

Migraine Research and Update

By

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- New thinking about migraine is that it is not just a headache but a complex neurological disorder centered in a “migraine generator” in the brain stem.
- The trigeminovascular system, whose key structures are the meninges or covering of the brains and the 5th cranial nerve or trigeminal nerve, may be an important part of pain activity. Signals originating in the brain’s migraine generator, the brain stem, somehow communicate through this system with the blood vessels in the head, face, and spinal cord causing inflammation and pain.
- Studies of the neurotransmitter serotonin have led to serotonin agonists and a new generation of triptan drugs for therapy.
- Researchers have linked possible migraine susceptibility genes to chromosome 4, 1q, 19p, and Xq, indicating a complex polygenic disorder involving multiple genes and interacting gene loci.
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Introduction

The Inca warrior's head hurt so badly that he could not endure to fight. Convinced that evil spirits caused the headache, the medicine man bored holes to release the trapped devils, an act called trepanning. Ancient practitioners from cultures as far back as the Stone Age cut away pieces of the sufferer's skull to give relief. Even Zeus, king of Greek gods, was not spared a tortuous headache, which ended when Hephestus split open his skull and out popped Minerva. In fact, the word "migraine" comes from the Greek "hemicranium" meaning "half a head."

Egyptians tied herb-stuffed ceramic crocodiles to the sufferer's head as a sure cure. In the British Isles in the Ninth Century, the doctor prescribed a cocktail of elderseed, cow's brain, and goat's dung dissolved in vinegar. Although the pain may be the same, today's migraineurs use less drastic measures- drugs, diet, and stress management- to fight the debilitating condition. Migraines affect about 28 million Americans, 75 percent or 21 million are women. Victims lose over 157 million workdays because of pain. Although migraines may begin in childhood, they usually start in the 20s or 30s, and infrequently after the age of 40. In fact, as a person ages, the attacks become less frequent.

What is Migraine?

Scientists believe that migraine is not a headache but a neurological disease with multiple symptoms. Headache is one of the symptoms. Several types of migraine exist:

- Classic migraine. Neurological symptoms with flashing lights, zig-zag lines, and loss of vision may occur 10 to 30 minutes before onset of

pain. Called an aura, these symptoms characterize a classic migraine. Sometimes the person may have speech difficulty, weakness of a limb, tingling of face and hands, and confusion. Felt in the forehead, temple, ear, jaw, or around the eye, pain is intense, pounding, and throbbing. The headache may start on one side of the head but eventually spreads to the other side for a pain-wracked one to two days. About 15 to 20 percent of sufferers have this type.

- Common migraine. Although this type is not preceded by aura, some experience vague symptoms such as mood changes, fatigue, retention of fluids, and mental confusion. The person may have diarrhea, vomiting, and increased urination during three to four pain-wracked days.

Both classic and common migraines can occur several times a week or as rarely as once every year or so.

- Hemiplegic migraine. Paralysis on one side of the body may occur 10 to 90 minutes before the onset of headache pain. These people may also have vision problems and vertigo, the sensation that the world is spinning.
- Basilar artery migraine. A disturbance of a major brain artery at the base of the brain may be preceded by symptoms, such as vertigo, double vision, and poor muscular coordination. Occurring primarily in adolescents and young adult women, this type is associated with the monthly cycle.
- Benign exertional headache. Headache beginning at the onset of activity like running, lifting, bending, or sneezing rarely lasts for more than several minutes.

- Status migrainous. This rare, severe type causes pain and intense nausea and may last for more than 72 hours. The person who may experience depression or anxiety before the attack may have to be hospitalized.
- Headache free migraine. Patients may have visual problems, nausea, vomiting, constipation, or diarrhea but no head pain.

Other types of vascular headaches are toxic- produced by fever and presence of foreign chemicals in the body, stress-related pain, and cluster headaches connected with a rise in blood pressure. See Table I.

