no longer be necessary.

Diet

As discussed above, all food allergens must be eliminated and a 4 day rotation diet utilized until the patient is symptom-free for at least 6 months. Foods containing

vasoactive amines should initially be eliminated. After symptoms have been controlled they can be carefully reintroduced. The primary foods to eliminate are alcoholic beverages, cheese, chocolate, citrus fruits, and shellfish. The diet should be low in sources of arachidonic acid (land animal fats) and high in foods which inhibit platelet aggregation, e.g. vegetable oils, fish oils, garlic, and onion.

Supplements

- Magnesium: 250–400 mg three times/day
- Vitamin B₆: 25 mg three times/day
- 5-HTP: 100–200 mg three times/day.

Botanical medicines

- *Tanacetum parthenium*: 0.25–0.5 mg parthenolide twice daily
- Ginger (*Zingiber officinalis*)
— fresh ginger: approximately 10 g/day (6 mm slice)

- dried ginger: 500 mg four times/day
- extract standardized to contain 20% of gingerol and shogaol 100–200 mg three times/day for prevention and 200 mg every 2 hours (up to six times daily) in the treatment of an acute migraine.

Physical medicine

- TENS to control secondary muscle spasm
- Acupuncture to balance meridians
- Biofeedback:
The Association for Applied Psychophysiology and Biofeedback
10200 West 44th Avenue, Suite 304
Wheat Ridge, CO 80033
(303) 422-8436
- Guided imagery:
The Academy for Guided Imagery
PO Box 2070
Mill Valley, CA 94942
1-800-726-2070

