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21st Century Prevention and Management of Migraine Headaches

In cooperation with the American Academy of Neurology, the American Headache Society, and the National Headache Foundation

Jointly sponsored by Jefferson Medical College of Thomas Jefferson University
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Target Audience

Neurologists throughout the United States

Learning Objectives

Upon completion of this program, participants will be able to:

- Discuss current research findings related to the epidemiology, etiology, pathogenesis, and mechanisms of migraine
- Explain how patients are evaluated and diagnosed with migraine, including the optimal use of diagnostic testing
- Describe current acute and prophylactic treatments for migraine
- Discuss cluster headache and chronic migraine, including how they are diagnosed and treated

Needs Assessment

Migraine is a biological disease that affects approximately 28 million Americans. Migraine symptoms vary for each individual sufferer, increasing the difficulty of diagnosis. By understanding the pathophysiology of migraine, physicians will be better able to make accurate diagnoses, which is the key to an effective treatment program.

Migraine is comorbid and may be pathophysically associated with a number of neurological and psychiatric disorders, including stroke, epilepsy, depression, and anxiety disorders.

Instructions For Continuing Medical Education Credit

This activity should take approximately 2 hours to complete. The participant should, in order, read the learning objectives listed above, read the monograph, answer the 10-question multiple-choice posttest and complete the evaluation form, both found on the insert. The evaluation form provides participants with the opportunity to comment on whether the educational objectives were met, the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and their views on future educational needs. To receive credit for this activity, follow the instructions provided on the posttest. This credit is valid through January 2004. No credit will be given after that date.

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in cooperation with the American Academy of Neurology, the
American Headache Society, and National Headache Foundation presents

21st Century Prevention and Management of Migraine Headaches

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Overview

Migraine exacts a tremendous toll on the quality of life of affected individuals, their families, and society as a whole. As a chronic disorder with prominent episodic manifestations, migraine is associated with considerable disability that undermines normal function and results in reduced productivity. Pain, associated symptoms, and restriction of activity not only pose personal burdens but also have broader economic implications.

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to advancing knowledge about the epidemiology, etiology, diagnosis, and management of headache disorders. Since these disorders affect the national economy, the US Congress has charged the NINDS with the responsibility of expanding the understanding of basic pain mechanisms and identifying potential new avenues of treatment. The NINDS has responded by creating greater opportunities for career training and grant support in the field of headache research. An important component of this effort is aimed at improving diagnostic and therapeutic strategies through the application of research findings in the clinical setting.

As part of its dedication to this initiative, the NINDS convened a group of recognized experts for a conference titled "21st Century Prevention and Management of Migraine Headaches," held June 8 and 9, 2000 in Bethesda, Maryland. The conference was presented in cooperation with the American Academy of Neurology, the American Headache Society, and the National Headache Foundation. Through state-of-the-art reviews and discussions of cutting-edge research, the participants examined advances in the management of migraine and other headache disorders, explored newly emerging perspectives on pathophysiologic mechanisms, and identified key scientific and clinical issues that remain to be addressed. Continued understanding of migraine will generate significant progress in the diagnosis, prevention, and treatment of migraine.

Epidemiology, Etiology, and Comorbidities of Migraine

Epidemiology and Impact of Migraine

Recent research has shed new light on trends in the prevalence and impact of migraine in the United States. These insights have emerged from a comparison of 2 methodologically identical investigations—the American Migraine Studies I and II—conducted in the United States in 1989 and 1999, respectively.[1,2] The data provide important perspectives on epidemiologic, diagnostic, and treatment patterns of migraine during the past decade.

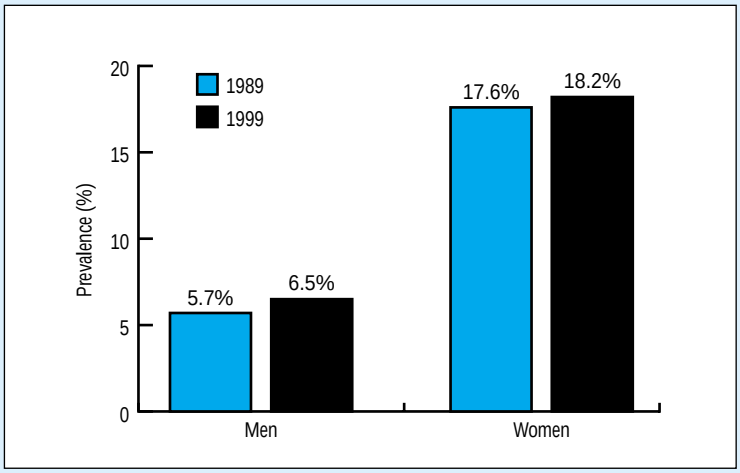
Questionnaires were used to collect information from individuals who selectively represented the US population in terms of age, geographic region, household size, and socioeconomic status. More than 20,000 individuals participated in the first study and nearly 30,000 in the second. Those identified as having migraine based on the criteria of the International Headache Society (IHS) received follow-up questionnaires regarding disease burden, diagnosis, treatment, and healthcare utilization.

The results showed that the prevalence of migraine has remained relatively constant since 1989 (Figure 1).[2] Yet, with the growth in the US population, the actual number of individuals with the disorder has increased from 23.6 to 27.9 million.[2] More than 18% of American women and 6% of American men have migraine.[2] Approximately 1 in every 4 households includes an individual who suffers from migraine.[2] The incidence of migraine peaks in adolescence; about half of all people who experience the disorder as adults have histories of onset during childhood or adolescence. The prevalence is greatest between the ages of 25 and 55 years and declines thereafter. After puberty, migraine is more common in women than in men, with an overall prevalence ratio of 3:1. Fluctuations in sex hormones, beginning with menarche, contribute to this discrepancy.[2]

In the second American Migraine Study, data on the frequency of migraine revealed that the majority of sufferers (48%) experienced severe headaches for 1 to 4 days of any given 3-month period.[2] Another 20% had migraines for 5 to 9 days, and 10% had no attacks at all. Notably, 13% of respondents had migraines for 10 to 19 days, and 10% had attacks for more than 20 days.[2]

Figure 1

Prevalence of Migraine in the United States



Adapted with permission from Lipton RB, et al. Prevalence and burden of migraine in the United States: results from the American Migraine Study II. *Headache.* 2001;41:650.

The individual burden of disease can be measured in terms of pain, associated symptoms, and activity limitations or disability. In the 1999 study, migraine pain was reported as extremely severe by approximately 46% of diagnosed respondents, and severe headache was reported by more than 43%.[2] Relatively few had pain that was mild to moderately severe. As shown in Figure 2, the study participants identified a broad range of associated symptoms. The prevalence of aura was higher than has been observed in most studies; this is probably because the questionnaire used in the American Migraine Study was self-administered and yielded some false-positive responses. A total of 53% of individuals reported experiencing severe impairment or requiring bed rest related to migraine, 39% indicated some impairment, and 91% said that they were not able to work or function normally.[2]

Figure 2

Prevalence of Migraine Complications in US Patients

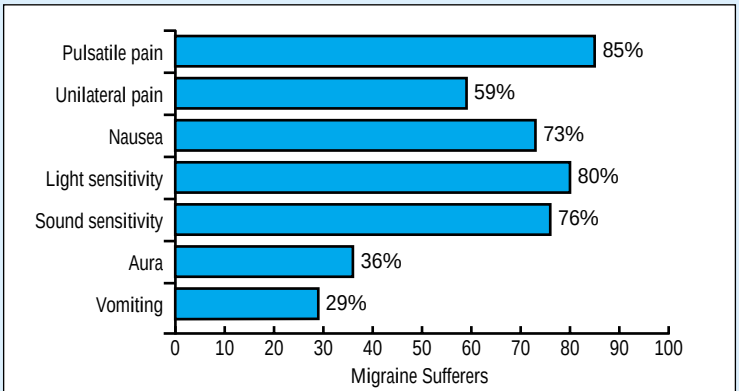


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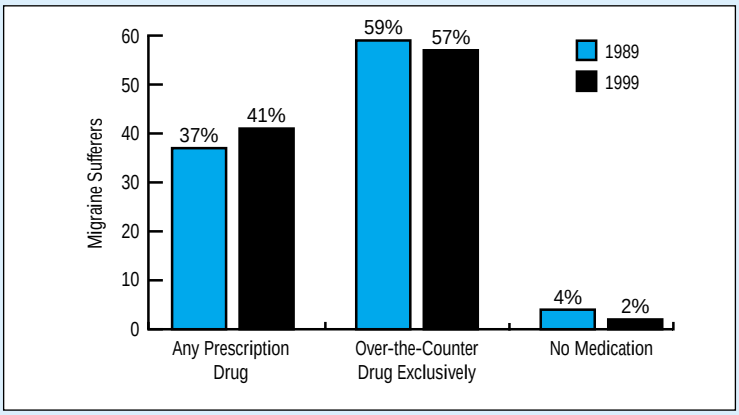
Figure 3

Patterns of Migraine Medication Use in the United States



Adapted with permission from Lipton RB, et al. Prevalence and burden of migraine in the United States: results from the American Migraine Study II. *Headache.* 2001;41:650.

The social impact of migraine can be assessed not only in terms of direct medical costs but also in terms of indirect (productivity loss) costs. Migraine is responsible for more than 112 million bedridden days per year in the United States.[3] Migraine costs American employers $13 billion per year because of missed work and reduced productivity at work.[3] Reduced productivity is the greater part of the economic burden, because migraine sufferers often go to work on headache days.[4] The distribution of the burden was explored in a 1996 analysis from the first American Migraine Study that focused on more disabled individuals who missed the equivalent of 6 or more days of work per year.[4] This definition applied to 51% of women and 38% of men with migraine. These individuals accounted for about 90% of the total workdays lost because of migraine.[4] From a public health perspective, therefore, the most disabled segment of the migraine population may be the most compelling target for treatment.

Despite the evident burdens, migraine is often not treated adequately. In both the first and second American Migraine Studies, approximately one third of all migraine sufferers said that they had never consulted physicians for this problem.[5] However, the proportion of respondents who had consulted physicians specifically for headache in the previous year had increased from 16% in 1989 to 47% in 1999.[6,7] Another notable finding was that the proportion of "lapsed consulters," those who had seen physicians for the treatment of headache at some point but not within the previous year, decreased from 50% to 21% during the 1990s.[7] The proportion of respondents who reported ever having received medical diagnoses of migraine rose modestly, from 38% in 1989 to 48% in 1999.[6]

Patterns of prescription versus over-the-counter medication use for migraine remained relatively constant between 1989 and 1999 (Figure 3).[6] A 1998 telephone survey found that 29% of migraine sufferers were very satisfied with their usual treatment for acute attacks. Among those expressing dissatisfaction, 87% noted that pain relief took too long, 84% indicated that not all pain was relieved, 84% stated that treatment did not always work, 71% complained that the headache came back, and 35% said that the medication had too many side effects. The survey did not question participants about their satisfaction with preventive treatment.[7]

The observations from the American Migraine Studies suggest that the epidemiology of migraine remains relatively unchanged. Over the last decade there has been some progress in diagnosis and management

of migraine, but important challenges remain. Several barriers may continue to undermine the prospects for optimal patient care. In many medical circles, for example, migraine still is not accepted as a legitimate medical disorder, because it cannot be evaluated using objective tests, is not life-threatening, and is episodic rather than chronic. The reluctance to view migraine as a legitimate disorder may also be influenced by gender bias, as migraine is more prevalent in women than in men. From the standpoint of the individual with migraine, obstacles to care may include denial of the condition, embarrassment, and the belief that no effective treatment is available. Family patterns of physician consultation may play a role as well; for instance, a migraine sufferer may not realize that the disorder is treatable if an affected family member has relied solely on self-management methods such as retreating to a dark, quiet room.

Another problem is that physician consultations are often ineffective, causing patients to discontinue care. Of particular concern is the fact that a comparison of data from the 1989 and 1999 American Migraine studies showed a marked increase in the number of patients who sought medical consultation but a much smaller increase in the number who took prescription drugs.[6] Several factors may account for this gap: the fact that many patients tend to mention headaches only as an afterthought at the end of an office visit; the tendency of some physicians to suspect that patients who complain of headaches are simply seeking narcotics; and the use, in many practices, of a step-care approach to treatment that may cause patients to become discouraged and discontinue care before efficacy can be achieved.

Greater recognition of the disability caused by migraine could help legitimize the disorder. In a recent analysis of World Health Organization disability ratings for 22 different medical disorders, the most disabling conditions were found to be active psychosis, quadriplegia, dementia, and severe migraine.[8] Increased awareness of the impact of migraine—in terms of reduced functional status, productivity, and quality of life—is essential for migraine diagnosis and treatment.

Migraine Comorbidities

Psychiatric and neurologic comorbidities are often observed in patients with migraine. The presence of such comorbid conditions carries etiologic, diagnostic, and therapeutic implications.

In general, the association between migraine and comorbid conditions can be (1) coincidental; (2) causative; (3) etiologically based, wherein the 2 disorders are linked by a common genetic or environmental factor; or (4) etiologically based, wherein an altered mental or neurologic state causes both disorders.[9] Certain psychiatric disorders (major depression, affective disorder, and anxiety disorder) and neurologic disorders (stroke, epilepsy, and sleep disorders) occur with greater-than-coincidental frequency in migraine sufferers.[10] A unidirectional causative relationship would exist if, for example, migraine increased the risk of epilepsy, perhaps by causing ischemic cortical damage during aura. Environmental risk factors, for example, head injury, may increase the risk of both migraine and epilepsy. An etiologic relationship arising from an altered neurologic state would be present if, for instance, both genetic and environmental factors produced hyperexcitability and increased the risk of both epilepsy and migraine.

