

Migraine – More than a Headache

Introduction

Migraine is a common clinical problem characterized by episodic attacks of head pain and associated symptoms such as nausea, sensitivity to light, sound, or head movement. It is generally thought of as a headache problem, but it has become apparent in recent years that many patients suffer symptoms from migraine who do not have severe headaches as a dominant symptom. These patients may have a primary complaint of dizziness, of ear pain, of ear or head fullness, “sinus” pressure, and even fluctuating hearing loss. Fortunately, treatment regimens long established for the treatment of “classic” migraine headaches are generally effective against these “atypical” symptoms of migraine.

How Common is Migraine?

There are currently 28 million Americans with “classic” migraine headaches. In a room with 100 people, 13 are likely to have migraine. This is as common as diabetes and asthma combined. The number of people suffering with atypical forms of migraine is unknown. Females are 3 times more likely to have migraine than males. Although any person can have migraine at any age, migraine is most common between ages 30 and 50. The peak incidence of migraine in females occurs at 35 years of age—at this age, 28% of all females have migraine headaches. The peak incidence of migraine in men occurs at 30 years of age—at this age, about 10% of all males have migraine headaches.

Migraine is a lifelong problem. It may start in childhood and disappear and reappear in new forms throughout an individual’s life. In general, there is a decrease in headache intensity and an increase in the incidence of atypical symptoms of migraine (vertigo, ear pain, bowel symptoms, etc) as patients mature.

Surveys show that only 48% of people with migraine headaches have had a diagnosis and are being treated for their headaches. Unfortunately, only 29% of US migraine sufferers are very satisfied with their treatment. This is usually a reflection of a lack of understanding of the nature of migraine and its treatment, or lack of commitment to effective treatments. We hope this material will help you to achieve better control of your migraine symptoms, whatever they are, and improve your quality of life.

How are People with Migraine Different?

Migraine is an inherited problem of ion channels in the brain. This may result in what is best described as a “sensitive brain”. Most individuals exposed to loud noise, bright light, or excessive motion can adapt to these strong stimuli within minutes, but in the brain of a migraineur, the strength of the stimulus continues to grow until a migraine crisis occurs. This lack of ability to adapt to strong sensory stimulation helps us understand why so many patients have migraine headache or other migraine symptoms that can be provoked by bright light, excessive noise, strong smells, excessive motion, and painful stimuli.

What Happens During a Migraine Attack?

Abnormal activity may occur in, on, and around the brain during a migraine attack. Hyperactivity deep in the brainstem and other brain centers that control pain and other sensations in the head has been found on brain imaging studies in patients having migraine attacks. This means a person having a migraine who senses pain, motion, or sound will tend to have an exaggerated, distorted experience of the pain, motion, or sound that may be so intense that it is difficult to tolerate. The patient may become so sensitive that he has no choice but to withdrawal to a quiet, dark place and sleep until the episode has passed.

Patients also have altered electrical activity at the surface of the brain during a migraine episode. This most commonly occurs over the vision areas of the brain and may result in unusual visual phenomena such as the appearance of spark-like bursts, wavy lines, blind spots, or even complete visual loss in rare cases. Abnormal cortical brain activity over other regions of the cortex can result in temporary confusion, inability to speak, numbness, or even paralysis of any part of the body. These symptoms which occur at the surface of the brain typically are brief, lasting no longer than 20 minutes.

Painful throbbing headache may be associated with sensitization of the blood vessels around the brain by abnormal chemicals which themselves irritate and cause the blood vessels to hurt.

What is a Migraine Trigger?

A migraine trigger is any environmental, dietary, or physiologic factor that can provoke migraine activity in the brain.

Environmental triggers

Examples of environmental triggers include odors, bright lights, noise, and other excessive sensory stimuli. Painful stimuli that trigger migraine usually occur in the head and neck. The most common of these are neck injury and spasm, temporomandibular joint pain, and sinus pain. 40% of migraineurs are affected by weather changes. The mechanism of this trigger is not currently understood.

Food triggers

There are hundreds of potential food triggers for migraine. Comprehensive lists of foods which may contribute to triggering migraine can easily be found on the Web. In general, these foods fall into two main categories: 1) byproducts of food aging and 2) foods with chemicals similar to neurotransmitters our brains use. Byproducts of food aging are found in fermented products like red wine, aged cheeses, and yeast in fresh bread and yogurt. Foods with chemicals similar to our own neurotransmitters which may aggravate migraine are coffee, chocolate, MSG, and the nitrates used as preservatives in many of our prepackaged foods. Food triggers are not the result of allergy, but are direct chemical sensitivities.

