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21st CENTURY PREVENTION AND MANAGEMENT OF MIGRAINE HEADACHES

MIGRAINE: A CALL TO ACTION

Chronic pain represents a common, puzzling, and frustrating treatment conundrum that exacts an enormous economic and personal toll on those who are afflicted, on their families, and, more broadly, on society. Migraine is one of the most common and painful of the chronic pain disorders. Migraine is a brain disorder characterized by paroxysmal episodes of acute head pain and associated symptoms. The profound impact of migraine extends beyond the burden of individual attacks and influences both health-related quality of life and the national economy through its effects on medical resources and on individual productivity. Though migraine treatments and preventive strategies have greatly improved, there is an enormous gap between the treatment that is available and the treatment that is actually delivered for migraine.

A greater understanding of migraine and the development and deployment of better therapeutic alternatives are clearly needed. As a call to action on behalf of migraine patients everywhere, the National Institute of Neurological Disorders and Stroke (NINDS; www.ninds.gov) urges continuing research in the clinical and scientific aspects of migraine. To convey the most recent findings on migraine, NINDS hosted a conference on June 8 and 9, 2000, in Bethesda, Maryland, in cooperation with the American Academy of Neurology, the National Headache Foundation, the American Headache Society, and Jefferson Medical College of Thomas Jefferson University.

A panel of experts focused on what is currently known about the etiology of migraine and its unusual underlying mechanisms, the pathophysiology of which is becoming increasingly clear. The treatment and prevention of migraine were discussed. In addition, the clinical characteristics and treatment of cluster headache were presented.

EDUCATIONAL OBJECTIVES

After reading this newsletter, the physician should be able to:

- Discuss current research findings related to the etiology, pathogenesis, and mechanisms of migraine;
- Explain how patients are evaluated and diagnosed with migraine, and review the optimal use of diagnostic testing;
- Define the categories of cluster headache and chronic migraine (CM) and the clinical characteristics of headaches falling under each group; and
- Describe current acute and prophylactic treatments for migraine, cluster headache, and CM.

EPIDEMIOLOGY OF MIGRAINE

Migraine affects nearly 1 in every 4 US households. In 1999, nearly 28 million Americans were found to have the disorder; more women than men suffer from migraine, with an overall gender prevalence ratio of 3:1 (Table 1). More than 18% of American women and 6% of American men have migraine.[1,2]

TABLE 1

ESTIMATED NUMBER OF MIGRAINE SUFFERERS IN THE UNITED STATES

	1989 (millions)	1999 (millions)
Overall	23.6	27.9
Women	18.0	20.9
Men	5.6	6.9

Data from Lipton RB, Stewart WF, Diamond S, Diamond M, Reed M. Prevalence and burden of migraine in the United States: Results from the American Migraine Study II. *Headache.* 2001; 41: 646-657. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine in the United States: Relation to age, income, race, and other sociodemographic factors. *JAMA.* 1992;267(1):64-69.

The disorder afflicts individuals in their most productive years, occurring most frequently in both men and women between the ages of 25 and 55 years (Figure 1, page 3).[2] This helps account for the major disease burden produced by migraine, with work absences and reduced productivity at work as major contributing factors. The onset of new migraine cases peaks during adolescence. Half of those who suffer from migraine headaches as adults experience their first migraine headache in childhood or adolescence.

Impact of Migraine Headaches

Migraine sufferers experience headache on an average of 7 days over a 3-month period.[3] Of patients with migraine, 33% report extremely severe pain during an attack, and 47% report severe pain; 85% report pulsatile pain.[1,4] With respect to associated symptoms, many migraine sufferers experience nausea (73%), sensitivity to light (80%), and sensitivity to sound (76%) in various combinations.[1]

During migraine attacks, 53% of sufferers experience severe functional disability, including self-imposed bed rest. Thirty-nine percent have some impairment of activity, whereas only 9% are able to function normally. These affected individuals are often unable to participate in school, work, and social activities. (Figure 2, page 3)[1]

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Present

21st Century Prevention and Management of Migraine Headaches

Release Date: September 2001

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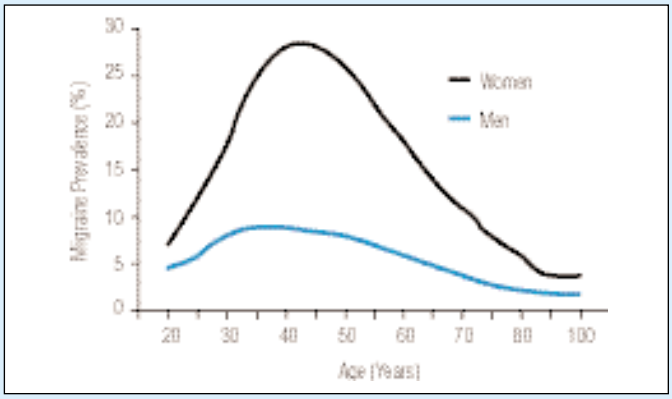
FIGURE 1

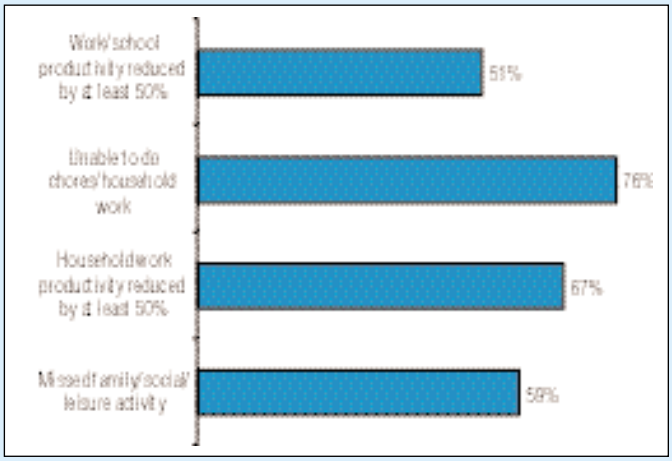
AGE-SPECIFIC PREVALENCE OF MIGRAINE BY GENDER – 1999



Adapted with permission from Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. *JAMA.* 1992;267(1):64-69.