Attention to prospective comorbid conditions can assist in diagnosis. When conditions are comorbid, the principle of diagnostic parsimony does not necessarily apply. Migraine having been diagnosed, it becomes more likely, not less likely, that certain other conditions are also present.[9]

Patients who have migraine may have headaches associated with alterations of mood. Patients with depression may have mood alterations and pain. Clinicians need to consider the issue of both differential diagnosis and concomitant diagnoses. In the setting of comorbidity it may be possible to treat both conditions with a single drug. An anticonvulsant, for example, may be effective for a patient with epilepsy and migraine. A tricyclic antidepressant (TCA) may treat both depression and migraine. On the other hand, knowledge of the existence of comorbidities can allow the clinician to tailor therapy more appropriately. One would be less likely, for instance, to use a TCA or neuroleptic agent (either of which may lower the seizure threshold) to treat migraine in an epileptic patient or to use a beta blocker (which may worsen depression) to treat migraine in a patient with depression.[10]

…knowledge of the existence of comorbidities can allow the clinician to tailor therapy more appropriately.

Psychiatric disorders

With regard to psychiatric comorbidities, studies have shown that migraine sufferers have an increased risk of affective and anxiety disorders (Table 1, page 4).[10,11] A study by Breslau and Davis shed further light on the connection between migraine and major depression.[12] The relative risk of new-onset migraine was 3.1 in patients with histories of major depression compared with those without such histories. Similarly, the risk of new-onset depression was 3.2 in patients with histories of migraine as opposed to those without such histories. This bidirectional pattern suggests that migraine is neither the cause nor the result of depression. Migraine and depression independently reduce health-related quality of life.[13]

Table 1

Lifetime Risk of Psychiatric Disorders in Migraineurs

Psychiatric Disorder	Odds Ratio	95% CI
Major depression	4.5	3.0 – 6.9
Manic episode	6.0	2.0 – 18.0
Panic disorder	6.6	3.2 – 13.9
Any anxiety disorder	3.2	2.2 – 4.6

CI = Confidence interval.

Silberstein SD, et al. Neuropsychiatric aspects of primary headache. In: Yudofsky SC, Hales RE, editors. *The American Psychiatric Press Textbook of Neuropsychiatry.* 3rd ed. Washington, DC: American Psychiatric Press; 1997:381-412.

Table 2

Classification of Migraine-Related Stroke

Category	Feature
I	Coexisting stroke and migraine
II	Stroke with clinical features of migraine
	A. Symptomatic migraine
	B. Migraine mimic
III	Migraine-induced stroke
	A. Without risk factors
	B. With risk factors
IV	Uncertain

Reprinted with permission from Welch KMA. Relationship of stroke and migraine. *Neurology.* 1994;44(10 suppl 7):S34.

In a study based on telephone interviews with more than 10,000 subjects, Stewart and colleagues found that individuals with histories of panic disorder were more likely to report that they had experienced headaches during the week preceding the interview than were responders without panic disorder. The relative risk of migraine in such individuals was 7.0 for men and 3.7 for women.[14] Other work by this group showed that migraine sufferers with comorbid psychiatric disease were much more likely to consult physicians for the complaint of headache. Among patients 24 to 29 years old who had recently consulted physicians for headache complaints, 15% of women and 13% of men had comorbid panic disorder.[15]

Although systematic data are lacking, physicians practicing in subspecialty clinics have long had the impression that migraine sufferers share certain personality traits. These patients are often observed to be rigid, perfectionistic, overly sensitive, highly competitive, and easily frustrated. In a population-based, case-control study using Eysenck's Personality Questionnaire, Brandt and colleagues found that migraineurs had higher scores for neuroticism, indicating greater levels of tension, anxiety, and depression. Women with migraine had significantly higher scores for psychoticism, reflecting greater levels of hostility and poor interpersonal skills.[16] This investigation was limited by the lack of controls for medication use, headache-related disability, and the presence of major psychiatric disorders. To address the latter issue, Breslau and Andreski conducted a study in which data obtained with Eysenck's Personality Questionnaire were adjusted for comorbid major depression or anxiety disorders. Migraine was significantly associated with neuroticism but not with psychoticism or extraversion. The researchers suggested that individuals with migraine may be more vulnerable to psychopathology and poor adjustment.[17]

Stroke

The risk of migraine-related stroke is difficult to determine because of variations in the definitions used in different studies. Moreover, many reports on epidemiologic studies have lacked details regarding the timing of stroke in relation to migraine attacks.[18]

Some studies have identified an increased risk of stroke in certain subgroups of individuals with migraine. For example, there is an independent association between migraine and the risk of ischemic stroke in women less than 45 years of age, although the absolute risk is low.[19,20] Anywhere from 1% to 17% of strokes in hospitalized patients less than 50 years of age appear to be associated with migraine.[21]

Stroke is also generally more common in migraine with aura. Overall, however, the occurrence of stroke during migraine attacks (true migraine-induced stroke) is rare.[18]

K. M. A. Welch proposed a classification system to help define the intricate relationships between the 2 disorders (Table 2).[18] Category I refers to clearly defined stroke occurring remotely in time from a typical attack of migraine from which the patient routinely suffers. The association between stroke and migraine may be coincidental in some such cases or may reflect shared underlying risk factors (such as mitral valve prolapse). Category II pertains to the existence of a structural lesion that is unrelated to the pathogenesis of migraine but is the source of the clinical features of migraine. This classification would apply, for example, to patients with cerebral arteriovenous malformation (AVM) in whom structural disease causes a typical episode of migraine with aura and repeated rebleeding related to the malformation. Alternatively, patients in this category may have a migraine mimic in which stroke is accompanied by headache and a transient evolution of neurologic events that resemble migraine but are actually due

to stroke. Category III describes cases in which the neurologic deficit of stroke is identical to the neurologic symptoms of prior migraine attacks. Stroke occurs during the course of a typical migraine headache. Other causes of stroke must be excluded. Category IV refers to cases in which it is unclear whether migraine is related to stroke. Consideration must be given to the possible roles of intrinsic and extrinsic factors such as systemic vasculitis, antiphospholipid antibody syndrome, mitochondrial encephalopathies, excessive use of vasoconstrictors, or the use of oral contraceptives (OCs) or other drugs.

Epilepsy

The association between migraine and epilepsy is well established. As shown in Table 3, the prevalence of epilepsy is considerably higher in migraineurs than in the general population. Moreover, the prevalence of migraine among epileptics is higher than in the general population.[22] In the Epilepsy Family Study, the cumulative incidence of migraine to 40 years of age was 24% in adults with epilepsy (the probands), 23% in relatives with epilepsy, and 12% in relatives without epilepsy (no higher than in the general population).[23] A Cox proportional hazards analysis controlling for years at risk and gender showed that the risk ratio for migraine was 2.4 among both probands and relatives with epilepsy compared with relatives without epilepsy.

The risk of migraine among epileptics was unrelated to the age at seizure onset, implying that migraine is not solely the cause or result of epilepsy. The risk of migraine was higher for patients with partial rather than with generalized seizures, and the highest risk was seen in those with posttraumatic epilepsy.[23] The latter observation suggests that head trauma may be a risk factor for both disorders, although the risk of migraine is elevated in idiopathic epilepsy also. On the other hand, it may be possible that alterations in brain state (involving, for instance, reduced levels of magnesium or altered levels of neurotransmitters) increase the risk of both disorders. Regardless of the etiology, migraine medications that lower the seizure threshold (such as TCAs) should be avoided by patients with coexisting migraine and epilepsy. Whenever possible, these patients should be treated with antiepileptic agents capable of addressing both disorders.

Sleep disorders

Although patients with migraine often complain that their sleep is disrupted by headache, limited information is available on the comorbidity of migraine and bona fide sleep disorders. Most published data have dealt with parasomnias, defined as undesirable physical phenomena that either occur exclusively during sleep or are exacerbated by sleep. One study found a markedly higher incidence of parasomnias among 100 migraine patients than among 100 controls.

Table 3
Prevalence of Migraine and Epilepsy

Disorder	Population	Prevalence
Epilepsy	General population	0.5%-1%
	Migraineurs	5.9%*
Migraine	General population	5%-10%
	Men	6%
	Women	18%
	Epileptics	8% to 15%

*Median (range, 1%-17%)

Stewart WF, et al. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA.* 1992;267(1):64-69.

Andermann E, Andermann FA. Migraine-epilepsy relationships: epidemiological and genetic aspects. In: Andermann FA, Lugaresi E, editors. *Migraine and Epilepsy.* Boston MA: Butterworth-Heineman;1987:281-291.

Pavor nocturnus (night terrors) occurred in 71% versus 11%, enuresis in 41% versus 16%, and somnambulism in 55% versus 16%, respectively.[24] The incidence of somnambulism among adult migraineurs was 22% in an investigation by Pradalier and colleagues.[25] In children, the incidence was 28% in a study by Giroud and colleagues and 30% in work by Barabas and colleagues.[26,27]

Several important neurologic and psychiatric conditions may coexist with migraine. The recognition of these disorders is essential for establishing differential diagnoses and identifying optimal treatment strategies. Additional population-based, longitudinal studies are needed to clarify the incidence and natural course of migraine comorbidities.

Special Populations

Elderly Patients

Management of headache in the elderly is often challenging. The rising prevalence of comorbidities with aging can often confound diagnosis and impose therapeutic limitations. Secondary headache disorders increase in prevalence with age, whereas primary headache disorders become less common.[28] Careful assessment is warranted to avoid mistaking a secondary headache for a primary headache. Primary headaches in the elderly include migraine, tension-type headache, cluster headache, and hypnic headache.[28] The hypnic headache syndrome is a rare, benign, sleep-related headache disorder that is unique to the elderly population.[29] Hypnic headache is characterized by easily recognizable stereotypic features that include awakening from sleep, often at the same time each night; generalized throbbing head pain; a duration of 30 to 60 minutes; and absence of accompanying autonomic symptoms.[30]

Although lithium carbonate appears to be one of the most effective therapies for hypnic headache, the side-effect profile of this agent renders it less than optimal for long-term therapy in the elderly.[29,31] Some patients may derive benefit from caffeine in the form of either a tablet or a cup of coffee before bedtime.[29] Indomethacin and flunarizine have also shown efficacy in case-report studies, although flunarizine is not available in the United States.[32,33]

Even though most headaches in older individuals are benign, primary headaches, the clinician should maintain a high index of suspicion of a relationship to organic disease (secondary headaches).[28] Laboratory tests and imaging studies should be performed to rule out systemic illness when appropriate. Secondary headaches in the elderly may be related to a number of conditions, including cerebro- or cardiovascular disease, subdural hematoma, stroke, or cancer. Giant cell (temporal) arteritis, a disease unique to the elderly, should be a major consideration in the differential diagnosis, since up to 90% of patients with temporal arteritis have headache symptoms.[28] The clinical manifestations of giant cell arteritis include headache of new onset or a change in a previously stable headache profile; jaw claudication; tenderness or edema of the temporal artery; and polymyalgia rheumatica. One of the most serious complications is blindness. The erythrocyte sedimentation rate is an effective screening test and is elevated in most cases. Temporal artery biopsy is the definitive diagnostic test. Patients with this condition should receive long-term glucocorticoid therapy.[34]

In view of the fact that many elderly patients take numerous drugs for a host of problems, the potential for headache related to medication side effects is an important concern.[28] Drug interactions must be ruled out as part of the differential diagnosis and in the selection of headache therapy. In the treatment of patients with headache of unknown origin, consideration should be given to tapering and eventually withdrawing any medications deemed not essential.

Preventive migraine medications are recommended when recurring migraine significantly interferes with a patient's daily routine; when symptomatic medications are ineffective or contraindicated; or when there are special concerns such as profound headache-related disability, prolonged migraine aura, or history of migrainous cerebral infarction.[28] Beta blockers may be effective but should be used with caution by older patients. These medications are contraindicated for individuals with coexisting asthma, congestive heart failure, hypotension, diabetes, or migraine with prolonged aura.[28] TCAs may be used, although elderly individuals may be especially sensitive to the anticholinergic effects of these agents. Moreover, TCAs are contraindicated in the presence of dysrhythmias, closed-angle glaucoma, or urinary retention or for men with prostatic hypertrophy.[28] The anticonvulsants divalproex sodium, gabapentin, and topiramate may be effective as migraine prophylaxis and have the advantage of an absence of significant cardiovascular risks.[28]

Headache medications should be started at low doses and titrated slowly upward to the lowest effective dose for elderly patients. Particular attention must be paid to the potential for age-related changes in drug metabolism, distribution, and elimination that can place older patients at risk for toxicity.[28] Doses should be appropriately adjusted for age, renal function, and hepatic function.

Women

Migraine is 3 times more common in women than in men.[2] Notably, most affected women suffer migraine during their peak productive years, when they are commonly faced with a multitude of family, household, and work responsibilities.

When evaluating women with possible migraine, clinicians should consider the influence of endocrinologic factors associated with the female reproductive cycle. Estrogen and progesterone affect neuronal function involving the serotonin, norepinephrine, and beta-endorphin systems.[35] Recent research has established a direct link between estradiol and pain modulation.[36] An association between migraine and fluctuations in levels of estrogen and progesterone in women, beginning at menarche, has also been documented.[37]

In one study, approximately 14% of women with migraine had headaches exclusively during menses,[37] whereas most female migraineurs of reproductive age have headaches at other times during the menstrual cycle as well. Most often, headache occurs during the first 3 days of menstruation.[38] Cyclic hormonal changes are the basis for menstrual migraine.

The risk of migraine is increased 10-fold in women taking OCs who have not had migraines previously.[39] Moreover, OCs have been found to increase the frequency of migraine attacks.[40] Attacks occur during the week women are taking placebo rather than active pills.[41] During pregnancy, almost half of women with migraine experience improvement in their headaches.[42]

Migraine symptoms have been observed to decrease in two thirds of women after natural menopause but in only one third after surgically induced menopause.[43] Among women taking hormone replacement therapy (HRT), migraines have been shown to improve in 45%, worsen in 46%, and remain unchanged in 9%.[44]

Cyclic or "mini"-prophylaxis with a triptan or nonsteroidal anti-inflammatory drug (NSAID) may be considered for women with menstrual migraine whose headaches occur in a predictable fashion. Treatment is typically started 2 to 3 days before menses and

continued for as long as 1 week.[45] Women who have a high frequency of attacks outside of menses may be candidates for continuous prophylaxis.[45] Because of the unpredictable timing of migraines, those who have irregular menstrual cycles may be better treated with aggressive acute therapy rather than with cyclic prophylaxis. The triptans are the treatment of choice for acute therapy.[45] Ergotamine may be considered for patients whose headaches are of longer duration or do not respond to triptans or NSAIDs.[46]

Ideally, a plan for the management of migraine during pregnancy should be agreed on by the patient and physician before the woman conceives. The risks of various medications during pregnancy and breast-feeding must be evaluated on the basis of animal data and retrospective studies, as pregnant women are usually excluded from clinical trials.