Women and Migraine

Although migraine may affect men, adult women have the most cases. The disorder may begin in infancy, but most cases begin between five and 35. Female hormones may have a great impact on migraine. Some women have “menstrual migraines” around their periods; these disappear during pregnancy. Others may develop the headaches during pregnancy and some during menopause. Likewise, oral contraceptives have a mixed effect. Some women on birth control pills have severe attacks while some have less severe attacks on the pills. Normal women who do not have headaches may develop them when beginning birth control pills.

What is the Migraine Process?

Sir Thomas Willis, a 17th Century physician, hypothesized that increased blood flow in the head caused terrible headaches and enlarged blood vessels then pressed the brain. For centuries, this “vascular” theory was the accepted explanation for headaches and migraines. However,

advances in looking inside the brain using magnetic resonance imaging (MRI), positron emission tomography (PET), and transcranial Doppler have enabled researchers to determine the changes are much more complex than simple swelling of blood vessels. And although blood vessels do get involved, they seem to play a secondary role.

Brain stem role

Using visual techniques, investigators are looking at activity especially in the brain stem region. Hans C. Diener, University of Essen, Germany, advocated the idea of a migraine “pacemaker” or generator in the brain stem (Weiller *et al.*, 1995 *Nature Medicine* 1:658 – 660). This study, which was hailed as a landmark of new thinking about migraine, used PET scans to show increased blood flow in the cortical areas and in the brain stem. When the pain reliever sumatriptan was given, blood flow returned to normal in the cortical area but remained increased in the brain stem. This study suggested that activation of the brain stem is not the result of headache but might be related to the migraine attack itself. Other studies have shown that two areas of the brain stem- the dorsal raphe nucleus and the nucleus raphe magnus- have large amounts of the neurotransmitter serotonin, also suspected as active in migraine.

The trigeminovascular system, whose key structures are the meninges or covering of the brain and the 5th cranial nerve or trigeminal nerve, may be an important part of pain activity. Signals originating in the brain’s migraine generator, the brain stem, somehow communicate through this system with the blood vessels in the head, face, and spinal cord causing inflammation and pain. However, the inflammation is neurogenic

resulting from release of pain chemicals such as substance P by the trigeminal nerve endings. Nerve cells, not blood vessels, act as the agent in migraine.

The new thinking about migraine also includes alteration in blood flow. Woods *et. al.*, (1994 *New England Journal of Medicine* 331: 1689 – 1692) found that at the onset of migraine head pain, blood flow decreases in the occipital area and spreads in wave-like fashion across the brain. While unclear about the precise cause of migraine, scientists generally agree that blood flow overreacts to certain triggers from outside. A trigger causes a spasm in the nerve-rich arteries at the base of the brain, causing several arteries like the scalp and carotid or neck arteries to constrict. To make things worse, as they narrow reducing the flow of blood, platelets clump together to release serotonin, a powerful constrictor of arteries. The reduced blood flow decreases the brain's supply of oxygen and causes other arteries to dilate to meet the brain's needs. The opened arteries cause the release of prostaglandins, pain-producing chemicals that cause swelling. These chemicals stimulate nociceptors, the endings of sensitive nerves, that send messages of pain.

Serotonin (5-hydroxytryptamine or 5-HT), a widely occurring chemical in the body, is found in many areas including the brain. Several studies have linked migraine and serotonin including a finding nearly 40 years ago that the drug methysergide antagonized 5-HT and could reduce migraine pain. Other studies led to antimigraine agents that could interact with serotonin receptors in the brain. When the mad search for

antimigraine agents began in the 1970s, several 5-HT receptors were discovered- 5-HT₁, 5-HT₂, 5-HT₃.