FIGURE 2

MIGRAINE DISABILITY ASSESSMENT



Data from Lipton RB, Stewart WF, Diamond S, Diamond M, Reed M. Prevalence and burden of migraine in the United States: Results from the American Migraine Study II. *Headache.* 2001; 41: 646-657.

The cost to American employers due to missed work and reduced productivity is estimated to be $13 billion per year.[5] Most migraine sufferers attempt to remain at work, even with reduced productivity; migraine results in 112 million days of bed rest per year in the United States.[5] Nearly half of women and 38% of men with migraine lose a week or more of work per year because of the disorder.[6]

Barriers to Effective Migraine Management

Methodologically identical studies were conducted in representative samples of the US population in 1989 and then again in 1999.[1,2] Surveys associated with these studies revealed that although the proportion of migraine sufferers consulting doctors increased over the last decade, the majority of migraine sufferers are not actively seeking medical care.[7,8] The studies also showed that more than 60% of migraine sufferers treat with over-the-counter medication to the exclusion of prescription drugs.[4,8] Although over-the-counter medications are an important treatment option for migraine, prescription drugs are often required, especially by more disabled migraine sufferers.

A 1998 survey by Lipton and Stewart found that only 29% of migraine sufferers were very satisfied, and 48% were somewhat satisfied with their usual acute treatment. Of those not satisfied, 87% believed that treatment takes too long to achieve pain relief, and 84% report that it does not relieve all of their pain and that it does not always work. For 71%, dissatisfaction resulted from the fact that the headache returns after treatment. More than one third reported that treatment is associated with too many side effects.[9]

One of the major barriers to providing effective treatment is that migraine is still not recognized by many physicians and patients as a significant medical illness. As an episodic disorder that is not life-threatening and for which there is a lack of objective tests, migraine often receives limited medical attention. Many migraine sufferers do not seek help for their disorder because of denial, embarrassment, or a belief that there is nothing that the doctor can do. Strategies for overcoming these barriers must change the perceptions of both clinical practitioners and the general public. Keys to improving outcomes for migraine patients include encouraging disabled migraine sufferers to seek care and improving communication about headache-related disability using tools such as the Migraine Disability Assessment (MIDAS) questionnaire (Figure 3).

FIGURE 3

MIDAS QUESTIONNAIRE

DO YOU SUFFER FROM HEADACHES?

This form can help you and your doctor improve the management of your headaches.

Once you have filled in the questionnaire, add up the total number of days from questions 1–5 (ignore A and B).

INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months.

Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? _____ days

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school) _____ days

3. On how many days in the last 3 months did you not do household work because of your headaches? _____ days

4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work) _____ days

5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches? _____ days

_____ **TOTAL** days

A On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day) _____ days

B On a scale of 0–10, on average how painful were these headaches? (Where 0 = no pain at all, and 10 = pain as bad as it can be) _____

Grading system for the MIDAS Questionnaire:
Grade Definition Score

I Little or no disability 0–5
II Mild disability 6–10
III Moderate disability 11–20
IV Severe disability 21+

MIDAS has been shown to correlate with physician judgments about severity of illness and to predict treatment needs.[10,11]

Migraine Comorbidity: Psychiatric and Neurologic Disorders

Disorders with which migraine has been associated include major depression, personality and anxiety disorders, stroke, epilepsy, and sleep disturbances.[12,13] Some of these conditions share similar characteristics with migraine; both migraine and epilepsy can cause headache and alterations in mental status, for example.

In addition, the same medications are often used to treat migraine and a comorbid disorder. For example, patients with migraine and epilepsy might be treated with an anticonvulsant. Those with migraine and depression could be treated with an antidepressant.

Conversely, the existence of a comorbid condition might rule out certain treatments for migraine. Tricyclic antidepressants (TCAs) or neuroleptic drugs would not be prescribed for the migraine patient with epilepsy, for instance, because they may lower the seizure threshold. In patients with migraine and depression, β-blockers should be given cautiously because of their potential to cause or exacerbate depression.

Psychiatric Disorders

Both affective and anxiety disorders are found more commonly in migraine sufferers. One study reported the odds ratios for the occurrence of major depression (2.2), bipolar illness (2.9), any anxiety disorder (2.7), simple phobia (2.4), social phobia (3.4), and panic disorder (3.3) in migraine sufferers.[14] Migraine with aura was found to be more strongly associated with these disorders than migraine without aura.

In a telephone survey of approximately 10,000 subjects, Stewart et al found the relative risk of migraine in subjects with a history of panic disorder to be 7.0 for men and 3.7 for women.[15] Patients with panic disorder reported a higher frequency of headaches in the previous week, headaches of longer duration, and headaches with more migrainous symptoms.