If evaluations (such as a 3-month patient diary) suggest that migraine is associated with hormonal factors in a postmenopausal patient, the use of HRT should be optimized. The variety of HRT regimens available permits treatment to be tailored to the individual. Patients who do not respond to the initiation of HRT or changes in regimens may be considered for standard prophylactic treatment. If no hormonal link is identified, provision for prophylactic and acute therapy should proceed as for other patients who have no hormonal triggers.

Mechanisms and Pathogenesis of Migraine

Clinical Features of Migraine: A Framework for Understanding Underlying Pathophysiology

Migraine attacks have a well-described spectrum of clinical manifestations that have provided a basis and stimulus for research into the complex pathophysiology underlying this disorder. These clinical features generally are divided into 4 distinct phases: prodrome, aura, headache, and resolution. The prodrome, which is experienced by approximately 25% of migraineurs,[47] consists of characteristic symptoms that occur up to 24 hours before the attack. Symptoms include changes in mental state such as euphoria or irritability, neurologic symptoms, and physical symptoms such as diarrhea, thirst, and food cravings.[48] The nature of these symptoms suggests that the hypothalamus, in particular the suprachiasmatic nucleus, may be involved.[48] The prodrome is followed by aura in approximately 15% of migraine attacks. The aura phase consists of focal neurologic symptoms that may include visual, sensory, motor, or language disturbances. Aura usually resolves within 60 minutes.[47] The pain of migraine then ensues and is typically unilateral, throbbing, and accompanied by nausea, vomiting, photophobia, or phonophobia.[48] The headache phase may persist for up to 72 hours before ending in a resolution phase often characterized by deep sleep.[48] Many patients experience malaise or fatigue for up to 24 hours after the headache has resolved.[48]

Evolving Concepts of the Basis for Aura

Many of the current concepts regarding migraine pathophysiology have arisen from studies of migraine aura. Early studies by Ray and Wolff led to the predominant vasogenic theory of aura.[48,49] Because aura is associated with a reduction in cerebral blood flow (CBF), it was proposed that aura was caused by intracerebral vasoconstriction and headache pain was caused by reactive vasodilation of the carotid artery. Although this theory accounts for several phenomena, including the throbbing nature of headache pain and its relief with ergot administration, it does not explain clinical features observed during the prodrome, the efficacy of certain drugs that have no vascular effects, and the cause of headache pain in patients (the majority of migraineurs) who do not have aura.

The aura of migraine is currently understood as primarily a neuronal event. This understanding is based on classic studies performed in the 1940s and new findings made possible by recent advances in neuroimaging techniques. In 1941, K. S. Lashley, a migraineur, mapped his own visual aura. He calculated the rate of progression of aura across his visual field to be approximately 3 mm per minute.[50] This rate of progression correlated well with the cortical phenomenon of spreading depression first described by Leao in 1944.[49] Noxious stimulation of exposed cerebral cortex had been shown to cause neuronal activation followed by spreading depression of normal neural activity at a rate of 2 to 3 mm per minute from the focal site of stimulation. The similar rates of progression of these 2 phenomena suggested that they are related and led to the theory that aura is due to spreading cortical depression.

More recent blood flow imaging studies have provided support for spreading depression as the basis of migraine aura. In xenon blood flow studies, Olesen and colleagues monitored changes in brain activity in patients with migraine with aura who underwent carotid angiography.[51] A wave of oligemia was shown to spread across the cortex beginning in the occipital lobe and to propagate over the parietal and temporal lobes. A phase of hyperemia preceded the oligemia in 4 of 7 patients.[51] In a later study, the temporal relationship between changes in CBF and the occurrence of aura and headache was established.[52] Two findings from these studies conflict with the vascular theory of migraine pathophysiology. First, the finding of initial hyperemia contradicts the vascular hypothesis that the initiation of aura occurs because of vasoconstriction and cerebral ischemia.[51] Second, the temporal relationship between CBF changes and initiation of headache pain indicated that the

headache phase began while blood flow was reduced,[52] contradicting the concept that headache is due to reactive vasodilation.

Cao and colleagues used functional magnetic resonance imaging-blood oxygenation level-dependent contrast to study the aura phase of migraine induced by visual stimulation. The onset of headache, visual change, or both was preceded by suppression of initial activation, which slowly propagated laterally and anteriorly across the occipital and parietal cortex at a rate ranging from 3 to 6 mm per minute. Neuronal suppression was accompanied by vasodilation and tissue hyperoxygenation. The authors hypothesized that this spreading suppression and accompanying vasodilation are associated with headache induction.[53]

Although many of the studies of spreading depression have involved migraine patients with aura, results of 1 recent study suggest that the same neuronal events occur in all patients with migraine. Woods and colleagues reported a series of blood flow measurements using positron-emission tomography (PET) in a patient during a spontaneous attack of migraine without aura. Headache was associated with a slow-propagating wave of cerebral oligemia, which spread forward from the occipital, parietal, and temporal cortices—findings consistent with spreading depression.[54] Whereas spreading depression and oligemia are clinically silent in patients who do not experience aura, this study implies a shared pathophysiologic substrate in patients with and without aura.

Headache Pain

Headache pain is generally believed to be the result of local vasodilation of meningeal blood vessels and consequent stimulation of trigeminal sensory nervous pain pathways. As the intracranial blood vessels swell, they activate perivascular sensory trigeminal nerves. Activation of the trigeminovascular system leads to the release of vasoactive neurogenic plasma proteins.[55] These neuropeptides, including substance P, calcitonin gene-related peptide, and neurokinin A, promote neurogenic inflammation (vasodilation, plasma protein extravasation, mast cell degranulation), thereby increasing nerve activation and intensifying headache pain.[55,56] Activated trigeminal nerves carry pain information from the peripheral sensory nerves to second-order sensory neurons within the trigeminal nuclei in the caudal brainstem and the upper cervical spinal cord. The trigeminal nuclei relay incoming pain signals to higher cortical centers where pain is perceived.[55]

Evidence for the additional involvement of brainstem mechanisms in migraine pathogenesis was provided by 2 recent studies. Weiller and colleagues used PET to detect brainstem regions with increased blood flow during spontaneous and unmedicated migraine attacks. Nine patients with migraine without aura were studied. Activation or increased CBF was shown to map to the locus ceruleus and to the dorsal raphe. This occurred both during the attack and after it was terminated by sumatriptan, suggesting that activation is not just a consequence of headache or related to the relief of headache but may be inherent in the pathophysiology of migraine itself.[57] Welch and colleagues reported on a patient with migraine in whom brain oxygenation was measured during aura. In this patient, hyperoxia was shown to occur in the red nucleus and substantia nigra concomitantly with hyperoxia in the cerebral cortex.[58] These studies, coupled with supportive evidence from experimental animal models, suggest that brainstem activation may be integral to migraine,[57] and further research into potential dysfunction in brainstem nuclei may someday provide explanations for many aspects of migraine.

The Concept of Neuronal Hyperexcitability in Migraine

Although study of the processes underlying the phases of migraine will eventually unravel the complex sequence of events from initiation of spreading depression to headache resolution, the reasons spreading depression is activated in certain individuals remain unknown. One theory advances the concept of central neuronal hyperexcitability. In individuals with lowered thresholds for stimulation and neuronal hyperexcitability, triggers of a migraine attack would more readily activate the pathways that mediate migraine.

The study of rare, genetically determined subtypes of migraine has provided genetic evidence for altered neuronal hyperexcitability. One or more mutations altering the function of P/Q-type calcium channels within the neuronal membrane have been shown to be associated with a specific form of migraine, familial hemiplegic migraine (FHM).[59] In 1996, Ophoff and colleagues characterized a gene in the FHM candidate region on chromosome 19p13 encoding a voltage-gated P/Q-type calcium channel alpha$_{1A}$ subunit (CACNA1A).[60]

The significance of these findings relates to the key role of calcium in cellular signaling and the importance of homeostatic mechanisms to control calcium inflow and outflow. Presynaptic neuronal voltage-gated calcium channels mediate the release of excitatory amino acid neurotransmitters such as glutamate and serotonin (5-hydroxgtriptamine, or 5-HT). They also regulate other ion channels and the electrical activity of the cell membrane. The P/Q calcium channels have been shown, in animals, to be responsible for spreading cortical depression.[61] Thus, these mutations in neuronal ion channels may provide the molecular basis of the cortical hyperexcitability seen in humans.

Additional biochemical and electrophysiologic evidence supports the concept that increased neuronal hyperexcitability may be the cause of migraine.

Reduced levels of intracellular magnesium during migraine attacks have been demonstrated both systemically and in the brain. Magnesium is important for mitochondrial oxidative phosphorylation as well as for N-methyl-D-aspartate–receptor modulation and thus may be implicated in hyperexcitability. Patients with migraine with and without aura have been shown to have increased excitatory amino acid-transmitter levels both ictally and interictally.[62] Additional evidence for central neuronal excitability comes from transcranial magnetic stimulation studies of the occipital cortex in patients with migraine with aura. These studies demonstrated that stimulation thresholds for the generation of phosphenes were significantly and drastically reduced in migraineurs relative to control patients ($P = .001$).[63]

Recent advances have offered new insights into the basic pathophysiology of migraine. Importantly, accumulating genetic, biochemical, and electrophysiologic evidence suggests that neuronal hyperexcitability may underlie susceptibility to migraine attack. Although much has been learned, continued research into the basic neural mechanisms of migraine is vital. A clearer understanding of this complex cascade of events that begins within the brain will facilitate the development of more effective and specific treatments for this often-debilitating disorder.

Genetic Component

Any given individual can develop a migrainelike headache. Migraine is a physiologic event that occurs in response to specific triggers; the abnormality is not the attack itself but rather the repeated occurrence of attacks. Research into genetic influences on individual thresholds of susceptibility may reveal more about the basic mechanisms of migraine and provide new targets for prophylactic drug treatments.

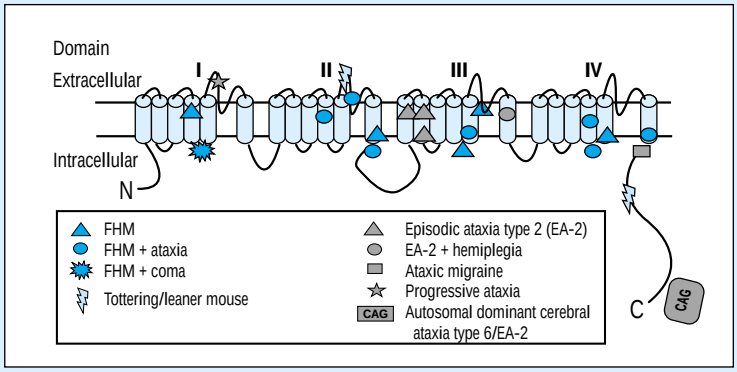
In one of the best studies of family aggregation in migraine, Olesen and colleagues found nearly a 4-fold increased risk of migraine with aura (but not migraine alone) in first-degree relatives of probands who suffered from migraine with aura.[64] First-degree relatives of probands who had migraine without aura likewise had a significantly increased, albeit less pronounced, risk of migraine with aura.[64] These same investigators also reported the results of a large study showing that concordance rates for migraine, either with or without aura, were greater for monozygotic twins than for dizygotic twins.[65] Although the study demonstrated that genetic factors are involved in migraine, concordance rates did not reach 100%, indicating that environmental factors are important as well.

Genetic heterogeneity, clinical heterogeneity, and environmental influences have hindered identification of the genetic factors involved in migraine and other episodic disorders, such as epilepsy and episodic ataxia. For these reasons, researchers have focused on rare, but clearly genetically determined, subtypes to gain insights that might help unravel the pathogenesis of the more frequently occurring forms. As discussed above, one such line of investigation centered on FHM and the P/Q-type calcium channel. Researchers determined that mutations in the brain-specific P/Q-type calcium channel alpha$_{1A}$ (CACNA1A) subunit gene are responsible for episodic ataxia as well as for FHM (Figure 4).[66] The most important function of the P/Q-type calcium channel is modulation of the release of certain types of neurotransmitters (monoamines, catecholamines, and excitatory amino acids). P/Q-type calcium channel expression in the brain appears to be restricted to the cerebellum. Studies have confirmed that the function of the channel is altered by CACNA1A subunit gene mutations in FHM.

Similar mutations have been identified in the CACNA1A subunit found in the tottering mouse and the leaner mouse, 2 naturally occurring mutants.[67,68] The tottering mouse is characterized by mild ataxia, absence-type seizures, and motor seizures.[68] The leaner mouse exhibits more severe ataxia as well as absence seizures but no motor seizures.[67] In addition to the CACNA1A subunit, other normally functioning subunits (α_2, β, δ, and γ) are required for normal function of the P/Q-type neuronal calcium channel. A mutation in the beta$_4$ subunit gene has been found to cause the syndrome manifested in the lethargic mouse, a naturally occurring mutant characterized by ataxia, lethargic behavior, absence-type seizures, and motor seizures.[69] A mutation in a gamma-subunit gene has been linked to the syndrome exhibited by the stargazer mouse, a spontaneously occurring mutant displaying spike-wave seizures characteristic of absence seizures in epilepsy.[70] Taken together, these observations extend the spectrum of clinical diseases associated with mutations in the CACNA1A subunit gene.

Figure 4

Mutations in the CACNA1A Gene



Adapted with permission from Ferrari MD, Haan J. Genetics of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain.* 7th ed. New York: Oxford University Press;2001:75.

This research also has paved the way for further investigations into the role of genetic mutations in the more common forms of migraine. Although the body of evidence continues to evolve, some work has suggested that the CACNA1A subunit gene is involved in migraine either with or without aura, but a stronger association is seen in migraine with aura.[71] Other studies in the tottering mouse have identified an increase in the spontaneous release of acetylcholine with increased rundown of high-rate evoked release at the neuromuscular junction.[72] If the same findings can be confirmed in humans, one would expect to identify changes at the neuromuscular junction in migraine patients. This would demonstrate, for the first time, that objective abnormalities exist in migraine at an easily accessible site.