There is a common misconception that if a person is sensitive to a food item, they will know it, because they will have migraine symptoms within an hour

of eating the particular food item. In fact, some effects may come immediately or sometimes days later. Added to this confusion is the reality that many real food triggers may not cause migraine alone, but only in combination with other partial triggers, which together may provoke an attack of migraine headache or symptoms. For example, some migraineurs can eat chocolate or red wine alone with no problem, but will suffer a migraine attack if chocolate and red wine are taken together. We generally recommend an initial dietary trial which avoids only the most common migraine triggers. If good results are not achieved within a few weeks, a comprehensive diet which eliminates all potential migraine triggers is recommended. It may take 6-10 weeks for a patient suffering from severe and debilitating migraine symptoms to respond, but most do. After an improvement in symptoms is achieved, suspect foods can be added to the diet one at a time to see whether they are an important trigger for that patient. Despite the difficulty of this kind of a trial, we have found that even the most severely affected migraineurs tend to respond and are generously rewarded for their efforts.

Physiologic triggers

Perhaps the most common trigger of migraine is stress. Patients commonly report increased symptoms when they are stressed, fatigued, and suffer lack of sleep. Many other physiologic stresses can also trigger migraine, such as hunger, exercise, and pain. Some patients suffer migraine from sleeping too much, and cannot understand why most of their weekends are ruined by headaches or dizziness. Migraines are commonly triggered by hormone changes, like the drop in estrogen levels before the menstrual period or after menopause.

Subtle physiologic stresses, like eye strain, can trigger migraine. It is not uncommon for someone with new-onset headaches to find their eyeglass prescription has changed. Updating the prescription can have dramatic positive results. You will be asked to consider an eye examination if other obvious triggers are not identified.

Other common physiologic triggers include pain from temporomandibular joint dysfunction, neck problems, and sinusitis. Treatment of these underlying problems can result in dramatic reduction in typical and atypical migraine symptoms.

Treatment of Migraine

It seems easy to take pain medications or abortive medications such as narcotics or triptans to suppress symptoms, but when taken frequently, these can worsen the problem by causing rebound symptoms more intense than the original attack. It is typical for patients to get themselves into a vicious cycle, resulting in decreased functioning at work and at home with the expected emotional consequences before treatment is sought. The best treatment results will be obtained by those patients who work to understand what migraine is and how migraine is affecting their lives. This allows a teamwork approach with the physician and better outcomes.

The mainstay of treatment for migraine headache and atypical migraine symptoms is **trigger identification and avoidance**. This requires education about migraine triggers and the use of a migraine diary in which the patient is asked to record their symptoms and the probable trigger for that particular episode. Unlike many environmental and physiologic triggers, dietary triggers can be avoided. In general, an attempt to improve lifestyle by reducing stress, improving sleep habits, and adding regular exercise are beneficial. When done maximally, many patients will obtain near complete freedom from their migraines with this treatment alone.

At times, symptoms may be so constant that individual events and their triggers cannot be easily identified. In these cases, it may be helpful to give **medications to elevate the threshold** above which migraine triggering in the brain occurs. These may be medications originally used for blood pressure control, depression, or seizures which have been found to be easily tolerated and very good at preventing frequent migraine attacks. When this is successful, the breakthrough attacks which do occur are usually easily attributed to some particular trigger or aggravating factor, which can then be avoided. It may take 6-8 weeks to respond to a medication, and it is not uncommon for a patient to have to try more than one medication. Patients requiring medications to elevate migraine threshold can realistically expect a 50-80% reduction in symptom intensity and frequency.

If after maximizing the benefits of trigger identification and avoidance and medications to elevate the threshold of migraine, breakthrough headaches are still occurring, **medications to abort acute attacks** may be prescribed. There are now excellent medications which can help improve migraine symptoms both deep in the brain and those painful symptoms associated with sensitized blood vessels around the brain. These new medications are called triptans. Because they can cause rebound, they should not be used more than 6-8 times a month. Doctors' opinions may vary on this.

Some patients will have occasional severe headaches which can be aborted effectively with triptans without the risk of rebound. These patients should always be on the lookout for an increase in headache frequency and intensity that are the first signs of rebound. Long term treatment of acute headaches with narcotics generally leads to increasing medication needs and must be considered very cautiously, especially in patients with histories of chemical dependency.