A study of migraine and major depression showed the relative risk for new onset of major depression to be 4.2 among migraine sufferers compared with those without migraine.[16] Similarly, the relative risk of new-onset migraine among patients with a history of major depression was 3.3 compared with those without such a history.[17] These findings suggest a bidirectional association between migraine and depression instead of a cause-and-effect relationship. Migraine and depression independently reduce health-related quality of life.[18]

Stroke

The risk of migraine-related stroke is difficult to determine because of variations in the definitions used in different studies.[19] Moreover, many reports on epidemiologic studies have lacked details regarding the timing of stroke in relation to a migraine attack, the cause of stroke, or whether stroke appeared to be induced by the attack.[19]

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 younger than 45 years of age, although the absolute risk is low.[20,21] Anywhere from 1% to 17% of strokes in hospitalized patients younger than 50 years of age appear to be associated with migraine.[22] Stroke is also generally more common in migraine with aura.[23] Overall, however, the occurrence of stroke during migraine attacks (true migraine-induced stroke) is rare.[19]

Epilepsy

The 1-year incidence of epilepsy in the general population is between 0.4% to 0.8%.[24] Among migraine sufferers, the prevalence of epilepsy ranges between 1% and 17%.[25] For patients with epilepsy, the prevalence of migraine has been reported to be in the range of 8% to 15% as opposed to 6% of men and 18% of women in the general population.[25,26,27,28]

In the Epilepsy Family Study, the cumulative incidence of migraine to 40 years of age was 24% in probands with epilepsy, 23% in relatives with epilepsy, and 12% in relatives without epilepsy (no higher than in the general population).[25] A Cox proportional hazards analysis adjusted for gender showed that the risk ratio for migraine was 2.4 (95% confidence interval, 2.02 to 2.89) among probands and 2.4 (95% confidence interval, 1.58 to 3.79) among relatives with epilepsy when compared with relatives without epilepsy. The risk of migraine is elevated in probands both with and without a positive family history of epilepsy.[25] Comorbidity cannot be explained by a simple unidirectional hypothesis indicating that migraine increases the risk of epilepsy or that epilepsy increases the risk of migraine, since migraine risk is increased both before and after the onset of seizures. Patients with posttraumatic epilepsy have been found to have a higher risk of migraine than those with other types of epilepsy, suggesting that head trauma may place patients at higher risk for both disorders. However, migraine risk also appears to be elevated in certain patients with idiopathic epilepsy.

Sleep Disorders

To date, little information is available in the medical literature on the comorbidity of migraine and sleep disorders. Recent available studies have focused on parasomnias. These are syndromes involving the occurrence or exacerbation of undesirable physical phenomena during sleep.

The largest study was performed by Dexter, who evaluated 100 migraine patients and 100 matched controls.[29] Compared with the control group, subjects with migraine had an increased incidence of nighttime terrors (71% for migraine patients vs 11% for controls), sleepwalking (55% vs 16%), and bedwetting (41% vs 16%). The author concluded that a relationship may exist between abnormalities of slow-wave sleep and migraine.[29]

Special Populations

Elderly

The diagnosis and management of headache in the elderly presents a special challenge to the clinician. This is often due to coexisting and comorbid conditions, which affect not only diagnosis but treatment. As in the young, headache in the elderly can be divided into primary and/or secondary headaches. The prevalence of primary headache disorders, such as migraine, cluster headache, and tension-type headache, declines with age. The hypnic headache syndrome is a rare, benign, primary headache disorder unique to the elderly.[30,31,32,33] Lithium carbonate is likely one of the most effective treatments, yet lithium's side-effect profile makes this medication less than ideal for long-term use in the elderly patient.[31,32] Caffeine, taken as either a tablet or a cup of coffee prior to retiring in the evening, may be effective for some patients.[32] Other therapies reported to be effective include indomethacin[33] and flunarizine.[34] Secondary headaches represent a symptom of an underlying organic disease, such as giant-cell arteritis, an intracranial mass lesion, or a metabolic disorder. Even in the elderly, the majority of headaches are of a benign nature. However, because the relative proportion of secondary headaches increases with advancing age, one must maintain a high index of suspicion for organic disease in this population. Migraine may be exacerbated by many common medications that the elderly may take for coexisting conditions. For example, vasodilating antihypertensive medications such as methyldopa or nifedipine may worsen or result in an increased frequency of attacks. Isosorbide dinitrate, when used for angina, may precipitate a migraine attack, particularly in those with a history of prior attacks. If a preventive medication is deemed necessary, it is advisable to start with the lowest dosage and titrate slowly to the lowest effective dosage.

Women

Migraine is 3 times more common in women than in men.[1,2] Research has established a link between migraine and fluctuations in the female sex hormones estrogen and progesterone, beginning at menarche.[35]

Cyclic hormonal changes are the basis for menstrual migraine. As many as 60% of women experience migraine in association with their menstrual cycles. Among women with menstrual migraine, attacks occur at increased rates for a day or 2 before and after the onset of flow.[36,37] Hormonal contraception can prompt new-onset migraine or alter the character and frequency of preexisting migraine, either aggravating or ameliorating symptoms. Migraine may begin to occur with pregnancy, and preexisting migraine typically worsens during the first trimester. However, improvement is usually evident by the second or third trimester. Menopause is often, but not always, associated with a reduction in symptom severity. Estrogen replacement therapy may actually worsen migraine.