Mechanisms of Action of Acute and Preventive Therapies

Advances in knowledge of the pathophysiology of migraine have allowed the development of more targeted strategies for acute and preventive treatment. In turn, responses to these therapies have enhanced understanding of the disorder.

The pain of primary headache arises from the dura mater and large blood vessels, with the brain remaining largely insensate.[73,74] The first, ophthalmic division of the trigeminal nerve innervates the pain-producing intracranial structures. A large proportion of the dural innervation sweeps back and gathers together in the middle cranial fossa to form the tentorial nerves. The tentorial nerves join the ophthalmic division shortly before entering the trigeminal ganglion. Intracranial structures below the tentorium cerebelli are innervated by branches of the C2 nerve root. Activation of these structures leads to cranial vasodilation and, in animal models, to a sterile neurogenic inflammation. Supratentorial and infratentorial pain projections synapse on the trigeminocervical complex—a functional group of second-order neurons in the trigeminal nucleus caudalis and the superficial dorsal horns of C1 and C2. This configuration of innervation accounts for the well-recognized patterns of pain referral in the head.[74,75]

Treatment of the acute migraine attack is largely based on interrupting trigeminal pain mechanisms through effects on 5-HT receptors. These actions are aimed at producing vasoconstriction (mediated by 5-HT_{1D} receptors), peripheral neuronal inhibition (likely mediated by either 5-HT_{1D} or 5-HT_{1F} receptors), or central inhibition of the trigeminal nucleus (probably mediated by a combination of 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors). The currently available ergot derivatives (ergotamine and dihydroergotamine [DHE]) and triptans (sumatriptan, naratriptan, rizatriptan, and zolmitriptan) are 5-$HT_{1B/1D}$ agonists. These agents constrict the large cranial vessels through an action at the 5-$HT_{1B/1D}$ receptor and inhibit the peripheral branches of the trigeminal nerve and its central terminations in the trigeminal nucleus caudalis. The ergot derivatives and triptans are highly effective for aborting acute migraine attacks in many patients, but not all individuals respond. Another limitation is the fact that 5-HT_{1B} receptors are expressed in human coronary arteries, prohibiting the use of these vasoconstricting agents by patients with cardiovascular disease.[74,75]

Although the mechanisms of action of preventive treatments have not been fully characterized, the currently available therapies appear to reduce the excitability of trigeminocervical neurons by regulating central modulatory systems. PET scans have clearly shown that the upper brainstem activation observed during migraine is specific to this disorder and is not seen in other forms of primary headache.[57] Patients with migraine undoubtedly have abnormal sensory processing that could explain symptoms such as photophobia and phonophobia. Brainstem aminergic dysfunction could, in fact, account for much of the syndrome.

As preventive treatments, antidepressants work by modifying aminergic dysfunction. Other agents exert stabilizing effects on calcium channels. This latter mechanism is of particular interest in light of the fact that both FHM and, perhaps, ordinary migraine map to chromosome 19. In 50% of families, FHM is characterized by missense mutations in the $alpha_{1A}$ subunit of the P/Q voltage-gated calcium channel. Calcium channel stabilization may contribute to the efficacy of certain anticonvulsants in the prevention of migraine.

The prospects for future advances in migraine prevention will depend on a better understanding of brainstem mechanisms of pain and the ways in which these processes can be modulated through effects on aminergic uptake systems, 5-HT_2 receptors, and ion channel stabilization.

Diagnosis/Diagnostic Testing in Migraine

Headache Classification/ IHS Criteria

The classification of primary and secondary headache disorders is based on the system developed by the IHS in 1988.[76] Primary headache disorders include migraine, tension-type headache, cluster headache, chronic paroxysmal hemicrania, and miscellaneous headaches unassociated with structural lesions. Secondary headaches include those associated with head trauma, vascular disorders, nonvascular intracranial disorders, substances or their withdrawal, noncephalic infection, metabolic disorders, disorders of cranial or facial structures, or cranial neuralgias, as well as those that cannot be classified. As shown in Table 4, the major forms of migraine are classified on the basis of the absence or presence of aura.

No subforms are designated for migraine without aura (previously referred to as common migraine). Migraine with aura (formerly known as classic migraine) is subclassified according to the characteristics of the aura or headache.[76]

The value of this hierarchical approach is that varying degrees of diagnostic precision can be brought to bear in different settings (eg, general practice, specialist practice, headache center, or research activity). Unambiguous diagnostic criteria are provided for all headache disorders. Because the categories of migraine are not mutually exclusive, a given patient may be classified under more than 1 category to receive a comprehensive diagnosis. The use of multiple diagnoses allows each type of headache to be treated as an individual entity.

Population-based studies have demonstrated that nearly all patients with headache can be classified using the IHS criteria.[77] The system has been found to be valid and reliable, with relatively low interobserver variability. In view of the success of this classification scheme, the second edition (currently in preparation) is not expected to contain major changes in the diagnostic criteria for the various types of migraine. However, the utility of the system will be enhanced by refinements in the classification of secondary headaches and the inclusion of additional subforms (such as those associated with metabolic and systemic disorders).

Diagnostic Testing

Apart from the quest for diagnostic certainty, a number of other reasons often underlie physicians' decisions to pursue extensive testing for migraine. In busy practice settings, for example, tests may be used as a shortcut, because time constraints do not permit a thorough review of the patient's history—even though this should be the most important part of the headache evaluation. Peer pressure may prompt a specialist to order both routine and more esoteric tests in an attempt to demonstrate professional competence to a referring colleague. Defensive medicine can come into play as physicians are forced to cope with an increasingly litigious society. The extent of testing is also influenced by variations in the financial incentives and disincentives that exist in different healthcare systems and practice environments. Furthermore, the attitudes and demands of patients (usually resulting from fear), their families, and their friends affect the decision to perform diagnostic tests. The concept of evidence-based medicine can minimize the impact of these factors and promote the appropriate use of diagnostic testing.

Based on a review of the evidence, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) has advised that electroencephalography (EEG) is not useful for routine evaluation of patients with headache.[78] The most consistent EEG abnormality in migraineurs is a prominent photic driving at high flash frequencies (the so-called H-response). In this setting, the EEG has a sensitivity in the range of 26% to 100% and a specificity of 80% to 91%. Although these sensitivities and specificities might suggest that the H-response would be useful for identifying migraine, it is no more effective or efficient than the neurologic history and neurologic examination, according to the AAN.[78] The AAN recommendations do not preclude the use of EEG for the evaluation of patients who have headache with altered mental status or associated symptoms suggesting a seizure disorder (such as atypical migrainous aura or episodic loss of consciousness). Nonetheless, the EEG should not be used to explore a structural basis of headache if neuroimaging facilities are readily available.

The [AAN] has advised that [EEG] is not useful for routine evaluation of patients with headache.

Guidelines issued by the AAN and the US Headache Consortium stipulate that neuroimaging is not usually warranted for patients with migraine who have normal

Table 4

International Headache Society Migraine Classification

1 Migraine
- 1.1 Migraine without aura
- 1.2 Migraine with aura
  - 1.2.1 Migraine with typical aura
  - 1.2.2 Migraine with prolonged aura
  - 1.2.3 Familial hemiplegic migraine
  - 1.2.4 Basilar migraine
  - 1.2.5 Migraine aura without headache
  - 1.2.6 Migraine with acute-onset aura
- 1.3 Ophthalmoplegic migraine
- 1.4 Retinal migraine
- 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
  - 1.5.1 Benign paroxysmal vertigo of childhood
  - 1.5.2 Alternating hemiplegia of childhood
- 1.6 Complications of migraine
  - 1.6.1 Status migrainosus
  - 1.6.2 Migrainous infarction
- 1.7 Migrainous disorder not fulfilling above criteria

Reprinted with permission from Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia.* 1988;8(suppl 7):13.

neurologic examinations and no recent change in headache pattern. However, imaging may be indicated in other situations, such as features of atypical headache, focal neurologic symptoms and/or signs, or a history of seizures. Table 5 lists some reasons for performing neuroimaging studies in migraineurs.

Magnetic resonance imaging (MRI) and computed tomography (CT) findings are for the most part normal in patients with migraine. White-matter abnormalities (WMAs) are the most common abnormal finding on neuroimaging in patients with migraine. These abnormalities are foci of hyperintensity on both proton density and T2-weighted images in the deep and periventricular white matter caused by either interstitial edema or perivascular demyelination. In 16 studies conducted from 1976 to 1991, only 5 intracranial abnormalities were identified among 1625 MRIs or CT scans from migraineurs; 4 of the abnormalities were brain tumors, and 1 was an AVM in an individual who had both migraine and seizures.[79] In other MRI studies, WMAs were identified in 12% to 46% of patients with any type of migraine as opposed to only 2% to 14% of controls.[78,79] Of 6 investigations comparing the prevalence of WMAs in migraine with and without aura, 4 studies noted a similar occurrence in both groups, and 2 studies reported a higher occurrence in the presence of aura.[79] Additional work has shown that older age (>50 years) and medical risk factors (such as hypertension, ischemic heart disease, or diabetes) are associated with an increased prevalence of WMAs among individuals with migraine.[80]

Although the cause of WMAs in migraine remains uncertain, researchers have hypothesized that these abnormalities may be related to increased platelet aggregability with microemboli, abnormal cerebrovascular regulation, or repeated attacks of hypoperfusion during the aura.[79] It also has been suggested that repeated episodes of spreading depression may lead to WMAs. A number of potential etiologies have been proposed, as listed in Table 6. The role of antiphospholipid (aPL) antibodies is a matter of controversy, as the reported prevalence in migraine has ranged from 0% to 42%.[81] In individuals less than 60 years of age, aPL antibodies are not associated with either migraine or transient focal neurologic events.[81] Furthermore, the presence of aPL antibodies is not an additional risk factor for stroke in migraineurs.[82] Also of interest is the prevalence of WMAs in patients with collagen-vascular disease. For example, an MRI study identified multiple, small punctate areas of increased signal of periventricular or subcortical white matter in 13 of 24 patients with central nervous system (CNS) lupus and in 10 of 20 patients with lupus but no CNS involvement.[83] Patients with multiple sclerosis (MS) commonly have WMAs as well, and some comorbidity is apparent between MS and migraine. A prospective study found a statistically significant (P<.05) increase in headache (tension and vascular) frequency in MS patients over the rate in controls. Of interest, however, is that the frequency of headache in the control group was lower than that found in some other surveys.[84] Certain features of WMAs are more typical of MS than of migraine. In MS, WMAs tend to have a primarily periventricular rather than peripheral distribution; to be oval rather than round or punctate; to be "fuzzy" or irregular rather than sharply defined at the margins; and to be oriented perpendicular to the ventricles as though

Table 5

Examples of Reasons to Perform Neuroimaging Studies in Headache Sufferers

Neuroimaging may be important for headache patients who have

- Abnormal unexplained neurological exam
- Rapidly increasing frequency and/or severity of headaches
- Change in headache clinical features
- First or "worst" headache ever experienced
- Headache with extremely abrupt onset
- New-onset headache after age 50
- Headache refractory to aggressive treatment
- Dizziness, numbness, or tingling

Frishberg B, et al. Evidence-based guidelines in the primary care setting: neuroimaging in patients with acute headache. Available at: http://www.aan.com. 2000: Accessed 11/14/01.

Evans RW, et al. Neuroimaging and other diagnostic testing in headache. In: Silberstein SD, Lipton RB, Dalessio DJ, editors. *Wolff's Headache and Other Pain.* 7th ed. New York, NY: Oxford University Press; 2001. p. 27-49.

Table 6

Potential Etiologies of WMAs in Migraine

- Incidental
- Related to migraine
- aPL antibodies
- Vasculitis (systemic lupus erythematosus, Sjögren's syndrome, etc)
- MS
- Stroke risk factors (hypertension, diabetes, hyperlipidemia, coagulopathies, etc)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes
- Infections (Lyme disease, human immunodeficiency virus, human T-cell lymphotropic virus-1)

Evans RW, et al. Neuroimaging and other diagnostic testing in headache. In: Silberstein SD, Lipton RB, Dalessio DJ, editors. *Wolff's Headache and Other Pain.* 7th ed. New York, NY: Oxford University Press; 2001. p. 27-49.

Cooney BS, et al. Frequency of magnetic resonance imaging abnormalities in patients with migraine. *Headache.* 1996;36(10):616-621.

radiating away from them. Corpus callosum or infratentorial lesions are more likely to be due to MS, as are lesions greater than 6 mm in diameter. Some patients with migraine may be misdiagnosed as having MS if the physician is not aware of the differences in WMA characteristics associated with the 2 disorders.

Occasionally, AVMs also may be confused with migraine. In up to 50% of cases, AVMs present with symptoms or signs other than hemorrhage. Migrainelike headaches (with or without visual symptoms) may occur, especially when the AVM is located in the occipital lobe (which is the predominant location for 20% of parenchymal AVMs). An important consideration in the differential diagnosis is that the pain always occurs on the same side in 95% of patients with AVM who have headache.[85] In contrast, headache consistently occurs on the same side in only 17% of patients who have migraine without aura and 15% of those who have migraine with aura. Other features more suggestive of a secondary headache due to AVM, as opposed to migraine, include unusual associated signs (such as papilledema, field cut, or bruit); short duration of headache attacks; brief scintillating scotoma; lack of a family history of migraine; atypical sequence of aura, headache, and vomiting; and seizures.[85] The diagnosis of late-life migraine may require testing to exclude the numerous causes of transient ischemic attacks (TIAs). Certain clinical features are more likely to be associated with late-life migraine than with TIAs (Table 7).[86]

For patients with migraine who present with the first or worst headache, lumbar puncture may be indicated to exclude subarachnoid hemorrhage and, in some individuals with focal neurologic episodes, to exclude other disorders such as meningitis or MS. The cerebrospinal fluid is usually normal in migraine, but protein levels may be elevated because of an altered blood-brain barrier.