How to Keep a Migraine Diary

Keeping a simple diary may be one of the most important tools you and your physician have for making treatment decisions. It is not necessary to keep extensive notes. In fact, the simpler the record keeping, the better. Use a monthly calendar, preferably a small one, like a checkbook calendar which you can keep with you. Use two pencils or pens of different color. With one color, mark the days you have headaches. With the other color, mark the days you have dizziness or symptoms other than headache (e.g. lethargy, head fullness, ear pain). Make a note of any possible physiologic, dietary, or environmental triggers

that have been present in the 24 hours prior to your symptoms. Remember to bring your diary with you to your appointments. It will allow you and your physician to see your progress at a glance.

Unusual Forms of Migraine

As you understand by now migraine is more than a headache. It is a constellation of symptoms and headache is not necessarily an essential part. It is extremely important to acknowledge this because although these atypical symptoms of migraine generally do not respond to abortive medication like the pain of a migraine headache does, the atypical symptoms *can* be managed by careful identification and avoidance of triggers or by taking medication for prophylaxis of migraine. These migraine symptoms which are not headaches but which are aggravated by typical migraine triggers are sometimes referred to as **migraine equivalents**. Some more common forms are mentioned here.

Cyclical vomiting is generally seen in childhood but may continue into adult life in some cases. The attacks are characterized by recurrent episodes of vomiting every 10-15 minutes and which typically continues for hours after the episode is triggered. There is no headache. Other patient's may experience **abdominal migraine** which presents as a pain in the upper central abdomen. The common stomachache of childhood is more likely to be caused by migraine than ingestion of foods which directly irritate the stomach. **Periodic diarrhea**, like cyclical vomiting, has symptoms most manifested as recurrent noninfectious diarrhea. These patient's often undergo extensive abdominal and intestinal workups for infection or other intrinsic diseases of the bowel which are negative. It is not unusual for our successfully treated migraine patient's to have such an improvement in their abdominal symptoms that they are able to discontinue medications they have been taking chronically for a diagnosis of irritable bowel syndrome. Migraine can also be the cause of spontaneous high **fevers**. This is especially common in children who may have no sign of infection that can be identified by their pediatrician. Many cardiologists and Emergency Room personnel have encountered patient's with chest pain who have no changes on the EKG and whose pain does not respond to antacid medication. These patient's with **precordial migraine** become well known to their physicians because their atypical episodes disappear when they begin taking medications for prophylaxis of migraine. Migraine equivalents may also manifest as dramatic **mood changes** particularly in the form of hyperactivity or irritability or an overwhelming tendency to very deep sleep that is often diagnosed as **narcolepsy**. It is not uncommon for women to experience some of these migraine equivalent symptoms as a portion of their premenstrual syndrome. Other migraine equivalents such as **vertigo**, **Meniere's disease**, **recurrent BPPV**, **otalgia** "ear pain" and **sinus pressure** are seen with particular frequency by otolaryngologists and are described separately below.

Migraine and Meniere's Disease

There is increasing interest among ENT physicians in the connection between migraine and Meniere's disease. Meniere's disease is a disorder of the inner ear characterized by episodic fullness, tinnitus (ringing), hearing loss, and vertigo whose cause is poorly understood. While the prevalence of migraine in the US population is 13%, the prevalence of migraine in patients with Meniere's disease is 56%, and the prevalence of migraine in patients with bilateral Meniere's disease is 85%.

We have recently discovered that the tiny blood vessels in the inner ear are innervated by branches of the same nerve that innervates the intracranial blood vessels severely affected in migraine attacks. Electrical stimulation of this trigeminal nerve has caused fluid changes in the inner ear which could affect it severely enough to cause a problem like Meniere's disease. Many patients with migraine and Meniere's disease who are treated effectively for migraine have experienced an improvement in their Meniere's symptoms.

For more information about Meniere's disease, go to <http://www.dbi.udel.edu/MichaelTeixidoMD/patientInfo/endolymphatic.html>.