PATHOGENESIS/MECHANISMS OF MIGRAINE

Contemporary researchers regard a migraine attack as a specific and unique pathologic brain disorder. What was once considered multiple causes of migraine are now thought to be a variety of triggers acting on a susceptible brain. This susceptibility is thought to be in part genetically determined and is probably due to abnormal neuronal excitability.[38] The typical migraine is paroxysmal; this suggests that there is a threshold that governs the brain's susceptibility to migraines or the tendency of neuronal membranes to depolarize, thus partially protecting against migraine.

The Clinical Phases of Migraine

The details of how migraines occur are not completely understood and remain the subject of heated debate. There are 4 different phases of a migraine headache (Figure 4):

1. Premonitory phase
2. Aura
3. Headache phase
4. Resolution/postdromal phase

FIGURE 4

CLINICAL PHASES OF A MIGRAINE ATTACK

Adapted from Blau JN. Migraine pathogenesis: the neural hypothesis reexamined. *J Neurol Neurosurg Psychiatry*.1984;47(5):437-442.

Premonitory Phase

Approximately 60% of migraine sufferers report premonitory symptoms 24 or more hours prior to the onset of the actual headache. During this phase, patients experience vague vegetative or affective symptoms, including mood shifts, abnormal food cravings, repetitive yawning, thirst, fluid retention, a stiff neck, a cold feeling, sluggishness, increased urination, anorexia, diarrhea, and constipation. Neurologic phenomena include photophobia, phonophobia, and hyperosmia, among others. These symptoms often disappear before headache pain begins, and they may represent the first clinical manifestation of the patient's hypersensitivity to migraine stimuli.

Aura (When Present)

Approximately 15% of patients with migraine experience aura. The typical aura is visual and migratory, spreading slowly over the visual field. However, some patients experience a sensory aura such as the sensation of pins and needles or numbness. This type of aura migrates in a similar way, spreading slowly over contiguous areas of the somatosensory system. Other types of migraine aura that sometimes occur include disruptions of language and motor systems. The aura usually precedes and resolves prior to the headache, but the aura may extend into or begin during the headache phase.

Headache

Pain intensifies and peaks after several hours, persisting for up to 3 days. Other symptoms that may occur include photophobia, phonophobia, nausea, heightened sensory perception, sensitivity to smells, dizziness, and difficulty with concentration and mental processing. Resolution of pain often occurs with deep sleep. This is not surprising, since sedating medication is often prescribed to patients for this phase of migraine, but resolution of pain without sleep also can occur when no sedating medication is taken.

Resolution/Postdromal Phase

Following resolution, many patients continue to experience movement-induced pain for a period of about 24 hours. During this phase, they no longer have spontaneous throbbing pain. However, upon bending over, coughing, or performing any activity that increases intracranial pressure, patients may experience a return of migraine pain.

The Vasogenic Theory Versus the Neurogenic Theory

Our current understanding of the pathogenesis of migraine is influenced by 2 theories that were developed more than 60 years ago. The vasogenic theory postulates that migraine aura results from transient vasoconstriction. Rebound vasodilation is hypothesized to be the event that results in activation of perivascular nociceptive neurons.

The neurogenic theory holds that vascular changes occur but do not always lead to pain, and migraine pain can occur in the absence of vascular changes. This theory postulates that a neurophysiologically driven process occurs and promotes the release of nociceptive substances.

The Pathophysiologic Phases of Migraine

Migraine can be described as occurring in 3 pathophysiologic phases:

1. Initiation
2. Activation and transmission in the primary afferent neurons
3. Activation and sensitization of the central nervous system

Initiation

The initiation of migraine pain is not thoroughly understood. Migraine pain is thought to be sensed through nociceptive neurons within the trigeminal nerve (which subserves different areas of the head and face) and cranial nerves C1 and C2 (which subserve the posterior portion of the head). Initiation represents an inappropriate and repeated activation of the trigeminal and cervical pain systems.

Migraine is believed to be a neurovascular disorder. Migraine with aura commonly begins in the occipital cortex.[39,40] Migraine without aura may be initiated at the vessel level or perhaps centrally, through different pathways.

The phenomenon of *spreading depression* may play a role in migraine with aura.[40, 41] Spreading depression is defined as a wave of neuronal activation followed by suppression. In experimental animal models, this phenomenon is induced by applying a small amount of potassium chloride to the cerebral cortex.[41] The wave of neuronal suppression is observed to move at the rate of 3 to 6 mm/min in these models. These data have been used to aid understanding of elements of visual aura in humans. The visual aura of migraine expands at a rate that is consistent with the time course of spreading depression observed in animal models.[40,41]

Activation and Transmission in Primary Afferent Neurons

Regardless of the exact method of initiation, trigeminal and/or C1 or C2 nociceptive neurons must be activated for headache to occur. In theory, it

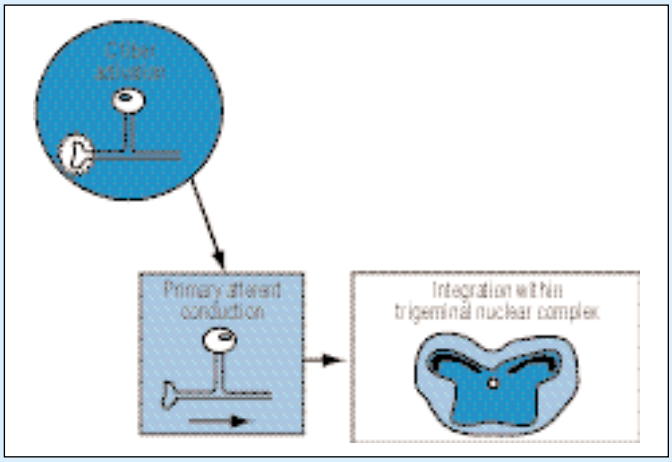
may be possible to generate headaches without involvement of peripheral innervation through selected activation of certain areas of the brain involved in nociceptive processing. However, preliminary work on the release of calcitonin-generated peptide suggests that peripheral neurons are involved in this phase of migraine.[42]