Table 7

Clinical Features of Late-Life Migraine Versus TIAs

- Gradual appearance of focal neurologic symptoms with spread or worsening over a period of minutes
- Headache present in 50% of cases
- Positive visual symptoms, such as scintillating scotoma or flashing or bright lights
- Serial progression from one accompaniment to another (for example, from flashing lights to paresthesias, paresis, or dysphasia)
- Diagnosis facilitated with the occurrence of ≥2 identical episodes
- Duration of 15-25 minutes (as opposed to <15 minutes in 90% of headaches associated with TIA)
- Characteristic "flurry" of accompaniments
- Usually benign natural history without permanent sequelae
- No other cause revealed by diagnostic testing performed when indicated

Fisher CM. Late-life migraine accompaniments-further experience. *Stroke.* 986;17(5): 1033-1042.

Treatment of Migraine

The frequency and severity of migraine, as well as its impact on quality of life, vary widely among individuals. The successful treatment of migraine requires that the physician and patient work together to identify specific short- and long-term goals.

The US Headache Consortium has developed the most comprehensive, evidence-based guidelines for the management of migraine.[87-90] These recommendations reflect a multidisciplinary effort involving representatives from the American Academy of Family Physicians, American Academy of Neurology, American College of Emergency Physicians, American College of Physicians–American Society of Internal Medicine, American Headache Society, American Osteopathic Association, and National Headache Foundation.

According to the consortium, the goals of acute therapy are to treat attacks "rapidly and consistently without recurrence; restore the patient's ability to function; minimize the use of back-up and rescue medications; optimize self-care and reduce subsequent use of resources; be cost-effective for overall management; and have minimal or no adverse events."[89] The goals of preventive therapy are to reduce the frequency, severity, and duration of migraine attacks; improve responsiveness to the treatment of acute attacks; improve function; reduce disability; educate patients to enable them to manage their disease; and reduce headache-related distress and psychological symptoms.[90]

Acute Treatment

Guidelines

The US Headache Consortium guidelines weigh the quality of evidence regarding the efficacy and safety of various agents for the acute treatment of migraine.[89] The strength of recommendations regarding the use of specific agents is based on this grading of the evidence. Grade A pertains to recommendations based on multiple well-designed, randomized clinical trials that are directly relevant and have yielded a consistent pattern of findings. Grade B refers to recommendations for which some evidence is available from randomized clinical trials, but the scientific support for the recommendation is not optimal. Grade C reflects a consensus of the consortium on a recommendation in the absence of relevant randomized, controlled trials.[89]

As a general grade C recommendation, the consortium advises that migraine-specific agents (ie, triptans and

ergot derivatives) should be used for patients with more severe migraine. These agents should also be used for patients whose headaches respond poorly to NSAIDs or combination analgesics (such as aspirin/acetaminophen/caffeine). Recommendations regarding specific agents with the level of evidence indicated are summarized below. Table 8 places specific medications into groups based on a combination of scientific evidence and clinical opinion.

Antiemetics[89]

The consortium recommends that antiemetics may be used as adjunctive therapy for the treatment of nausea associated with migraine (grade C). Studies of specific agents, such as prochlorperazine, have suggested some clinical benefit, but the data are limited. No studies have examined antiemetics as monotherapy for acute migraine attacks.

Intravenous (IV) metoclopramide may be considered as adjunctive therapy for migraine pain or nausea in the appropriate setting (grade C). In addition, IV metoclopramide may be considered as monotherapy for the relief of migraine pain (grade B). Two of 3 studies have found IV metoclopramide to be effective as acute migraine treatment.

Parenteral or rectal prochlorperazine may be used to treat migraine in an appropriate setting (grade B). The latter formulation may also be used as adjunctive therapy for acute migraine with nausea and vomiting. One study each of intramuscular (IM), IV, and rectal prochlorperazine found these agents to be relatively safe and effective for treating migraine and associated nausea and vomiting.

Barbiturate Hypnotics[89]

The use of butalbital-containing analgesics should be limited and carefully monitored (grade B). These agents have been associated with concerns regarding overuse, overuse-related headache, and withdrawal. No randomized, placebo-controlled studies have

Table 8

US Headache Consortium Rankings of Acute Migraine Therapies[92]

Group 1: **Proven pronounced statistical and clinical benefit** *(≥2 double-blind, placebo-controlled studies + clinical impression of effect)*	**Group 2:** **Moderate statistical and clinical benefit** *(1 double-blind, placebo-controlled study + clinical impression of effect)*	**Group 3:** **Statistical but not clinically proven OR clinical but not statistically proven effective** *(conflicting or inconsistent evidence)*	**Group 4:** **Proven to be statistically or clinically ineffective** *(failed efficacy vs placebo)*	**Group 5:** **Clinical and statistical benefits unknown** *(insufficient evidence available)*
Acetaminophen + aspirin + caffeine PO*	Acetaminophen + codeine PO	Butalbital + aspirin, + caffeine PO	Acetaminophen PO	Dexamethasone IV
Aspirin PO	Butalbital + aspirin + caffeine + codeine PO	Ergotamine PO	Chlorpromazine IM	Hydrocortisone IV
Butorphanol IN	Butorphanol IM	Ergotamine + caffeine PO	Granisetron IV	
DHE SC, IM, IV	Chlorpromazine IM, IV	Metoclopramide IM, PR	Lidocaine IV	
DHE IV + antiemetic	Diclofenac K, PO			
DHE IN	Ergotamine + caffeine + pentobarbital + bellafoline† PO			
Ibuprofen PO	Flurbiprofen, PO			
Naproxen sodium PO	Isometheptene compound, PO			
Naratriptan PO	Ketorolac IM			
Prochlorperazine IV	Lidocaine IN			
Rizatriptan PO	Meperidine IM, IV			
Sumatriptan SC, IN, PO	Methadone IM			
Zolmitriptan PO	Metoclopramide IV			
	Naproxen			
	Prochlorperazine IM, PR			

*Studies conducted in restricted populations, which exclude migraine sufferers who usually require bedrest.
†Hyoscyamine and scopolamine
PO = oral; IN = intranasal; PR = rectal.

either proven or disproven these agents to be effective in the acute treatment of migraine.

Ergot Alkaloids and Derivatives[89]

Oral ergot derivatives may be considered for certain patients with moderate to severe migraine (grade B). The results of studies on the efficacy of ergot alkaloids have been inconsistent, and a higher incidence of adverse events has been observed than with placebo, NSAIDs, isometheptene, sumatriptan, or dextropropoxyphene compounds.

Parenteral DHE may be used for patients with nausea and vomiting who may be unable to tolerate oral medications (grade C). The consortium also noted that initial therapy with subcutaneous (SC) or IM DHE is a reasonable choice if the headache is moderate to severe or if an adequate dosage of an NSAID or other nonopiate analgesic (including combinations such as acetaminophen/aspirin/caffeine) has failed to provide adequate relief in the past. In addition, SC or IM DHE may be considered for patients with moderate to severe migraine (grade B). No placebo-controlled trials have confirmed the efficacy of parenteral DHE as monotherapy for migraine. Nonetheless, clinical opinion suggests that the SC formulation is relatively safe and effective compared with other migraine treatments and has fewer adverse effects than the IV formulation. The use of IV DHE plus antiemetics is considered appropriate for patients with severe migraine (grade B). This combination has been found to be effective and moderately safe compared with parenteral opiates in the treatment of moderate to severe migraine.

DHE nasal spray is safe and effective and should be considered for patients with moderate to severe migraine (grade A). This treatment is also appropriate for patients with nausea and vomiting because of their inability to tolerate oral medications (grade C). Initial treatment with DHE nasal spray is deemed a reasonable choice if the headache is moderate to severe or if an adequate dosage of an NSAID or other nonopiate analgesic (including combinations such as acetaminophen/aspirin/caffeine) has failed to provide adequate relief in the past (grade C).

NSAIDs, Combination Analgesics, and Nonopiate Analgesics

Oral NSAIDs are a reasonable first-line acute treatment for mild to moderate or severe migraine attacks that have responded previously (grade A). This recommendation is based on good tolerability and consistent evidence of the efficacy of aspirin, ibuprofen, naproxen sodium, and the combined formulation of acetaminophen/aspirin/caffeine. Studies of acetaminophen/aspirin/caffeine excluded more-disabled migraine sufferers and therefore do not support treatment for that group. The evidence for other NSAIDs is limited.[89]

IM ketorolac can be considered an option for the acute treatment of migraine in a physician-supervised setting (grade C). No conclusions concerning the efficacy of this agent can be reached at this time. Small comparative trials have suggested equivalence between ketorolac and some other agents.[89] In one comparative trial, ketorolac was inferior to meperidine. No placebo-controlled trials of the efficacy of ketorolac have been published.[89]

A recent study, published after the US Headache Consortium guidelines, shows that acetaminophen has efficacy in the treatment of migraine.[91] Had these data been available at the time the guidelines were written, acetaminophen would have qualified as a group 2 drug. However, prior evidence did not show that it had specific efficacy in the treatment of migraine.

Opiate Analgesics

Based on both clinical experience and expert consensus, the consortium guidelines note that butorphanol is a treatment option for some patients with migraine. This is specified as a grade A recommendation.[92] However, the guidelines also include a grade C recommendation that butorphanol may be considered when other medications cannot be used or as rescue medication when significant sedation would not place the patient at risk. Overuse and dependence issues should always be considered.[92]

Opiate combinations may be considered when sedative side effects will not place the patient at risk and when the potential for abuse has been addressed (grade A).[92] Studies have demonstrated the effectiveness of oral opiate combination agents with regard to pain relief.[89]

The consortium advises that parenteral opiates may be considered for rescue therapy for acute migraine, provided treatment takes place in a supervised setting (grade B). Sedative side effects and the risk of abuse must be discussed with the patient before treatment is initiated. Only one placebo-controlled study has been published on the use of IM methadone and IM meperidine. This study found these opiates to be effective for pain relief.[89]

Triptans

Triptans are the most extensively studied agents in the history of migraine. Despite their proven safety and effectiveness in the acute treatment of migraine, the use of triptans is often delayed for patients who are treated using a step-care approach.

In step care, triptans are considered only after many other medications have been tried and have failed. The US Headache Consortium recommends stratified care when initial treatment is individualized based on an evaluation of the patient's medical needs. A recent study by Lipton and colleagues showed that stratified care provides significantly better clinical outcomes than step-care strategies and that the approach is

cost saving, supporting the US Headache Consortium recommendations.[93]

The available triptans (sumatriptan, zolmitriptan, naratriptan, and rizatriptan) are recommended for consideration for patients with moderate to severe migraine who have no contraindications to these agents (grade A). The triptans are effective and relatively safe for acute treatment, but no evidence is available to support their use during aura.[89]

Sumatriptan was the first agent in its class to be introduced, in the early 1990s, specifically for the acute treatment of migraine.[56] It became the benchmark for the triptans that followed. In the late 1990s, zolmitriptan, naratriptan, and rizatriptan were marketed as second-generation triptans. At least 3 other triptans (eletriptan, almotriptan, and frovatriptan) are expected to be approved for use in the United States in the near future. All the triptans have the same proposed mechanisms of action, inhibiting the release of vasoactive neuropeptides and causing vasoconstriction and central neuronal inhibition within the brainstem. Compared with sumatriptan, the newer agents have a greater tendency to cross the blood-brain barrier, but other actions may counteract this effect, and the net result in humans remains unknown. For example, the brain-penetrating effect of eletriptan may be partially counteracted by its active expulsion from the brain by the P-glycoprotein pump.[94,95] The bioavailability of the newer triptans is higher than that of oral sumatriptan—a property that would be expected to result in more consistent protection from multiple migraine attacks. Some of the newer drugs also have slightly longer half-lives than sumatriptan, but it is not clear if duration of action predicts recurrence rates.

Additional head-to-head trials of oral triptans are needed to examine efficacy in terms of multiple attacks, pain-free response, and sustained response, as well as safety. More important, additional studies are needed to assess optional approaches to sequencing and combining treatment.[92] Recent evidence indicates that triptans may be more effective if given early in the attack, while pain is still mild. Studies suggest that triptans may effectively treat nonmigraine headaches in persons with migraine.

Nonoral Triptans

Though most patients with migraine prefer oral tablets,[7] nonoral treatments sometimes provide advantages. Migraine sufferers with prominent nausea or vomiting may find that oral therapies exacerbate their gastrointestinal symptoms. In addition, gastric paresis during migraine attacks may delay the absorption of oral treatments. As a consequence, triptans are sometimes given by SC injection, nasal spray, or suppository. The US Headache Consortium recommends consideration of nonoral therapy for patients with prominent nausea or vomiting.[89]

The only triptan available by SC injection, sumatriptan, provides the highest headache-response and pain-free rates of any available acute treatment. Headache-response rates are 82% at 2 hours and 70% at 1 hour.[96] Sumatriptan is also available as a nasal spray, which probably has a more rapid onset than the tablet.[97] Zolmitriptan may soon be available as a nasal spray.

Other Agents[89]

Isometheptene-containing compounds are cited as a reasonable choice for patients with mild to moderate headache, based on clinical evidence and favorable tolerability profiles (grade B). Studies have found these compounds to have a small but statistically significant advantage over placebo.

Corticosteroids (dexamethasone or hydrocortisone) may be considered for rescue therapy for patients with status migrainosus (grade C).

At present, insufficient evidence is available to define a role for either IN or IV lidocaine in the acute treatment of migraine (grade B). Limited studies have found IN lidocaine superior to placebo with respect to relieving migraine headache within 15 minutes; data on the incidence of recurrence have been mixed. Some small studies have suggested that IV lidocaine is not significantly superior to placebo and is less effective than other parenteral therapies for acute migraine.

Preventive Treatment

Guidelines

According to the US Headache Consortium guidelines, preventive therapy is indicated when migraine is exerting a substantial impact on a patient's life despite the use of acute treatments; when the frequency of attacks is so high that acute treatments would be overused, raising the risk of rebound headache; when acute therapies are contraindicated, have failed, or are associated with considerable side effects; when a patient expresses a preference for preventive therapy; or when a patient exhibits an uncommon migraine condition (such as hemiplegic migraine, migraine with prolonged aura, basilar migraine, or migrainous infarction).[90] Both pharmacologic and nonpharmacologic measures can be used for migraine prophylaxis.