Migraine and Vertigo

25% of migraineurs experience vertigo along with their other migraine symptoms. In many patients seen at our balance center, vertigo is the predominant feature of their migraine. We typically find that they have had more classic migraine headaches at some time in the past, or have a family history of migraine. Migraine symptoms of new onset in a patient with no personal or family history of migraine can also occur. This is particularly common after head injury or whiplash with chronic neck symptoms. Neck symptoms and spasm tend to increase weeks to months after an initial whiplash injury, causing headache and associated episodes of vertigo. These symptoms are generally not associated with pressure in the ear or hearing changes and may originate in the brainstem from faulty central processing of balance information from the inner ears. This may explain why many patients with migraine associated vertigo do not respond to vestibular suppressant medications such as meclizine or diazepam, which work only in the inner ear and vestibular nerves, but not in the brainstem. These patients are often best treated with physical therapy to decrease neck muscle stiffness and pain, medications to decrease neck muscle stiffness and pain, as well as traditional migraine therapy.

Most migraineurs have a lifelong history of motion sickness and can relate a history of motion intolerance that includes car-sickness, sea-sickness, or an inability to tolerate amusement park rides. A new onset of motion intolerance in an adult is more commonly associated with migraine activity than any other vestibular disorder.

Migraine and Otalgia (Ear pain)

Up to 40% of migraineurs report sharp ear pains which last only seconds. These may occur infrequently and spontaneously between migraine headaches. Ear pain has many causes, including infection and Eustachian tube problems in the ear, TMJ, and referred pain from the extensive lining of the throat.

Migraineurs who present to the doctor with ear pains frequently complain that their ears are hypersensitive to touch, to wind, and to cold. When an otolaryngologist has ruled out all of these other causes of ear pain in a patient with a history of migraine, migraine treatment is often effective in eliminating the pain.

Where can I Learn More about Migraine?

Beyond these brief pages, I typically recommend that my patients read the book, *Heal your Headache the 1-2-3 Program* by David Buchholz, MD. This book provides a comprehensive diet plan composed completely of foods that do not trigger migraine. It is much easier to follow this diet than to be suspicious of every food you have in your cabinet at home or that you see in the supermarket. It also teaches and emphasizes the concepts of rebound and the additive character of migraine triggers. Patients who have severe migraine-related vertigo may not be able to read a whole book because of their condition. They will benefit greatly from reading the book together with a family member who can help them to stay on track and to understand all the concepts in the book.

Those patients who do love to read and who have very atypical manifestations of migraine often find great comfort in the experiences of Oliver Sacks, MD, in his book, *Migraine*. Dr. Sacks is an extremely insightful neurologist with a gift for writing and who himself had migraine at age 2. He has collected an astonishing series of patient stories with both common and extremely unusual symptoms, all attributable to migraine mechanisms.

Treatment Guidelines for Physicians

For treatment we first encourage a strict migraine control diet, eliminating common migraine culprits including chocolate, wines, caffeine, certain cheeses, monosodium glutamate (MSG) as well as less frequently recognized problem foods containing yeast (yoghurt, sourdough, freshly made bread), nuts, and nut products. We also encourage a regular sleep schedule and aerobic exercise program. Patients are also counseled to avoid vasoconstrictive medications such as pseudoephedrine, and to minimize the use of triptans, which may cause rebound symptoms.

When patients follow these guidelines and still have migraine-associated symptoms, we emphasize prophylactic medications in preference to the “quick fix” agents such as Fiorinal, triptans, narcotics, or steroids. Effective prophylactic medications are chosen based on the patient’s other medical problems and tolerance of side effects. Some suggested regimens follow:

Calcium channel blockers: Diltiazem CD 120 mg/day increasing as tolerated to 240-480 mg total/day, often in two divided doses. Constipation and hypotension are the most common side effects, but this is often the best-tolerated regimen.

Antidepressants: Nortriptyline starting at LOW doses (10 mg/day) and slowly increasing to 50-100 mg at night. Many patients respond to this medication at low

doses (20 mg/day). Higher doses (100-200 mg) may occasionally be needed. Levels can help guide therapy. Dry mouth and sedation are the most common side effects. Sedation is usually not a problem if the medication is taken before bed. If morning drowsiness is a problem, the medication can be taken earlier in the evening. An occasional patient will respond well to nortriptyline, but experience increased energy that prevents sleep. In this case, the medication should be taken in the morning. SSRI agents have less proven benefit in migraine control.

Beta-blockers: Propranolol LA 60 mg/day increasing as needed up to 160 mg/day. Reactive airway disease and diabetes are the usual contraindications. Depression may be worsened by beta-blockers. Nadolol has fewer such CNS side effects; it is started at 20 mg/day and increased as needed up to 120 mg/day.