After initiation, it is thought that activation of the primary nociceptor takes place, followed by central conduction of neural stimuli through the trigeminal ganglion. Bipolar neurons of the trigeminal ganglion innervate the large cerebral arteries and dura mater. From there, neural stimuli proceed into areas of pain processing within the trigeminal nucleus complex, an area of the brainstem analogous to the dorsal horn of the spinal cord (Figure 5).[43]

Within the trigeminal nucleus complex, the primary afferents synapse on the second-order neurons. Pain signals from the afferent neural fibers are integrated and transmitted through ascending second-order neural axons to the central pain-processing areas of the brain: the thalamus, the limbic system, and the neocortex (Figure 6).[43,44]

FIGURE 5

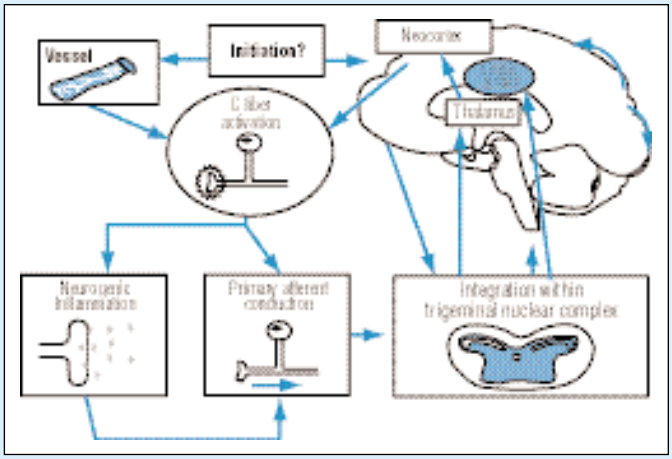
ACTIVATION OF PRIMARY AFFERENT NEURONS



Adapted from Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia.* 1997;17(2):93-100.

FIGURE 6

MIGRAINE/PATHOPHYSIOLOGY



Adapted from Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia.* 1997;17(2):93-100.

Why Migraines Persist

The pathways described above are more than passive conduits for nociceptive stimuli, since migraine headaches last longer than their initiating stimuli. To account for this, investigators have hypothesized that there may be either peripheral or central events that reinforce and perpetuate the nociceptive signals, resulting in a headache that lasts for hours.

The development of a migraine headache appears to be based on a cascade of events occurring in susceptible individual, and probably occurs as a result of multiple irritating processes in the brain and peripheral nervous system. However, many of the details of these events require further study. In addition, researchers are only beginning to understand and investigate the potential opportunities for interrupting these events to prevent or to end an episode of migraine.

The Genetics of Migraine

The genetic nature of migraine is supported by family aggregation studies, twin studies, and the identification of specific genetic defects for certain rare forms of migraine.[45,46] Though migraine is a multifactorial as well as an episodic disorder, evidence is accumulating that it may originate from fundamental neurophysiologic abnormalities caused by genetic mutations. In support of this hypothesis, research indicates that the brain of the patient with migraine is neurophysiologically different from the normal brain, even between attacks.[47]

In studying the genetics of migraine headache, researchers have searched for genetic causes of rare, familial subtypes of migraine and attempted to extrapolate their work to the more common migraine types. Familial hemiplegic migraine is a rare, inherited subtype of migraine that is often confused with epilepsy. Patients with familial hemiplegic migraine experience hemiparesis during the aura preceding a migraine attack.

In 1993, Joutel et al reported evidence linking familial hemiplegic migraine to chromosome 19.[48] Three years later, the gene on chromosome 19 responsible for this syndrome, called *CACNA1A*, was identified.[49] This gene codes for the α_{1A}-subunit of the brain-specific P/Q-type calcium channel. Subsequent studies have confirmed the link between the *CACNA1A* gene and other rare migraine subtypes, such as hemiplegic migraine with cerebellar ataxia and migraine coma. Mutations in the *CACNA1A* gene are associated with cerebellar ataxia even without migraine.[50,51,52,53]

Could this gene also be linked to the more common, widely known type of migraine? Preliminary, unpublished data suggest that in one series of patients, the *CACNA1A* gene may be linked to migraine with aura but not to migraine without aura.[54] Moreover, if mutations in the *CACNA1A* gene were linked to common migraine, one would expect to see abnormalities in the P/Q-type calcium channel in migraine patients. There are a number of clinical arguments supporting the hypothesis that migraine may be a channelopathy, including the extent of similarity between the clinical characteristics of migraine and those of known neuromuscular channelopathies.

Migraine and Abnormalities in the P/Q-Type Calcium Channel

The primary function of the P/Q-type neuronal calcium channel appears to be modulation of neurotransmitter release. Three types of neurotransmitters are known to be modulated by this channel: the monoamines, the catecholamines, and the excitatory amino acids. Studies of the effects of missense mutations in the *CACNA1A* gene indicate that even small mutations can alter the biophysical properties of the P/Q-type calcium channel and thus impact its functioning.[55] P/Q type calcium channels are expressed only in the cerebellum, presenting some confusion as to their role in migraine and the cerebral cortex.