If possible, preventive pharmacotherapy should be instituted using agents that have the highest level of evidence-based efficacy. Medication should be started at the lowest effective dosage, then titrated upward slowly until clinical benefits are attained in the absence of, or are limited by, adverse events. The medication should be given an adequate trial (this could take up to 2 or 3 months).[90] Many patients do not achieve responses within the first few weeks and may prematurely discontinue the medication at the first occurrence of breakthrough headache before giving

it a chance to work. To promote good adherence, physicians should educate patients about the potential for delayed response. Long-acting formulations also may improve adherence. The overuse of acute treatments should be avoided. The patient's response should be monitored with a headache diary, and therapy should be reevaluated periodically. If migraine is well controlled after a reasonable period, the physician may consider tapering or discontinuing treatment.[90]

Table 9 summarizes the quality of evidence regarding the efficacy and frequency of adverse events associated with various therapies for the prevention of migraine. Based on the available evidence, the US Headache Consortium has ranked preventive treatments in 5 groupings, as shown in Table 10, page 18. When selecting the most appropriate preventive medication for a given patient, the physician also should take into account the variety of comorbid conditions that are common in migraineurs—stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, and affective or anxiety disorders. If a comorbid condition is present, the physician should select a drug capable of treating both the comorbidity and migraine whenever feasible. Care should be taken to determine that treatments selected for migraine are not contraindicated for the comorbidity and that treatments for the comorbidity do not exacerbate migraine. The possibility of drug-drug interactions must be weighed as well. Special care should be taken in choosing therapies for women who wish to conceive or who are pregnant.[90]

Older Drugs

With the exception of methysergide, none of the older drugs currently used for the prevention of migraine were originally marketed for this purpose. Rather, these therapies entered the clinical armamentarium because of chance observations that prompted subsequent studies or because of actions that appeared promising based on evolving knowledge of the pathophysiology of migraine. Older agents may be effective and well tolerated in the setting of migraine prevention, although none of these drugs is effective for all patients.

Methysergide

Four placebo-controlled trials suggested that methysergide was significantly better than placebo at reducing headache frequency. Because of its side-effect profile, however, methysergide should be used only in severe cases when other migraine-preventive drugs are not effective.[98] Of particular concern is the fact that the continuous use of methysergide for several months increases the risk of retroperitoneal and retropleural fibrosis.[98]

Antidepressants

Antidepressants came into use for the treatment of migraine after research in the early 1960s revealed a high prevalence of headache in patients with depression. These headaches (migraine as well as tension headache) were found to respond to antidepressant agents. This clinical experience led to the broad use of these drugs in the setting of migraine, despite the lack of rigorous clinical trials.

Of the TCAs available in the United States, only amitriptyline and clomipramine have been widely studied for the prevention of migraine. The efficacy of amitriptyline is comparable to that of propranolol, whereas clomipramine has not proven to be effective.[90] Because adverse effects are a limiting factor in the use of amitriptyline, attention has turned toward other agents in this class, such as doxepin, imipramine, desipramine, nortriptyline, and protriptyline.

Table 9

US Headache Consortium Assessment of Migraine-Preventive Therapies

Drug	Quality of Evidence*	Scientific Effect†	Clinical Impression‡	Adverse Effects
Antiepileptics				
Divalproex	A	+++	+++	Occasional to frequent
Gabapentin	B	++	++	Occasional to frequent
Topiramate	C	?	++	Occasional
Antidepressants				
Amitriptyline	A	+++	+++	Frequent
Fluoxetine	B	+	+	Occasional
Beta blockers				
Atenolol	B	++	++	Infrequent
Calcium channel blockers				
Diltiazem	C	?	0	Occasional
Verapamil	B	+	+	Occasional
NSAIDs				
Aspirin	B	+	+	Infrequent
Ibuprofen	C	?	+	Infrequent
5-HT antagonists				
Methysergide	A	+++	+++	Frequent

*A = multiple well-designed, randomized clinical trials; directly relevant, consistent pattern of findings; B = some evidence from randomized clinical trials, supported; scientific support not optimal; C = consortium consensus in absence of relevant randomized, controlled trials.

†+++ = statistically significant/far exceeds minimal clinically significant benefit; ++ = statistically significant/exceeds minimal clinically significant benefit; + = not statistically/clinically significant; ? = unknown benefit.

‡+++ = very effective (most patients); ++ = effective (some patients); + = somewhat effective (few patients); 0 = ineffective.

Adapted with permission from Ramadan NM, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2001:56. Available at: http://www.aan.com. Accessed July 24, 2001.

Table 10

US Headache Consortium Rankings of Migraine-Preventive Therapies

- Group 1: medium to high efficacy; good strength of evidence; mild to moderate side effects
  - Amitriptyline
  - Divalproex sodium
  - Propranolol
  - Timolol
- Group 2: lower efficacy than group 1 or limited strength of evidence; mild to moderate adverse events
  - Beta blockers (atenolol, metoprolol, nadolol)
  - Calcium channel blockers (nimodipine, verapamil)
  - NSAIDs (aspirin, fenoprofen, flurbiprofen, ketoprofen, mefenamic acid, naproxen, naproxen sodium)
  - Others (fluoxetine {racemic}, gabapentin, feverfew, magnesium, vitamin B_2)
- Group 3: Clinically efficacious (consensus and clinical experience); no scientific evidence of efficacy
  - Antidepressants (doxepin, fluvoxamine, imipramine, mirtazapine, nortriptyline, paroxetine, protriptyline, sertraline, trazodone, venlafaxine)
  - Others (cyproheptadine, diltiazem, ibuprofen, tiagabine, topiramate)
  - Side-effect concerns (methylergonovine, phenelzine)
- Group 4: medium to high efficacy; good strength of evidence; side-effect concerns
  - Methysergide
- Group 5: evidence indicating no efficacy over placebo
  - Acebutolol
  - Carbamazepine
  - Clomipramine
  - Clonazepam
  - Indomethacin
  - Nicardipine
  - Nifedipine
  - Pindolol

Adapted with permission from Ramadan NM, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2001:56. Available at: http://www.aan.com. Accessed July 24, 2001.

The latter drugs have not been well studied in migraine prevention, although experience in clinical practice would suggest that they may be effective. In general, the advantages of TCAs include their efficacy in migraine as well as in tension headache and their potential to act as a single treatment for both migraine and comorbid depression[90]. The doses required to treat migraine are typically lower than those used to treat depression, which may help improve tolerability. Nonetheless, the anticholinergic, antihistaminic, and alpha-adrenergic effects of the agents may be a concern. The side-effect profiles of the various TCAs vary greatly depending on their individual actions at various neurotransmitter receptor sites. Thorough familiarity with the clinical pharmacology of these agents is needed to maximize their efficacy and safety.

The selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, paroxetine, and sertraline, are used broadly in the treatment of migraine despite a lack of clinical investigations or only limited success in trials. Other antidepressants, including bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine, may be administered to patients with resistant headaches. The widespread use of selective serotonin reuptake inhibitors and other antidepressants in migraine management may stem from their positive adverse-effect profiles, their efficacy in treating comorbid psychiatric conditions, and a perception among primary care physicians that stress plays a major role in migraine. Nevertheless, there is little or no evidence that selective serotonin reuptake inhibitors are effective in migraine prophylaxis in placebo-controlled trials.[90]

Beta Blockers

Beta blockers have been used for several decades as preventive medications for migraine. The US Headache Consortium has divided beta blockers into first-tier therapies (propranolol and timolol) and second-tier therapies (atenolol, metoprolol, and nadolol).[90] The key to the effectiveness of these particular drugs is a lack of the partial agonist activity associated with other beta blockers. Consistent efficacy has been demonstrated in extensive trials in migraine prophylaxis.[90] These agents are also effective for patients with comorbid cardiovascular disease or anxiety disorders. Disadvantages include adverse effects such as fatigue, depression, sleep disturbances, nausea, dizziness, reduced exercise tolerance, and relative contraindications for use by patients with comorbid depression, diabetes mellitus, or asthma. Case reports have implicated beta blockers in the development of migrainous infarction (propranolol) or increasing visual symptoms (atenolol, metoprolol) in patients with migraine with aura.[99-101]

Calcium Channel Blockers

The adverse effects of beta blockers contributed to an intense interest in calcium channel blockers for the treatment of migraine, beginning in the early 1980s with verapamil and continuing with the introduction of other drugs in this class. Although no clear data are available, clinical impressions suggest that at least some patients who have migraine with aura respond better to calcium channel blockers than to beta blockers. Calcium antagonists may be used by some patients with coincident cardiovascular disease and offer an alternative to beta blockers for patients with depression, asthma, or diabetes. Unfortunately,

trials to date indicate that calcium channel blockers are less effective than beta blockers or TCAs (with the exception of flunarizine, the most effective calcium antagonist for migraine, which is not available in the United States).[90] Moreover, verapamil can cause significant constipation. Flunarizine may be associated with weight gain and somnolence and may give rise to extrapyramidal and depressive symptoms.[47] Nifedipine has not demonstrated efficacy in the migraine population,[90] and headache is a commonly reported side effect of nifedipine. The cost of nimodipine may be prohibitive in the United States.[47]

NSAIDs

Like the ergot derivatives, NSAIDs have been used for both acute and preventive treatment of migraine. Many of these agents appear to offer efficacy similar to that of beta blockers in the latter setting.[90] The NSAIDs may be particularly useful as interval therapy in menstrual migraine, and these agents may be considered for patients with coexisting arthritic disorders. The widespread use of NSAIDs has been limited by gastrointestinal side effects as well as concerns regarding the potential for renal or hepatic dysfunction with long-term therapy. Newer NSAIDs and related agents may offer additional treatment options in the future.

Anticonvulsants

In recent years, the concept of migraine due to CNS hyperexcitability has gained more credence. Accordingly, the following section will examine in greater detail emerging data regarding anticonvulsants.

Divalproex Sodium

Divalproex sodium was initially introduced as an antiepileptic medication but subsequently received US Food and Drug Administration (FDA) approval for migraine prophylaxis and for the treatment of mania. Divalproex dissociates to the valproate ion in the gastrointestinal tract. Valproate may elevate brain γ-aminobutyric acid (GABA) levels by modulating GABA synthesis or degradation.[102]

Four large-scale trials documented the efficacy of divalproex for the prevention of episodic migraine, noting that 43% to 50% of patients achieved more than a 50% reduction in headache frequency.[103-106] Similar findings emerged from studies of divalproex in patients with severe migraine.[107] Response to the agent cannot be predicted by the presence or absence of aura; some case reports have suggested that response might be predicted by EEG abnormalities, but this possibility has not been confirmed. Divalproex is effective at dosages of 500 to 1000 mg/day, with no clear dose-response relationship, although patients who attain only a partial response at a lower dosage may have an improved response to a higher dosage.[108] Because of the increased incidence of adverse events at higher dosages, a reasonable approach is to start with the lowest dosage and follow the patient for 4 to 6 weeks, at which point response or lack of response should be evident. Patients who fail to respond, at least partially, within this time frame rarely improve with continued treatment (even if the dosage is increased). In responders, the optimal duration of stabilization therapy required to achieve a long-term carryover effect after discontinuation of treatment is unknown.[109]

Recent data indicate that many patients who receive divalproex for migraine prophylaxis continue to do well.[102] However, many will experience at least one treatment-emergent adverse event. The most common side effect reported during the early weeks of a long-term, open-label study that evaluated the safety of divalproex in migraine prophylaxis was nausea (39%), but the incidence decreased significantly as therapy was continued.[102] Approximately 20% of patients will discontinue treatment at some point because of tolerability issues. The most frequent reasons for stopping the drug were alopecia (8%), tremor (2%), weight gain (2%), and nausea (1%). Although clinicians are often concerned about the potential for hepatotoxicity with divalproex, this complication rarely occurs when the drug is used as monotherapy for migraine prevention.[102] Of note, however, is that adverse endocrinologic effects were reported in a long-term study of valproic acid in epilepsy.[110] A total of 64% of women had polycystic ovaries, hyperandrogenism, or both after a mean of 7 years of treatment with the agent.[110] Valproic acid (or sodium valproate) is a known teratogen. Its use during pregnancy should be discouraged, as the absolute risk of neural tube defects and other abnormalities is increased.[111]

Gabapentin

Gabapentin is an anticonvulsant that is approved as adjunctive therapy for partial seizures with or without secondary generalization in adults with epilepsy. Gabapentin is not currently FDA approved for the treatment of migraine.

Although its mechanism of action is not understood completely, gabapentin is known to interact with the alpha2δ subunit of the calcium channel and to increase the concentration and probably the synthesis of GABA in the brain. It also inhibits the release of monoamine neurotransmitters (including norepinephrine, dopamine, and 5-HT) and affects total cellular calcium content.[112]

Gabapentin was evaluated as migraine prophylaxis in a multicenter, double-blind, placebo-controlled trial. After screening and a 4-week placebo run-in phase, 145 patients were randomized to receive gabapentin or placebo. During the 4-week dose-titration phase, the gabapentin dosage was gradually increased to either 1800 or 2400 mg/day. Patients remained at these dosages throughout an 8-week stabilization period. A modified intent-to-treat analysis showed that during the last 4 weeks of the stabilization period,

46% of patients in the gabapentin group versus 16% of patients receiving placebo experienced at least a 50% reduction in migraine rate (*P*=0.008). The most common adverse events reported in this study were dizziness (25%), somnolence (24%), and asthenia (22%). A total of 13 (of 98) patients in the gabapentin group and 3 (of 45) in the placebo group discontinued the trial because of adverse events. One patient in each group withdrew because of treatment failure.[113]

Based on limited evidence, gabapentin appears to be effective in the treatment of migraine. It is fairly well tolerated except for moderate somnolence and dizziness.