Anticonvulsants: Sodium valproate 250-500 mg BID (twice daily) is usually well tolerated, but liver function tests and platelets should be monitored. Gabapentin at a low dose of 300 mg a day, with weekly escalating doses to a first target dose of 300 mg three times a day (900 mg total). Then it can be increased gradually to another target dose of 1800 mg total a day (in 3 divided doses), or until side effects (usually sedation) appear. It has the inconvenience of frequent dosing, but with a low adverse effect profile. Dosing adjustments are necessary for renal insufficiency, and the medication should not be used in children under 12 years old. Topiramate (Topamax) has recently been shown to be a very effective migraine prophylactic agent. It is started at 25 mg PD and increased weekly to a goal of 100-200 mg BID. Monitoring for metabolic acidosis and nephrolithiasis is recommended.

All patients are cautioned that migraine symptoms often do not respond quickly to these interventions. Great patience is required of the patient and physician as 6-8 weeks of diet changes or the full dose of any new medication may be needed before benefits are seen.

Anxiety, depression, and even panic attacks are frequent accompanying diagnoses in these patients. These diagnoses should be recognized and discussed. The choice of a prophylactic medication may also be influenced by these other conditions.

One of the best resources for migraine therapeutics currently available is Lawrence Robbins' *Management of Headache and Headache Medications*. It very clearly outlines strategies for first line, second line, and combination therapy for migraine and other headache types in an easy-to-use handbook format.

BIBLIOGRAPHY

1. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-657.
2. <http://www.cdc.gov/nedss/>
3. <http://www.arthritis.org>
4. <http://www.census.gov>
5. Lipton RB, Stewart WF. Migraine in the United States: a review of epidemiology and health care use. *Neurology*. 1993;43 (suppl 3):S6-S10.
6. Stewart WF, Linet MS, Celantano DD, et al. Age- and sex-specific incidence rates of migraine with and without visual aura. *Am J Epidemiology*. 1991;134:1111-1120.
7. Lipton RB, Stewart WF, Simon D. Medical consultation for migraine: results from the American Migraine Study. *Headache*. 1998;38:87-96.
8. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology*. 2002;58(6):885-894.
9. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. *Ann Emerg Med*. 2002;39(3):215-222.
10. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? *Headache*. 1999;39 (suppl 2):S20-S26.
11. Lance JW, Goadsby PJ. *Mechanism and Management of Headache*. London, England: Butterworth-Heinemann; 1998.
12. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. 2nd ed. London, England: Martin Dunitz; 2002.
13. Olesen J, Tfelt-Hansen P, Welch KMA. *The Headaches*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.
14. Honkasalo ML, Kaprio J, Winter T, et al. Migraine and concomitant symptoms among 8167 adult twin pairs. *Headache*. 1995;35:70-78.
15. Ophoff RA, Terwindt GM, Vergouwe GM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell*. 1996;87:543-552.
16. May A, Ophoff, RA, Terwindt GM, et al. Familial hemiplegic migraine locus on chromosome 19p13 is involved in common forms of migraine with and without aura. *Hum Genet*. 1995;96(5):604-608.
17. Nyholt DR, Lea RA, Goadsby PJ, et al. Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. *Neurology*. 1998;50:1428-1432.
18. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) NcoI alleles. *Neurology*. 1997;49:201-206.
19. Welch KM, D'Andrea G, Tepley N, et al. The concept of migraine as a state of central neuronal hyperexcitability. *Neurol Clin*. 1990;8(4):817-828.
20. D'Andrea G, Cananzi AR, Joseph R, et al. Platelet excitatory amino acids in migraine. *Cephalgia*. 1989;9 (Suppl 10):105-106. [Poster Presentation]