Over-the-Counter (OTC) Treatments

While there is no cure, people with migraine can manage with proper medication, diet, exercise, and lifestyle modification. An occasional migraine is considered headache pain about once a week. These headaches may be controlled with relaxation, a short nap, and OTC pain relievers. A study by Vaitkur *et. al* (2001 *Journal of Neurological Science* 187:S74) noted the majority of patients took OTC medications or prescription medications that were not specific for migraine. Only 12.6 percent took specific medications for migraine, and of these only 4 percent took triptans, medications designed specifically for migraine.

For those with mild to moderate pain, OTC drugs may help. In January 1998 an extra strength version of Excedrin® called Excedrin Migraine® was the first OTC approved specifically for migraine. The following groups of products are used including combination products:

- Aspirin products
- Acetaminophen products
- NSAIDs- non-steroid anti-inflammatory products
- Combination products such as those that contain pain relievers and caffeine.

Each group has positives and negatives. The sufferer should choose medications balancing desired effects versus side effects. OTC labels give the possible hazards and a warning that different people may have varied effects. See Table II for contents of OTC products.

A risk of OTC overuse is rebound headaches. As the dose wears off, the headache may return causing one to use more and more medication.

Exercise and Diet

Many migraine sufferers note the frequency of their headaches decrease when they exercise. Regular aerobic exercise like brisk walking, swimming, and bicycling help many cope with migraine.

Potential dietary triggers are:

- Alcoholic drinks, especially red wine
- Food with tyramine, such as aged cheese, sour cream, yogurt
- Chocolate
- Dairy products
- Food additives like nitrites, MSG, aspartame.

Keeping a food diary and relating what is eaten to the occurrence of headache may help pinpoint the trigger. Generally, a healthful diet with three nutritious meals is sufficient.

Treatment by Prescribed Drugs

Serotonin Agonists

Serotonin or 5-HT₁ receptors- especially the 5-HT_{1D} subtype- are widely distributed in intracranial blood vessels and the dorsal raphe nucleus and nucleus raphe magnus. These receptors are targets for certain drugs like sumatriptan, dihydroergotamine (which acts on 5-HT_{1A} receptors), and ergotamine.

Because serotonin constricts blood vessels, scientists think that serotonin agonists relieve headaches by constricting swollen cranial blood vessels and reducing inflammation around the vessels thereby reducing pain transmission through the trigeminal system. Other data suggest that during migraine the blood-brain barrier opens up allowing sumatriptan or dihydroergotamine to reach neurons and possibly down to the proposed migraine center in the brain stem.

In 1993 the U.S. Food and Drug Administration (FDA) approved Imitrex® (sumatriptan) as the first migraine drug. Since then, a new generation of triptan drugs that include zolmitriptan, rizatriptan, naratriptan, eletriptan, and alniditan may have quicker onset and longer duration than sumatriptan as well as fewer side effects. According to a study by R.E. Ryan *et. al.* (2001 *Archives of Internal Medicine* 161:2545 – 53) migraineurs describe their perfect migraine medicine: rapid pain relief, complete pain relief, ability to return to normal functioning, relief of migraine-associated symptoms, reduction in headache occurrence, minimal adverse effects. The study found differences in the ability of specific triptans to satisfy individual preferences.

On May 7, 2001 the FDA approved Axert® (almotriptan maleate tablets) for acute treatment of migraine with or without aura in adults. Almotriptan is not an ordinary pain reliever and may have serious side effects in people with heart or blood vessel disease.

Oral eletriptan (80mg.) showed significantly greater improvement when compared to oral sumatriptan. Goadsby *et. al.*, (2000 *Neurology* 54:156 –

164) hypothesized that the better response may be due to the drugs greater affinity for 5-HT_{1B} and 5-HT_{1D} receptors.