Naturally occurring strains of mice with mutations in the mouse homologue of the *CACNA1A* gene, such as tottering mice, provide us with a model for studying gene function. Contrary to expectations, Ayata et al found a 10-fold greater resistance to spreading cortical depression in tottering mice than in wild-type

mice.[41] However, in studies of the P/Q-type calcium channel at the neuromuscular junctions of tottering mice, Plomp et al detected an increased spontaneous release of acetylcholine.[56] They also were able to block synaptic transmission using lower concentrations of the acetylcholine antagonist tubocurarine in tottering mice than in wild-type mice.

If similar events occur in humans with *CACNA1A* mutations, then it should be possible to demonstrate alterations in the neuromuscular junction in migraine patients. Preliminary evidence suggests that in certain migraine patients, there are subclinical single-fiber electromyographic abnormalities.[57] Assuming this finding can be replicated in further studies, it demonstrates for the first time the presence of objective, physical abnormalities in migraine at a readily accessible site, the neuromuscular junction.

Directions for Future Study

Mice with knockout of the P/Q-type calcium channel α_{1A} - subunit have now been reported by Jun et al.[58] The mice develop rapidly progressive ataxia and dystonia before dying at the age of about 3 to 4 weeks. There also is complete elimination of P/Q-type currents in the cerebellum, with sparing of synaptic transmission in the hippocampus and increased reliance on other calcium channels. Although this compensatory mechanism might not occur in all alpha (1A) knockout mice, it should be investigated in further studies.

Other genetic links to migraine warrant investigation. Familial subtypes of migraine have been associated with chromosome 1 as well as chromosome 19.[59] However, they do not account for all familial forms of migraine, suggesting that one or more additional genes may be involved, including, in some cases, an X-linked gene. Additionally, mitochondrial abnormalities may play a part and also should be investigated further.

DIAGNOSIS OF MIGRAINE

IHS Classification of Headache Disorders

The systematic classification of headache disorders now in widespread use was developed in 1988 by the International Headache Society (IHS).[60] The IHS system identifies 6 different types of migraine or syndromes closely associated with migraine, as well as the migrainous category for patients who do not fit into the preceding 6 categories. The new system provides more descriptive names for 2 of the most important migraine types, migraine with aura, which replaces the old terminology of "classic" migraine, and migraine without aura, which replaces the term "common" migraine (Table 2).[60]

Definitions

In the IHS system, an aura is defined as the focal neurologic symptoms that usually occur immediately before or during headache. Typically, the aura lasts for approximately 20 to 60 minutes.[60] A migraine aura should not be confused with premonitory symptoms. Premonitory symptoms occur hours to days before an attack of migraine and may precede both migraine with and migraine without aura.

Diagnostic Criteria

Migraine Without Aura

The IHS defines migraine without aura as a recurring headache disorder with attacks lasting from 4 to 72 hours. The patient also must have had a history of at least 5 attacks to establish the diagnosis. The occurrence of repetitive attacks over time helps exclude secondary headache disorders, which can mimic migraine.

To meet criteria, episodes of migraine without aura are characterized by a pattern of pain and associated symptoms. At least 2 of the following pain features are required: unilateral location, pulsing quality, moderate or severe intensity, or aggravation through routine physical activity. In addition, the headache must have at least 1 of the following associated symptoms: nausea and/or vomiting or photophobia and phonophobia.[60]

TABLE 2

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	Ophthalmic 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

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):1-96.

Migraine With Aura

Migraine with aura is a recurring disorder characterized by focal neurologic symptoms that usually develop over 5 to 20 minutes and usually last less than an hour. These symptoms are usually followed by a headache with the feature of migraine without aura, though aura can occur without headache. Each episode of aura must be characterized by 3 of the following: reversibility of focal aura symptoms; gradual development of aura symptoms, ie, over 4 minutes, or 2 or more symptoms occur in short succession. No aura symptom last for more than an hour; and headache follows aura after no more than 60 minutes.[60]

Patients who have migraine with typical aura have all 4 characteristics. When only 3 of the characteristics apply, the patient's migraine is classified under 1 of the other subtypes for migraine with aura, such as migraine with prolonged aura, migraine aura without headache, or migraine with acute-onset aura.

Issues in Clinical Diagnosis

One challenge is differentiating visual aura from a transient ischemic attack or visual symptoms produced by cerebrovascular disease. This is particularly problematic in individuals over age 50, because cerebrovascular disease becomes more common and the headaches of migraine become less prominent. Typically, migraine aura affects only 1 side of the patient's body; involves symptoms that begin at 1 point and spread out gradually; and does not last longer than an hour, with headache usually following. The exact type of symptoms vary: Patients may have expanding visual display, with flickering or zigzagging edges, and scotoma, or an advancing sense of "pins and needles" (Table 3, page 8).[61]

TABLE 3

CLINICAL FEATURES FAVORING LATE-LIFE MIGRAINE VERSUS TRANSIENT ISCHEMIC ATTACKS

- Gradual appearance of focal neurologic symptoms with spread or worsening over a period of minutes
- Positive visual symptoms, such as scintillating scotoma or flashing or bright lights
- History of similar episodes associated with more severe headache
- Serial progression from 1 accompaniment to another (for example, from flashing lights to paresthesias, paresis, or dysphasia)
- Occurrence of 2 or more similar episodes
- Focal neurologic symptom duration of 15 to 25 minutes (as opposed to <15 minutes in 90% of headaches associated with transient ischemic attack)
- Characteristic "flurry" of accompaniments
- Usually benign natural history without permanent sequelae
- No other cause revealed by diagnostic testing performed when indicated

From Fisher CM. Late-life migraine accompaniments—further experience. *Stroke.* 1986;17:1033-1042.