Topiramate

Topiramate is a broad-spectrum anticonvulsant approved as adjunctive therapy for partial or primary generalized tonic-clonic seizures in adults and children more than 2 years of age with epilepsy and for seizures associated with Lennox-Gastaut Syndrome in adults and children more than 2 years of age. Topiramate is not currently FDA approved for the treatment of migraine. Topiramate has multiple mechanisms of action that may counteract CNS hyperexcitability and thereby play a potential role in the prevention of headache. Topiramate blocks voltage-activated sodium channels, enhances the action of the inhibitory neurotransmitter GABA, inhibits the excitatory neurotransmitter glutamate, partially blocks voltage-sensitive calcium channels, and inhibits some isozymes of carbonic anhydrase.[114]

Topiramate was evaluated in 2 randomized, double-blind, placebo-controlled, parallel-group studies with patients who suffered from episodic migraine.[115,116] Both trials enrolled men and women between 18 and 65 years of age who had migraine with or without aura (IHS criteria). Topiramate was started at 25 mg/day and slowly titrated up to a maximum dosage of 100 mg BID.

In the first study, involving 30 patients, 47% of patients in the topiramate group achieved at least a 50% reduction in migraine frequency compared with 7% in the placebo group (*P*=0.035). The most frequently reported adverse events in the topiramate group were paresthesias (60%), diarrhea (27%), altered taste (20%), and somnolence (20%). Dry mouth and memory impairment occurred in 13% of both the topiramate and placebo groups. Patients also experienced a mean weight reduction of 6.2%. Four patients in the topiramate group withdrew from the study because of adverse events.[115]

Forty patients participated in the second study. The proportion of patients achieving at least a 50% reduction in headache frequency was 26% in the topiramate group and 10% in the placebo group (*P*=0.226). Side effects were generally mild and included paresthesias (68%), altered taste (37%), anorexia (21%), memory impairment (21%), emotional lability (16%), dysarthria (16%), urinary frequency (16%), and abnormal vision (16%). Weight loss was observed in 53% of patients taking topiramate (n=10). Patients lost an average of 4.9 pounds. Two patients in the topiramate group withdrew from the study because of adverse events.[116]

The results of these investigations suggest a potential role for topiramate in the treatment of migraine. Topiramate is currently being evaluated in multicenter, controlled trials.

Other Drugs

Cyproheptadine (a 5-HT and histamine antagonist) is often used for children with migraine, but it is not well tolerated by adults because of adverse effects such as weight gain and sedation.

Behavioral Treatments

Patients with headache disorders are increasingly turning to behavioral treatments as adjuncts to or substitutes for pharmacotherapy. It is therefore incumbent on physicians to become familiar with the empirical data on these therapies so that they can counsel patients concerning the potential efficacy and safety.

Relaxation therapy involves a systematic training procedure to reduce sympathetic outflow and muscle activity. Biofeedback training supplements this approach with electronic monitoring of physiologic responses. The information is then presented to the patient, who uses the “feedback” as a means of learning to regulate the response. Electromyographic biofeedback is most commonly used for tension-type headache, whereas thermal (“hand-warming”) biofeedback is typically used for migraine.

A primary goal of behavioral therapy is to enable patients to identify and manage factors that increase vulnerability to, trigger, or maintain headaches. Other objectives are to help patients manage pain, distress, and disability when headaches occur and to manage the psychological consequences of headaches (for instance, depression or feelings of helplessness). Treatment consists of 3 phases: (1) education to familiarize the patient with a biopsychosocial model of headache; (2) skills training to help the patient learn cognitive and behavioral headache management techniques; and (3) application of these skills in progressively more challenging situations.

In a meta-analysis, the Agency for Health Care Policy and Research identified a 30% to 50% improvement in headaches with the use of cognitive-behavioral therapy, biofeedback, biofeedback plus relaxation training, or relaxation training alone.[117] Another meta-analysis of 35 trials of biofeedback/relaxation training and 25 trials of propranolol showed equivalent prophylactic efficacy with the 2 treatment approaches for patients with migraine.[118]

Responses to behavioral interventions are likely to be poor in cases involving chronic migraine (CM; nearly continuous and often severe headaches), excessive use of analgesics or ergotamine, or

comorbid psychiatric disorders, as well as in older adults. More research is needed to explore the efficacy of behavioral interventions in moderately severe migraine and frequently disabling migraine.

Chronic Migraine

Members of the IHS recently proposed a new classification system for CM that will allow scientific validation. "Chronic daily headache" (CDH) comprises several primary headache disorders: CM, chronic tension-type headache, new daily persistent headache, and hemicrania continua. Each of these disorders may occur with or without overuse of medication.[119]

Epidemiology, Clinical Features, and Pathogenesis

On the basis of various studies, CDH is defined as a headache that occurs 15 or more days per month for 4 or more hours each day. Estimates indicate that CDH affects 4% to 5% of the general population and up to 80% of patients seen at headache clinics. Using the proposed revised IHS criteria, patients with CM (formerly called transformed migraine) constitute approximately 77% of the patient population with CDH.[119] Individuals with CM typically have histories of intermittent migraine beginning during adolescence or in their 20s and progressing to a more chronic pattern (daily or almost-daily headache). CM is characterized by mild to moderate daily or almost-daily pain in the head, neck, or face with reduction or absence of other migraine symptoms such as photophobia, phonophobia, and nausea. Superimposed acute migraine attacks are frequently observed as well.[119] Common findings include a family history of headache medication overuse (in approximately 80% of cases), neuropsychiatric comorbidities (such as depression, anxiety, or panic disorder), irritable bowel syndrome, and, possibly, fibromyalgia. The overuse of medications may give rise to secondary illnesses such as gastritis or renal insufficiency (associated with NSAIDs) or fibrotic disease (associated with ergot derivatives).

Although the clinical syndrome of CM has been well described, pathophysiologic factors remain under investigation. Several mechanistic possibilities have been suggested, including receptor effects resulting from medication overuse, genetic alterations of central brain and pain-modulating systems, deficiencies or excesses of important neurotransmitter systems, and assaults on the nervous system (such as those related to emotional stress or physiologic and pathologic trauma).[119]

Diagnosis

There are no known studies available to confirm a diagnosis of CM. Nonetheless, it is important to conduct appropriate evaluations to exclude organic causes of headache (for example, intracranial, cervical, dental, infectious, metabolic, endocrinologic, toxic, and CSF pressure disturbances). Neuroimaging would seem to be indicated for nearly all patients with CM to rule out a host of conditions (such as cerebral vein thrombosis, Arnold-Chiari malformation, or meningioma) that would otherwise be missed.

Treatment

Treatment principles for CM are summarized in Table 11. Nonpharmacologic interventions are often a critical part of management. Such strategies may include exercise, regulation of eating and sleeping habits, biofeedback, supportive and behavioral psychotherapy, and health education. Limited pharmacotherapy should be instituted for the management of both daily, persistent pain and acute migraine attacks. Medications used for headache disorders in general are appropriate for this population as well.[119]

Rebound syndromes require aggressive treatment. The term *rebound* refers to a phenomenon of increasingly frequent headaches and the increasingly frequent use of medication to the point of a self-sustaining rhythm of predictable and escalating headache episodes. The offending medication should be withdrawn and alternate treatments should be initiated during the tapering period.[119] The creative use of antidepressants, beta blockers, valproate, calcium channel blockers, methysergide, and other agents, either alone or in combination, is sometimes necessary in difficult cases of rebound headache.

Hospitalization should be considered for patients with severe symptoms of CM that are refractory to outpatient treatment. Several types of IV protocols are available to interrupt the persistent headache cycle, allow discontinuation of any offending agents, and permit the implementation of preventive therapy. Psychotherapy, behavior modification, and pharmacotherapy are often used concurrently to address comorbid conditions. Additional indications for hospitalization include cases in which the symptoms of CM

Table 11

Principles for the Treatment of Chronic Migraine

- Reduction in use of symptomatic medications
- Use of preventive medication
- Behavioral and physical therapy to reduce stress
- Pharmacotherapy for daily pain and acute migraine attacks
- Pharmacotherapy and psychotherapy for neuropsychiatric and neurobiologic comorbidities and behavioral disorders
- Aggressive pharmacotherapy for rebound headache, if present

Silberstein SD, Lipton RB. Chronic daily headache including transformed migraine, chronic tension-type headache, and medication overuse. In: Silberstein SD, Lipton RB, Dalessio DJ, editors. *Wolff's Headache and Other Head Pain.* 7th ed. New York: Oxford University Press; 2001. p. 247-282.

are accompanied by drug overuse or toxicity that is not amenable to outpatient management, intense neuropsychiatric or behavioral comorbidity renders outpatient treatment ineffective, confounding medical illnesses undermine proper treatment of the pain disorder, or an individual is in urgent need of care that cannot be delivered in an appropriate time frame on an outpatient basis.[119]

Overall, 50% to 90% of patients with CM can be expected to achieve prolonged benefit with acute medical and psychological care, maintenance of detoxification, rebound treatment, frequent outpatient visits, and continuity of care. Unfortunately, however, CM is a chronic disorder and, as such, carries a considerable risk of relapse.

Cluster Headache

Cluster headache is one of the most painful primary headache disorders. The term describes a grouping of attacks that occur anywhere from every other day to 8 times per day for weeks or months, separated by attack-free (remission) periods lasting for days to years. This episodic pattern is evident in approximately 85% of patients with the disorder. However, 15% of affected individuals have a more chronic form in which the cluster period lasts for more than 1 year without remission or with periods of remission lasting less than 14 days.[120]

Epidemiology, Clinical Features, and Pathogenesis

Cluster headache is much less common than migraine. The prevalence of cluster headache in the general population has been calculated at up to 0.4%. Also unlike migraine, cluster headache predominantly affects men; the ratio of men to women ranges from 2:1 to 7:1.[120] The mean age of onset is 20 to 29 years.[121]

One of the most striking features of cluster headache is its periodicity, which is both circannual and circadian in nature.[120] Most affected individuals have 1 or 2 attack phases (cluster periods) per year. A seasonal pattern is evident in many patients (although it is not as common after a few years), who experience peak incidence shortly after the winter and summer solstices. The incidence decreases following the switches to and from daylight savings time, suggesting that the occurrence of headache may be related to the number of daylight hours.[120] The majority of patients suffer 1 to 3 attacks per day, although some may have as many as 8 daily attacks.[121] Cluster periods typically last for 2 months but may range from 6 to 12 weeks.[120] Cluster phases are followed by relatively longer remission periods that may last for 6 months to 2 years. The pattern remains relatively consistent within each individual. Attacks are likely to occur more frequently at night and with clockwise regularity.

The attack profile of cluster headache is as distinctive as its periodicity. Most patients have almost exclusively unilateral attacks, mainly around the eye and orbit, with intensely severe pain. The side on which the attack occurs may alternate from one cluster attack to the next. The attacks have a rapid onset (with peak intensity at 5 to 10 minutes) and a short duration (45 to 90 minutes). Unlike migraine sufferers, individuals with cluster headache are highly agitated and restless during the attack. Symptoms such as nausea, photophobia, phonophobia, and aura appear to be more common than previously recognized and may suggest a shared underlying pathophysiology with migraine or a common final pathway of expression. A distinguishing characteristic of cluster headache is its association with autonomic features, which are experienced by more than 80% of patients during attacks. The most common of these symptoms are conjunctival injection and lacrimation, nasal congestion and rhinorrhea, partial Horner's syndrome, and facial flushing, sweating, or edema on the ipsilateral side.[120]

Limited information is available on the natural history of cluster headache. One study found that 13% of 189 patients transformed from an episodic to a chronic pattern during 10 years of follow-up. Conversely, 33% of patients transformed from a chronic to an episodic pattern.[122] Other work, focusing on 124 patients with CH for at least 20 years, found that the duration of remission periods had increased for 39% of patients over time, even though attack durations remained unchanged.[123]

No unifying hypothesis is available to explain all 3 cardinal features of cluster headache: pain, autonomic signs and symptoms, and periodicity. A growing body of evidence suggests that the pain and autonomic symptoms are due to dual activation of the trigeminal vascular system and the cranial parasympathetic system.[120] Studies have shown substantial elevations in levels of calcitonin gene-related peptide (a marker peptide for the trigeminal vascular system) and vasoactive intestinal peptide (VIP, a marker for the cranial parasympathetic system) in the cranial venous circulation during cluster attacks, suggesting activation of both systems.[120] Levels of these marker peptides are reduced to normal in the presence of effective therapy such as oxygen or sumatriptan. Some recent observations have implicated nitric oxide as an important mediator in the pathogenesis of cluster headache. Plasma nitrate is elevated in patients with cluster headache, both during and between attacks, and nitroglycerin commonly precipitates attacks.[120] Nitric oxide is present in the parasympathetic ganglia of animals and is known to colocalize in the same neurons that contain VIP, suggesting that VIP is released when the system is activated and nitric oxide is likely released as well. Additional studies have demonstrated an abundance of neurons containing nitric oxide synthase in human cranial parasympathetic ganglia.[124] The type of Horner's syndrome observed in two thirds of patients during cluster attacks is postganglionic, suggesting that it is

distal to the sympathetic ganglia. Therefore, this syndrome must involve the sympathetic plexus investing the carotid artery.[121] Imaging data have demonstrated dilatation of the proximal carotid artery around the cavernous sinus, which may secondarily involve the sympathetic plexus and lead to the transient Horner's syndrome that occurs during cluster attacks.[121]

No unifying hypothesis is available to explain all 3 cardinal features of cluster headache: pain, autonomic signs and symptoms, and periodicity.