21. Ferrari MD, Odink J, Bos KD, et al. Neuroexcitatory plasma amino acids are elevated in migraine. *Neurology*. 1990;40(10):1582-1586.
22. Wang W, Schoenen J. Interictal potentiation of passive "oddball" auditory event-related potentials in migraine. *Cephalalgia*. 1998;18(5):261-265.
23. Aurora SK, Cao Y, Bowyer SM, Welch KM. The occipital cortex is hyperexcitable in migraine: experimental evidence. *Headache*. 1999;39(7):469-476.
24. Wray SH, Mijovic-Prelec D, Kosslyn SM. Visual processing in migraineurs. *Brain*. 1995;118 (Pt 1):25-35.
25. Afridi SK, Matharu MS, Lee L et al. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. *Brain*. 2005;128:932-939.
26. Lashley KS. Patterns of cerebral integration indicated by the scotomas of migraine. *Arch Neurol Psych*. 1941;46:331-339.
27. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain*. 1994;117(Pt 1):199-210.
28. Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol*. 1990;28(6):791-798.
29. Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *N Engl J Med*. 1994;331(25):1689-1692.
30. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. 2001;98(8):4687-4692.
31. Cutrer FM, Sorensen AG, Weisskoff RM, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. *Ann Neurol*. 1998;43(1):25-31.
32. Goadsby, PJ, Lipton RB, Ferrari, MD. Migraine. Current Understanding and Treatment, Jan. 24, 2002 New England Journal of Medicine, No. 4, Volume 346:257-270 Copyright (C) 2002. Massachusetts Medical Society. All rights reserved.
33. Knight YE, Edvinsson L, Goadsby PJ. Blockade of calcitonin-gene-related peptide release after superior sagittal stimulation in cat: a comparison of avitriptan and CP122,288. *Neuropeptides*. 1999;33(1):41-46.
34. Ray BS, Wolff HG. Experimental studies on headache. Pain sensitive structures of the head and their significance in headache. *Arch Surg*. 1940;41:813-856.
35. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain*. 7th ed. New York, NY: Oxford University Press; 2001:57-72.
36. Cutrer FM, Limmroth V, Woeber C, et al. New targets for antimigraine drug development. In: Goadsby PJ, Silberstein SD, eds. *Headache: Bluebooks of Practical Neurology*. Vol. 17. Philadelphia, PA: Butterworth-Heinemann; 1997:59-120.
37. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal

- and supraspinal nociceptive neurons in migraine. *Brain*. 2000;123 (Pt 8):1703-1709.
38. Diener HC et al. A practical guide to the management and prevention of migraine. *Drugs*. 1998; 56(5):811-824.
39. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
40. Lipton RB, Stewart WF, Ryan RE. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol*. 1998;55(2):210-217.
41. Goadsby PJ. The pharmacology of headache. *Prog Neurobiol*. 2000;62(5):509-525.
42. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet*. 2001;358(9294):1668-1675.
43. Worldwide Product Safety and Pharmacovigilance Document. December 1999.
44. Gray RN, Goslin RE, McCrory DC, et al. *Drug Treatments for the Prevention of Migraine Headache*. Technical Review 2.3. Duke University: US Department of Health and Human Services, Agency for Health Care Policy and Research; February 1999. NTIS Accession No. PB99-127953. Available at: <http://www.clinpol.mc.duke.edu/>.
45. Lipton RB, Diamond S, Reed M, et al. Migraine diagnosis and treatment: Results from the American Migraine Study II. *Headache*. 2001;41(7):638-645.
46. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population – a prevalence study. *J Clin Epidemiol*. 1991;44:1147-1157.
47. Raskin NH. *Headache*. 2nd ed. New York: Churchill Livingstone; 1988.
48. Barbanti P, Fabbrini G, Pesare M, Cerbo R. Neurovascular symptoms during migraine attacks. [abstract] *Cephalalgia*. 2001;21(4):295.
49. Kaniecki R. Migraine headache exacerbation with sumatriptan injection: a sign of suprathreshold dosing? [abstract] *Cephalalgia*. 2001;21(4):413.
50. Kayan A, Hood JD. Neuro-otological manifestations of migraine. *Brain*. 1984;107:1123.
51. Wladislawosky-Waserman P, Facer G et al. Meniere's disease: a 30-year epidemiologic and clinical study in Rochester, MN, 1951-1980. *Laryngoscope*. 1996;94:1098-1102.
52. Vass Z, Dai CF et al. Co-localization of the vanilloid capsaicin receptor and substance P in sensory nerve fibers innervating cochlear and vertebro-basilar arteries. *Neuroscience*. 2004;124:919-927.
53. Buchholz D. *Heal your Headache the 1-2-3 Program*. Workman Publishing Company, New York, NY. 2002.
54. Sacks O. *Migraine*. Vintage Books, New York, NY. 1992.
55. Robbins L. *Management of Headache and Headache Medications, 2nd Edition*. Springer-Verlag, New York, NY. 2000.