REFERENCES

1. Rubenstein E, Federman DD. Scientific American medicine. New York, NY: Scientific American. 1987; p 11: XI: 1–3, CTM: II: 10
2. Rose FC. The pathogenesis of a migraine attack. *TINS* 1983; 6: 247
3. Shinhoj E. Hemodynamic studies within the brain during migraine. *Arch Neurol* 1979; 29: 257–266
4. Blacklow RS. Macbryde's signs and symptoms. 6th edn. New York, NY: JB Lippincott. 1983; p 64–68
5. Olesen J. The ischemic hypothesis of migraine. *Arch Neurol* 1987; 44: 321–322
6. Hanington E. The platelet and migraine. *Headache* 1986; 26: 411–415
7. Spence JD, Wong DG, Melendez LJ et al. Increased incidence of mitral valve prolapse in patients with migraine. *Can Med Assoc J* 1984; 131: 1457–1460
8. Gamberini G, D'Alessandro R, Labriola E et al. Further evidence on the association of mitral valve prolapse and migraine. *Headache* 1984; 24: 39–40
9. Lanzi G, Grandi AM, Gamba G et al. Migraine, mitral valve prolapse and platelet function in the pediatric age group. *Headache* 1986; 26: 142–145
10. Welch KMA. Migraine. A biobehavioral disorder. *Arch Neurol* 1987; 44: 323–327
11. Ferrari MD, Odink J, Tapparelli C et al. Serotonin metabolism in migraine. *Neurology* 1989; 33: 1239–1242
12. Fioroni L, Andrea GD, Alecci M et al. Platelet serotonin pathway in menstrual migraine. *Cephalalgia* 1996; 16: 427–430
13. Lance JW et al. 5-hydroxytryptamine and its putative aetiological involvement in migraine. *Cephalalgia* 1989; 9: 7–13
14. Sicuteri F. Migraine, a central biochemical dysnociception. *Headache* 1986; 16: 145–149
15. Fozard JR, Gray JA. 5-HT_{1c} receptor activation. A key step in the initiation of migraine? *Trends Pharmacol Sci* 1989; 10: 307–309
16. Ferrari MD, Saxena PR. Clinical effects and mechanism of action of sumatriptan in migraine. *Clin Neurol Neurosurg* 1992; 94: Suppl: S73–77
17. Kagaya A, Mikuni M, Kusumi I et al. Serotonin-induced acute desensitization of serotonin₂ receptors in human platelets via mechanism involving protein kinase C. *J Pharmacol Exp Ther* 1990; 255: 305–311
18. Mathew NT. Chronic refractory headache. *Neurology* 1993; 43: S26–S33
19. Mathew NT. Transformed migraine. *Cephalalgia* 1993; 13: 78–83
20. Isler H. Migraine treatment as a cause of chronic migraine. In: Rose FC, ed. *Advances in migraine research and therapy*. New York, NY: Raven Press. 1982; p 159–164
21. Mansfield LE, Vaughan TR, Waller ST et al. Food allergy and adult migraine. Double-blind and mediator confirmation of an allergic etiology. *Ann Allergy* 1985; 55: 126–129
22. Carter CM, Egger J, Soothill JF. A dietary management of severe childhood migraine. *Hum Nutr Appl Nutr* 1985; 39A: 294–303
23. Hughes EC, Gott PS, Weinstein RC, Binggeli R. Migraine. A diagnostic test for etiology of food sensitivity by a nutritionally supported fast and confirmed by long-term report. *Ann Allergy* 1985; 55: 28–32
24. Egger J, Carter CM, Wilson J et al. Is migraine food allergy? *Lancet* 1983; ii: 865–869
25. Monro J, Brostoff J, Carini C, Zilkha K. Food allergy in migraine. *Lancet* 1980; ii: 1–4
26. Grant ECG. Food allergies and migraine. *Lancet* 1979; i: 966–969
27. Little CH, Stewart AG, Fennessy MR. Platelet serotonin release in rheumatoid arthritis as studied in food intolerant patients. *Lancet* 1983; ii: 297–299
28. Peatfield RC. Relationship between food, wine, and beer-precipitated headaches. *Headache* 1995; 35: 355–357
29. Jarisch R, Wantke F. Wine and headache. *Int Arch Allergy Immunol* 1996; 110: 7–12
30. Wantke F, Gotz M, Jarisch R. Histamine free diet. Treatment of choice for histamine induced food intolerance and supporting treatment for chronic headaches. *Clin Exp Allergy* 1993; 23: 982–985
31. Jarman J, Glover V, Sandler M. Release of (¹⁴C)5-hydroxytryptamine from human platelets by red wine. *Life Sci* 1991; 48: 2297–2300
32. Martner Hewes PM, Hunt IF, Murphy NJ et al. Vitamin B6 nutrition and plasma diamine oxidase activity in pregnant Hispanic teenagers. *Am J Clin Nutr* 1988; 44: 907–913
33. Sabbah A et al. Antihistaminic or anti-degranulating activity of pregnancy serum. *Allergy Immunol Paris* 1988; 20: 236–240
34. Lindberg S. 14C-histamine elimination from blood of pregnant and non-pregnant women with special reference to the uterus. *Acta Obst Gynecol Scand* 1963; 62: 1–25