In view of the circadian and circannual rhythmicity of cluster headache, the suprachiasmatic nucleus located in the hypothalamus (the so-called human circadian pacemaker) has been implicated as a pathogenetic mechanism. This hypothesis was supported by early biochemical studies showing altered circadian rhythm of hypophysial hormone release in patients with cluster headache.[125] Of additional interest is the fact that the suprachiasmatic nucleus regulates the synthesis and secretion of melatonin from the pineal gland, and the rhythm of melatonin secretion is dysregulated in individuals with cluster headache.[125] The most convincing evidence favoring the role of the hypothalamus in cluster headache has come from a series of experiments in which nitroglycerin was used to precipitate attacks in 9 patients. Eight patients who had cluster headache but were not having headaches at the time served as controls. A comparison of PET scans from the 2 groups revealed that the medial area of the hypothalamus was specifically involved in the cluster attack. This pattern of activation is not apparent in migraine.[126] In a subsequent study, voxel-based morphometry revealed an increase in the volume of the ipsilateral hypothalamic gray matter of patients with cluster headache, raising the possibility that brain structure in the hypothalamic regions of patients with cluster headache is not normal.[127]

Until recently, genetic factors were not believed to play a role in cluster headache. However, studies have now shown that 7% of patients have family histories of the disorder.[65] First-degree relatives of probands have a 14-fold increased risk, and 100% concordance was observed in 5 pairs of identical twins. These observations raise the possibility that cluster headache may reflect an autosomal dominant disorder in some individuals.[65]

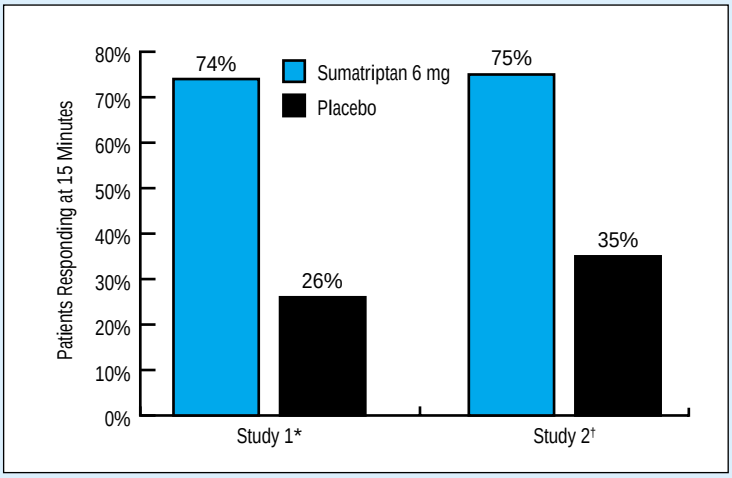
Treatment

The rapid onset of cluster attacks and the short time to peak intensity mandate the use of fast-acting acute treatments. Oxygen is the standard recommended therapy; 75% of patients in one study achieved pain relief after the administration of 100% oxygen at a rate of 7 L/minute for 15 minutes.[128] Unfortunately, oxygen may simply delay rather than completely abort the attack in some individuals. Lack of accessibility also limits the utility of this treatment approach. A high degree of efficacy can be achieved with the use of DHE (1.0 mg IV, IM, or SC) or sumatriptan (6 mg SC).[120] Both SC formulations offer the convenience of self-injection, but sumatriptan is clearly the more efficacious of the 2 agents. Consistent results from 2 placebo-controlled trials showed that sumatriptan significantly improved 15-minute rates of response (defined as a ≥2-point reduction in headache severity) compared with placebo (Figure 5).[129] Approximately 75% of actively treated patients responded in each study. Of further note was the fact that 49% of patients obtained relief with sumatriptan at 10 minutes in the second study. Sumatriptan also has been shown to provide consistent, long-term efficacy over multiple attacks (Figure 6, page 24).[130,131] Sumatriptan is effective for both episodic and chronic cluster headache, although patients with the latter headache pattern exhibit a more delayed response. This agent was not associated with tachyphylaxis, and prolonged use did not increase the frequency of attacks.[130]
A lesser degree of efficacy has been apparent with zolmitriptan (5 to 10 mg PO). Also, unlike sumatriptan, zolmitriptan does not appear to be effective in patients with chronic, as opposed to episodic, cluster headache.[132] Only limited efficacy has been observed with IN DHE or lidocaine in cluster headache.[120]

Preventive therapy for cluster headache is aimed at rapid suppression of attacks (transitional therapy) and maintenance of suppression over the expected duration of the cluster period (maintenance therapy). Few

Figure 5

Proportion of Patients With Cluster Headache Responding at 15 Minutes to Sumatriptan Versus Placebo

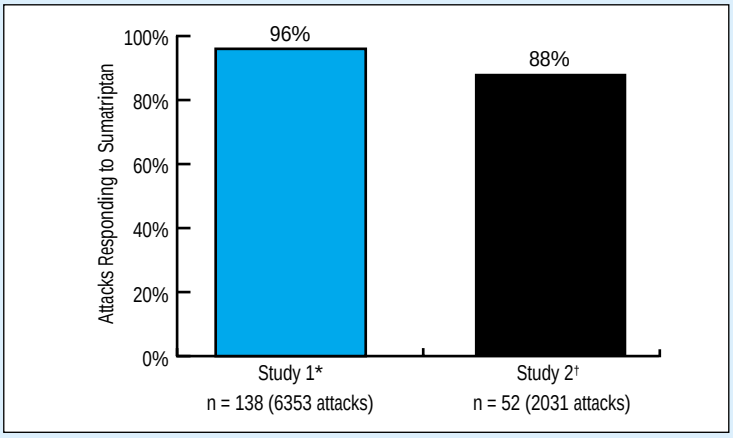


*Ekbom K, et al. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand.* 1993;88(1):63-69

†Ekbom K, Monstad I, Prusinski A, et al. *Acta Neurol Scand.* 1993;88:63-69.

Figure 6

Efficacy of Sumatriptan in Acute Treatment of Cluster Headache Over Multiple Attacks



*Ekbom K, et al. *Cephalalgia.* 1995;15:230-236.
†Gobel H, Lindner V, Heinze A, et al. *Neurology.* 1998;51(3):908-911.

randomized, controlled clinical trials have examined prophylaxis for cluster headache, and the selection of therapy must be individualized and prioritized on the basis not only of these studies but also of open-label data and clinical experience. Cluster headaches can be suppressed rapidly in 75% of patients who receive prednisone.[120] Short-term therapy with prednisone will suppress headaches while a maintenance prophylactic agent is initiated and allowed to take effect.[120] Verapamil is the agent of choice for preventive therapy over the expected duration of the cluster period. In a recent double-blind, placebo-controlled, randomized trial involving 30 patients with episodic cluster headache, verapamil (120 mg TID) significantly reduced attack frequency, by more than 50%, in 80% of individuals at 2 weeks.[133] Almost one third of patients were free of pain at that point. Although nearly half the patients who responded did so during the first week, the majority required 2 weeks to obtain relief. This observation underscores the need for a transitional prophylactic agent such as prednisone.

In more than 28 studies examining lithium as prophylaxis, efficacy was observed in approximately 78% of patients with chronic cluster headache but in fewer (approximately 63%) with episodic cluster.[120] Although only 1 open-label study has suggested that divalproex is effective (eliciting responses in 73% of patients),[120] this agent is being used more frequently, because some of the alternatives, such as ergotamine derivatives, limit the ability to use sumatriptan as acute treatment.[120] Early investigations showed methysergide to be effective in as many as 70% of patients, but these effects apparently diminish over time.[120] Also, the potential for fibrotic complications limits its long-term use. Sumatriptan is not effective for cluster headache prophylaxis or when used before an expected attack to prevent it.

Melatonin and topiramate have been investigated as adjunctive therapies for the prevention of cluster attacks and may prove to be suitable choices for some patients.[134,135] More data are needed.

Approximately 10% of patients develop chronic cluster headache that is not responsive to monotherapy.[120] Polytherapy may be helpful. Possible combinations include lithium plus verapamil or methysergide plus verapamil. Medication combinations such as ergotamine/verapamil/lithium may even be considered as a short-term option.[120] Among the small minority of patients for whom all attempts at prophylaxis fail, some individuals may benefit (at least temporarily) from referral to a tertiary care center for treatment with IV DHE. Histamine “desensitization” may be useful but requires a prolonged hospital stay with repetitive administration of IV antihistamine.[120] Ablative surgery should be considered as an option only for patients who have truly intractable cluster headache, multiple contraindications to drug therapy, or intolerable side effects from medications. Even then, surgery should be performed only on patients who have unilateral disease, as a history of contralateral headaches may be associated with an increased risk of recurrence of such headaches postoperatively.[120] A variety of surgical procedures directed at the sensory trigeminal or cranial parasympathetic pathways have been attempted, but radiofrequency trigeminal rhizotomy has been used most often, with variable degrees of short-term and long-term success. Recently, an electrode was implanted into the inferior posterior hypothalamus of a 38-year-old man with intractable chronic cluster headache. After 136 days, the patient was completely pain free, with no side effects.[136] This case report supplies additional evidence that cluster headache is generated in the hypothalamus.

CONCLUSIONS

Migraine affects nearly 28 million Americans, diminishing quality of life and costing society billions of dollars per year in terms of lost productivity. Despite notable advances, several obstacles have persistently undermined the prospects for optimal management of the disorder and its various comorbidities. Chief among these barriers is the widely held belief among the general population, as well as some healthcare providers, that migraine is not a legitimate, treatable medical condition. Expanded educational endeavors are warranted to counter this misperception.

Efforts to enhance awareness of available treatments must be coupled with a commitment to improving migraine therapy in the future. The scientific community is continuing to make headway in its attempt to increase knowledge of the pathogenetic underpinnings of headache disorders. As new findings are translated into the clinical setting, physicians may be able to offer patients even more effective therapeutic options in the 21st century.

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December 2001

Dear Colleague:

Migraine is a common, chronic, and often disabling disorder that exacts a tremendous toll on the quality of life of affected individuals and their families. Its physical and economic burdens are steadily increasing with the growth of our population. Studies have shown that migraine is substantially underdiagnosed and undertreated in the United States and around the world. Migraine frequently coexists with other disorders, complicating diagnosis and treatment and creating opportunities to explore common risk factors and biological mechanisms that underlie migraine and its comorbid conditions.

Fortunately, recent insights in the neurobiology of migraine have lead to the development of more effective acute and preventive treatments. These agents, which arise from a number of drug classes, target one or several mechanisms that are believed to cause migraine headache.

This comprehensive monograph represents the proceedings of a conference presented by the National Institute of Neurological Disorders and Stroke (NINDS) in cooperation with the American Academy of Neurology (AAN), the American Headache Society (AHS), and the National Headache Foundation (NHF). The faculty, which consisted of opinion leaders from around the world, provided insights into the evaluation, genetics, mechanisms, diagnosis, and treatment of migraine headache.

This educational activity is jointly sponsored by Jefferson Medical College of Thomas Jefferson University and SynerMed Communications. It is supported by an unrestricted educational grant from Ortho-McNeil Pharmaceutical, Inc. We hope you find this monograph to be a useful educational resource.

Sincerely,

Richard B. Lipton, MD
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Professor of Neurology,
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21st Century Prevention and Management of Migraine Headache

Posttest

If you wish to receive CME credit for your participation in this program, you must complete both the posttest and the evaluation form. Review the learning objectives to determine if the monograph's content relates to your individual learning needs. Read the monograph carefully, paying particular attention to the tables and other illustrative materials. Complete the CME Information/ Registration form. Please type or print your full name and address in the space provided. To be processed, information must be complete and legible. Evaluation of the activity is integral to the CME process. CME certificate requests cannot be processed if the Evaluation portion is not complete. Send the completed form to:

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1. The prevalence of migraine is highest in
   a. children
   b. adolescents
   c. adults 25 to 55 years old
   d. elderly individuals 65 to 75 years old

2. The risk of migraine in individuals with epilepsy is
   a. related to younger age at seizure onset
   b. elevated in individuals with both partial and generalized seizures
   c. higher in individuals with generalized tonic-clonic seizures than in those with posttraumatic seizures
   d. limited to migraine with aura

3. Spreading depression refers to
   a. a wave of neuronal excitation followed by suppression
   b. a decrease in neuronal hyperexcitability and migraine susceptibility
   c. the trend toward an increased prevalence of depression in migraineurs
   d. none of the above

4. The most widely effective tool for diagnosing migraine is
   a. electroencephalogram
   b. neuroimaging
   c. lumbar puncture
   d. patient examination and history

5. According to the US Headache Consortium, an agent selected for migraine prevention should be given a trial of
   a. 2 to 3 weeks
   b. 1 month
   c. 2 to 3 months
   d. a minimum of 6 months

6. Which anticonvulsant has not been effective for preventing migraine in placebo-controlled trials?
   a. divalproex
   b. carbamazepine
   c. gabapentin
   d. topiramate

7. What are the potential sites of action of triptans in the acute treatment of migraine attacks?
   a. vasoconstriction at cranial arteries
   b. inhibition of transmitter release from trigeminal nerve endings
   c. central inhibition of the trigeminal nucleus caudales
   d. all of the above

8. A meta-analysis of 33 clinical trials found that cognitive-behavioral therapy reduced migraine activity by
   a. 10% to 20%
   b. 20% to 30%
   c. 30% to 40%
   d. 40% to 50%

9. Chronic migraine
   a. is defined as headache occurring at least 25 days per month for at least 8 hours per day
   b. affects 4% of patients seen at headache clinics
   c. involves medication overuse by 80% of patients with chronic (transformed) migraine in headache subspecialty centers
   d. should be managed only with monotherapy in cases of rebound

10. Cluster headache
    a. is episodic in 90% of patients and chronic in 10%
    b. is more common in women than in men
    c. has a low rate of response to acute therapy with sumatriptan
    d. has a low rate of response to short-term preventive therapy with prednisone

CME Self-Assessment Answer Sheet

Please record your posttest answers, complete the evaluation form, and mail to address above.

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____ 9. _____ 10. _____

We hope this monograph has provided information that will be useful in your practice.

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21st Century Prevention and Management of Migraine Headache

Evaluation

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Your evaluation will help us plan future programs. May we have your comments?

On a 5-point scale where 5 is "excellent" and 1 is "poor", please rate the following:

	Excellent				Poor
1. Have program objectives been achieved?	5	4	3	2	1
2. How was program content flow?	5	4	3	2	1
3. Value of the topic	5	4	3	2	1
4. Quality of information	5	4	3	2	1

5. Do you feel that the topic was relevant to your practice? ❑ Yes ❑ No
   Please explain:

   _____

   _____

6. Did you find that this program was free of commercial bias? ❑ Yes ❑ No
   Please explain:

   _____

   _____

7. Which one of the following best describes a change you might consider making in your practice as a result of this activity? Please circle only one response.
   a. Slightly modify what I currently do
   b. Make a major change in what I currently do
   c. Not considering any changes

8. Please describe any change(s) you plan to make in your practice as a result of the activity.

   _____

   _____

9. On a scale of 5 (high) to 1 (low), how committed are you to making the change(s)?
   5 (highest) 4 3 2 1 (lowest)

10. What comments and/or improvements, if any, would you recommend?

    _____

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13. Actual amount of time I spent in this activity:
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