Another potential challenge is distinguishing a migraine headache from another disorder, such as head trauma with migrainelike headaches. The decisive factor here is the temporal relationship between the headaches and the other disorder. Migraines that first occur immediately after trauma are considered secondary, posttraumatic headaches. However, if they occur 6 months or more after the head trauma, they are diagnosed as primary migraines, not secondary headaches.

Finally, in cases in which a patient has more than 1 type of headache according to IHS criteria, the recommended solution is to give him or her more than 1 diagnosis. In this way, the patient's headaches are all characterized without the need for a very broad category of headaches. However, since the patient's symptoms may change over time, only the headaches that the patient suffers at the time of diagnosis are considered in this manner.

Future Directions for Clinical Diagnostic Criteria

The second edition of the IHS classification system is now in development and will include a number of new diagnostic entities, as well as significant work on the classification of secondary headaches. In the future, perhaps in a third edition of the classification system, it may be possible to include more information about the genetics of migraine and to base more of the classification system on genetic principles.

Diagnostic Testing in Migraine

In most cases, the diagnosis of migraine can be correctly made based on a detailed history and examination without any testing at all. However, diagnostic testing can be valuable in certain instances, ie, distinguishing first-time migraine headaches from other pathologies (eg, subarachnoid hemorrhage), and when ruling out the possibility of structural neurologic abnormalities causing secondary headaches.

Electroencephalography

The only electroencephalographic (EEG) abnormality that is consistently found in patients with migraine is a prominent photic driving response at high flash rates (the "H response").[62] Based on a review of the literature, the Quality Standards Subcommittee of the American Academy of Neurology advised against using EEG to assess possible structural abnormalities in patients with migraine,[63] since head imaging techniques are superior for this purpose. EEG may be useful, however, for evaluating patients with headache who have symptoms of a seizure disorder.

Neuroimaging Studies

Two position papers have been published addressing the issue of neuroimaging for patients with migraine. The first, by the American Academy of Neurology,[64] stated that the routine use of neuroimaging is not warranted in an adult patient with recurrent migraine headaches if there has been no recent change in symptoms, no history of seizures, and no other focal neurologic signs or symptoms.

The second position paper, by the US Headache Consortium,[65] reached a similar conclusion. The authors stated that neuroimaging usually is not warranted for patients with migraine and a normal neurologic examination, as the prevalence of abnormalities is comparable to the general population. However, neuroimaging may be performed in patients with atypical headache features, symptoms that do not fit the strict definition of migraine, or other risk factors for secondary headache (Table 4).[65]

TABLE 4

EXAMPLES OF REASONS TO PERFORM NEUROIMAGING STUDIES IN HEADACHE SUFFERERS

Neuroimaging may be important for headache patients who have:

- Abnormal unexplained neurological exam
- 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 55
- Headache refractory to aggressive treatment

From Frishberg BM, Rosenberg JH, Matchar DB, et al. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. US Headache Consortium. Available at: http://www.aan.com.

White matter abnormalities are the most common type of pathology visualized on diagnostic magnetic resonance images of patients who meet the IHS criteria for migraine. The prevalence ranges from 12% to 46% compared with 2% to 14% for controls.[66,67,68] The clinical significance of these abnormalities for patients with migraines is unclear. They may represent an incidental finding or occur as a result of comorbidity. Nonspecific white matter abnormalities associated with migraine are sometimes confused with those of multiple sclerosis. Although variations in the appearance of these lesions can occur for both disorders, lesions related to multiple sclerosis are more likely to have a periventricular distribution, to have an oval (rather than round) shape, to have irregular margins, to be more than 6 mm in diameter, and to be found in the corpus callosum or infratentorium. In addition, there are numerous other causes of white matter abnormalities (Table 5).[69,70]

Lumbar Puncture

A diagnostic lumbar puncture is often performed for patients complaining of the sudden onset of headache, often an unusually severe headache, to rule out the possibility of a subarachnoid hemorrhage.

TABLE 5

POSSIBLE ETIOLOGIES OF WHITE MATTER ABNORMALITIES IN MIGRAINEURS

- Incidental
- Related to migraine
- Antiphospholipid antibody syndrome
- Vasculitis (systemic lupus erythematosus, Sjögren's syndrome, etc)
- Multiple sclerosis
- Stroke risk factors (high blood pressure, diabetes, hyperlipidemia, coagulopathies, etc)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes
- Infections (Lyme disease, HIV, HTLV-1, etc)

From: Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. *Headache.* 1996;36:616-621; Evans RW, Rozen TD, Adelman JU. Neuroimaging and other diagnostic testing in headache. In: Silberstein SD, Lipton RB, Dalessio, DJ, eds. *Wolff's Headache and Other Head Pain.* 7th ed. New York, NY: Oxford University Press, 2000:27-49.