Cady *et. al* reporting for the Rizatriptan-RPD Study Group reported on a new convenient wafer formulation that dissolves rapidly in the mouth and can be taken without liquids. Several studies compared rizatriptan to other triptans for acute treatment of migraine. Alderman *et. al* (2001 *Journal Neurological Science* 187:S77) compared overall efficacy of rizatriptan to sumatriptan, almotriptan, and naratriptan two hours after dosing. Thirty-one percent of patients that took 10 mg. Rizatriptan were pain free compared to lesser percentage with higher dosages of the others. Ferrari *et. al* (2001 *Lancet* 308:1668-75) did a meta-analysis of 53 clinical trials involving 24,089 patients. Ten mg. Rizatriptan showed better efficacy and consistency and similar tolerability.

Adis International, New Zealand has a new serotonin receptor agonist black triangle Frovatriptan (2001 *CNS Drugs* 15:969-76). The drug has high affinity for serotonin 5-HT_{1B} and 5-HT_{1D} receptors subtypes and is a potent stimulator of contractions in human basilar arteries. The drug has a long terminal elimination half-life of about 26 hours that is independent of dose, age, gender, and renal function. Frovatriptan provided consistent relief and reduced occurrence.

Other Serotonin Agonists

Nausea and vomiting associated with migraines may involve 5-HT₃ receptors in the medulla, site of the vomiting center. Anti-emetic drugs like ondansetron, a 5-HT₃ antagonist may help. Serotonin 1D agonists that act on 5-HT₂ receptors include methylsergide, tricyclic antidepressant

amitriptyline, certain beta blockers, and calcium channel blockers. Serotonin fluctuation suggests people with migraine may have mood disorders such as anxiety, panic attacks, and depression. This may suggest mood disturbances may be part of a “migraine syndrome” or comorbid mood disorder.

Ergot Alkaloids

Dihydroergotamine and ergotamine belong to the ergot alkaloids and are used to treat throbbing headaches. However, these medications cause blood vessels to constrict and may cause serious side effects by decreasing flow of blood to many parts of the body., and the belladonna alkaloids, cyclizine, dimenhydrinate, and diphenhydramine help relieve nausea and vomiting. Caffeine may be combined to help medications be absorbed more rapidly. Examples of drugs approved specifically for migraine include ergotamine tartrate (Cafergot, Wigraine, Ergostat), isomethetryptine mucate combinations (Midrin, Iocom), and dihydroergotamine (DHE-45). A nasal spray form of DHEA (Migranol) has been developed for fast drug delivery.

Preventing Migraine

For those whose migraines are three or more times a month or are specially disabling, the physician may use a variety of drugs to attempt prevention.

Drugs may include:

- methysergide maleate that constrict blood vessels
- propranolol hydrochloride to stop dilation
- amitriptyline, an antidepressant
- valporic acid, an anti-convulsant
- verapamil, a calcium channel blocker
- MAO inhibitors to block pain.

However, prevention for many still remains elusive and the subject of continued studies. Friede (2001 *Journal Neurological Science* 187:78 AB PO204) reviewed all published randomized, double-blind, placebo-controlled trials that use herbal remedies for prevention. Although few clinical trials have been held, evidence that *Petasitis folium* and *Tanacete parthenii herba* had a positive ratio using meta-analysis from five clinical trials.

Sheftell, *et. al.*, (2000 *Headache* 40:158 – 163) found the leukotrine antagonist- monteleukine- may have a role in migraine prophylaxis. Leukotrines are preinflammatory mediators that have been implicated in migraine and cluster headaches. This open-label study using 17 subjects who kept diaries over three months of oral therapy showed a beneficial effect. The drug may warrant blinded studies.

Edwards (2001 *Journal of Neurological Science* 187:S78) focused on the use of topiramate in an open-label study for preventing migraine. Evaluating data from 48 patients, 73 percent experienced reduction on this therapy where multiple medications had failed as prophylaxis in 86 percent of these patients. In an open trial study of zonisamide, patients reported modest reduction in pain as well as good tolerance of the medication.

Genetics of Migraine

Genetics seems to play a part in whether a person will develop migraine. According to the American Council for Headache Education, up to 90 percent of people with migraine have a family history of the condition. About 70 percent of sufferers have a first degree relative with migraine.