35. Gerrard JM, White JG, Krivit W. Labile aggregation stimulating substance, free fatty acids and platelet aggregation. *J Lab Clin Med* 1976; 87: 73–82
36. Sanders TAB, Roshanai F. The influence of different types of omega-3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. *Clin Sci* 1983; 64: 91–99
37. Woodcock BE, Smith E, Lambert WH et al. Beneficial effect of fish oil on blood viscosity in peripheral vascular disease. *Br Med J* 1984; 288: 592–594
38. 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
39. Swanson DR. Migraine and magnesium: eleven neglected connections. *Perspect Biol Med* 1988; 31: 526–557
40. Ramadan NM, Halvorson H, Vande-Linde A et al. Low brain magnesium in migraine. *Headache* 1989; 29: 590–593
41. Gallai V, Sarchielli P, Morucci P et al. Magnesium content of mononuclear blood cells in migraine patients. *Headache* 1994; 34: 160–165
42. Mazzotta G, Sarchielli P, Alberti A et al. Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients. *Headache* 1996; 36: 357–361
43. Pfaffenrath V, Wessely P, Meyer C. Magnesium in the prophylaxis of migraine—a double-blind placebo-controlled study. *Cephalalgia* 1996; 16: 436–440
44. Peikert A, Wilimzig C, Kohne-Volland R et al. Prophylaxis of migraine with oral magnesium. Results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; 16: 257–263
45. Galland LD, Baker SM, McLellan RK. Magnesium deficiency in the pathogenesis of mitral valve prolapse. *Magnesium* 1986; 5: 165–174
46. Lindberg JS, Zobitz MM, Poindexter JR et al. Magnesium bioavailability from magnesium citrate and magnesium oxide. *J Am Coll Nutr* 1990; 9: 48–55
47. Majumdar P, Boylan M. Alteration of tissue magnesium levels in rats by dietary vitamin B6 supplementation. *Int J Vitamin Nutr Res* 1989; 59: 300–303
48. Mauskop A, Altura BT, Cracco RQ et al. Intravenous magnesium sulfate rapidly alleviates headaches of various types. *Headache* 1996; 36: 154–160
49. Mauskop A, Altura BT, Cracco RQ et al. Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels. A pilot study. *Clin Sci* 1995; 89: 633–636
50. Mauskop A, Altura BT, Cracco RQ et al. Intravenous magnesium sulfate relieves cluster headaches in patients with low serum ionized magnesium levels. *Headache* 1995; 35: 597–600
51. Parker GB, Tupling H, Pryor DS. A controlled trial of cervical manipulation for migraine. *Aust NZ J Med* 1978; 8: 589–593
52. Watts PG, Peet KMS, Juniper RP. Migraine and the temporomandibular joint. The final answer? *Br Dent J* 1986; 161: 170–173
53. Solomon S, Guglielmo KM. Treatment of headache by transcutaneous electrical stimulation. *Headache* 1985; 25: 12–15
54. Doeer-Proske H, Wittchen HU. A muscle and vascular oriented program for the treatment of chronic migraine patients. A randomized clinical comparative study. *Z Psychosom Med Psychoanal* 1985; 31: 247–266
55. Vesnina VA. Current methods of migraine reflexotherapy (acupuncture, electropuncture, and electroacupuncture). *Zh Nevropatol Psikhiatr* 1980; 80: 703–709
56. Kurkland HD. Treatment of headache pain with auto-acupressure. *Dis Nerv Sys* 1976; 37: 127–129
57. Lenhard L, Waite PM. Acupuncture in the prophylactic treatment of migraine headache. Pilot study. *NZ Med J* 1983; 96: 663–666
58. Facchinetti F, Nappi G, Savoldi F, Genazzani AR. Primary headaches: reduced circulating beta-lipotropin and beta-endorphin levels with impaired reactivity to acupuncture. *Cephalalgia* 198; 1: 195–201
59. Markelova VF, Vesnina VA, Malygina SI, Dubovskaia LA. Changes in blood serotonin levels in patients with migraine headaches before and after a course of reflexotherapy. *Zh Nevropatol Psikhiatr* 1984; 84: 1313–1316
60. Laiten J. Acupuncture for migraine prophylaxis. A prospective clinical study with six months' follow-up. *Am J Chin Med* 1975; 3: 271–274
61. Holroyd KA, Penzien DB. Pharmacological versus non-pharmacological prophylaxis of recurrent migraine headache: a meta-analytic review of clinical trials. *Pain* 1990; 42: 1–13
62. Johnson ES, Kaddam NP, Hylands DM et al. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J* 1985; 291: 569–573
63. Murphy JJ, Heptinstall S, Mitchell JRA. Randomized double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988; ii: 189–192
64. Barsby RWJ, Salan U, Knight BW, Hoult JRS. Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. *Planta Medica* 1993; 59: 20–25
65. Heptinstall S, Awang DV, Dawson BA et al. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 1992; 44: 391–395
66. Kiuchi F, Iwakami S, Shibuya M et al. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. *Chem Pharm Bull* 1992; 40: 387–391
67. Srivastava KC. Isolation and effects of some ginger components on platelet aggregation and eicosanoid biosynthesis. *Prostaglandins Leukotri Med* 1986; 25: 187–198
68. Mustafa T, Srivastava KC. Ginger (*Zingiber officinale*) in migraine headaches. *J Ethnopharmacol* 1990; 29: 267–273