Pelotie *et. al.*, (2002 *American Journal of Genetics* 69: March) studied 50 Finnish families with many members that suffered from classic migraine. They found three common genetic markers linked to a region on chromosome 4 in 30 percent of the study participants. Pelotie believes that the field has been narrowed to find the gene itself.

Wieser *et. al.*, (2001 *American Journal of Genetics* 69:AB 664) found a region on Chromosome X for possible identification of susceptibility loci. Griffiths *et. al* (2001 *American Journal of Genetics* 69:ab2007) found localization of migraine susceptibility genes linked to chromosome 1q, 19p, and Xq.

Results of genetics studies indicate migraine is a complex polygenic disorder involving multiple and possibly interacting gene loci.

Conclusion

While at present there is simply no cure for migraine, learning to manage the condition with diet, stress reduction, and available drugs is the answer. But the search is on for more effective and safer drugs.

Clarifying the phases of a migraine attack could lead to specific answers to the questions of what in the brain triggers the attack and the role of inflammation. The new theories give rationale for combining two or three different types of medication to achieve relief. For example, a medication that worked on serotonin may be coupled with an anti-inflammatory that curtails activity in the trigeminal system. However, although understanding the precise mechanism could in time lead to successful therapies, the ultimate blockbusters will come in the finding of preventative drugs- and ultimately a cure.

Table I Comparison of Migraine to Other Headaches

	Migraine	Tension-headache	Cluster headache
Location of pain	One or both sides of head	Both sides of head	One side of head
Duration	4 to 72 hours	2 hours to days	30 – 90 minutes
Severity	Mild, moderate, or severe	Mild or moderate	Excruciating
Nausea, sensitivity to light, sound, odors	Yes	No	No
Redness or tearing of eyes; stuffy or runny nose	Sometimes	No	yes

Source: Adapted from American Medical Association “Migraine and Other Headaches: A Patient Guide to Headache Management” 1997

Table II OTC Products

OTC	Product kind	Active ingredient
Bayer®	Aspirin	Aspirin
Bufferin®	Aspirin	Buffered aspirin
Ecotrin®	Aspirin	Aspirin
ExcedrinPM®	Acetaminophen/ Diphenhydromine	Acetaminophen
Tylenol®	Acetaminophen	Citrate
Advil®	NSAID	Ibuprofen
Aleve®	NSAID	Naproxen sodium
Motrin IB®	NSAID	Ibuoprofen
Actron®	NSAID	ketoprofen
Orudis KT®	NSAID	Ibuprofen
Excedrin® Extra Strength	Combination	Aspirin, acetaminophen,caffeine
Excedrin aspirin free	Combination	Acetaminophen, caffeine
Anacin®	Combination	Aspirin, caffeine

- Do not use aspirin, ibuprofen and naproxen with bleeding disorders, asthma, ulcers, kidney, or liver damage.

Source: DM&D

Table III Selected Migraine Treatments

Generic Drug	Action	Trade name	Company	Comments
Sumatriptan	Serotonin agonist (SA)	Imitrex	Glaxo SmithKline	First migraine drug to be approved- in 1993; triptans may have serious side effects in those with heart or blood vessel disease
Almotriptan	SA	Axert	Pharmacia	Approved May 7, 2001
Zolmitriptan	SA	Zomig		Side effects heart or blood vessel disease
Eletriptan	SA- acts at serotonin 5-HT _{1d} receptors	Relpax	Pfizer	Received approvable letter in 1999; in meta-analysis by Ferrari 80 mg. had better consistence but lower tolerability
Rizatriptan	SA	Maxalt	Merck	Approved June 29, 1998; may be available in wafer form

Naratriptan	SA	Amerge	Glaxo Wellcome	Approved 2/10/98; Krenz and Nett of Anodyne Pain Care, Dallas, found to reduce occurrence of migraine pain
Alniditan	SA		Janssen	

Source: D&MD