TREATMENT OF MIGRAINE

Treatment Approaches

Migraine treatment is divided into nonpharmacologic and pharmacologic management. Nonpharmacologic management requires establishing and communicating a credible diagnosis and educating patients about their disorder. Patient education is needed to develop and maintain a strong working relationship between the patient and physician and to minimize the risk of medication abuse. Specific behavioral and physical interventions, including relaxation training, biofeedback therapy (often administered in conjunction with relaxation training), and cognitive-behavioral training (also known as stress-management training), are recommended by the US Headache Consortium as discussed below.[71]

Pharmacologic treatment is divided into acute and preventive. Acute treatment is used during an attack to minimize impact. Preventive treatments are used on a daily basis whether or not headache is present to reduce the occurrence of headache. The emphasis on therapy and the exact treatment combinations chosen depend on many factors such as the severity of headaches, their frequency, and their impact on the patient's functioning and quality of life.

Guidelines for Acute Treatment

According to evidence-based guidelines developed by the US Headache Consortium,[72] the goals of acute treatment are to treat migraine attacks rapidly and consistently without recurrence of pain from the acute attack; to restore the patient's ability to function; to optimize the patient's ability to provide self-care, thus reducing the use of outside health resources; and to minimize the use of backup and "rescue" medications for migraine. Ideally, these acute treatment goals are met in a cost-effective manner, with minimal or no adverse events from treatment.[72]

Medications that may be used as acute treatment of migraine include nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, the serotonin $5HT_{1B/1D}$ agonists (triptans), the ergot alkaloids, isometheptene and isometheptene-combination agents, prochlorperazine, and chlorpromazine or other dopamine antagonists. Additionally, antiemetic medications may be used to control nausea and vomiting. Opiates, intravenous (IV) dihydroergotomine (DHE), intravenous prochlorperazine, and IV metoclopramide may also be used as rescue medications, to provide relief in the event of an acute attack that is unresponsive to other interventions.

NSAIDs and Analgesics

The US Headache Consortium found consistent clinical trial evidence supporting the use of ibuprofen, naproxen sodium, tolfenamic acid, aspirin, and the combination agent acetaminophen plus aspirin plus caffeine for treating acute migraine.[72] The tolerability of these agents makes them a reasonable treatment choice for patients with mild to moderate attacks or even those with severe migraine if they have previously responded to NSAIDs and combination analgesics. It should be noted that the studies of ibuprofen in over-the-counter doses[73] and of aspirin plus caffeine[74] excluded patients who usually required bed rest with their headaches or who vomited more than 20% of the time.[73] As a consequence, these findings are applicable only to the less disabled segment of migraine sufferers who enrolled in these studies.[74]

Migraine-Specific Agents

Oral Triptans

The triptans are very effective in treating migraine and are quite safe for appropriately selected patients. However, in clinical practice, the use of triptans is often delayed. The step-care strategy requires that patients with acute attacks begin treatment at the bottom of the therapeutic pyramid with simple analgesics and escalate treatment through a series of steps on a trial-and-error basis. Specific medications such as triptans are used only when the initial treatments fail. The value of step care has been questioned by the US Headache Consortium. A recent study showed that as headache-related disability increased, the benefits of aspirin plus metoclopramide declined; among patients in the highest disability group, aspirin plus metoclopramide was effective only in one quarter of migraine sufferers.[10] In another arm of this study, triptans were given to more disabled patients as the first intent (stratified care). Stratified care led to better outcomes than the step-care approach.[10] This supports the US Headache Consortium's rejection of the most restrictive form of step care as clinical policy.[75]

All triptans are $5HT_{1B/1D}$ agonists, which inhibit the release of vasoactive peptides and cause vasoconstriction and inhibition of nociception within the brainstem. The first marketed triptan, sumatriptan, was introduced in 1991 in the Netherlands and is considered the therapeutic standard for the subsequent triptans. Zolmitriptan and naratriptan were FDA approved in 1997 and rizatriptan in 1998. At least 3 more triptans, eletriptan, almotriptan, and frovatriptan, are currently under evaluation. Though all triptans share a similar mechanism of action, they possess different pharmacokinetic profiles, which may affect headache response, recurrence rates, and tolerability. Although statistically significant differences may be achieved between different agents and/or doses, the clinical relevance of these differences is not clear. Firm conclusions on a differential efficacy among the various triptans cannot be established at this time.

Nonoral triptans

Though most patients with migraine prefer oral tablets,[9] 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 subcutaneous (SC) injection, nasal spray, or suppository. The US Headache Consortium recommends consideration of nonoral therapy for patients with prominent nausea or vomiting.

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 (PDR, 2000). Sumatriptan is also available as a nasal spray, which probably has a more rapid onset than the tablet.[76] Zolmitriptan may soon be available as a nasal spray.

Ergot Alkaloids

Ergot alkaloids and derivatives include ergotamine in oral or rectal formulations and in formulations combined with caffeine; SC, IV, or intramuscular (IM) DHE; IV DHE plus IV antiemetics; and DHE nasal spray. Oral or rectal ergotamine—and its caffeine combination—may be used for selected patients with moderate to severe migraine. However, evidence that supports its efficacy is somewhat inconsistent, and the incidence of adverse events is higher than with sumatriptan or NSAIDs. SC, IV, and IM DHE are all possible choices for patients with acute migraine, especially those with nausea and vomiting severe enough to prevent the ingestion of oral medications.

According to the US Headache Consortium,[72] SC or IM DHE may be a reasonable choice as initial therapy for patients with a moderate to severe episode of acute migraine, particularly if they have failed to find relief with NSAIDs or other nonnarcotic analgesics in the past. With respect to adverse events, SC DHE is better tolerated than IV DHE. For patients with severe migraine, IV DHE (with an added antiemetic) is effective and reasonably safe, compared with the administration of IV opiates, and represents an appropriate treatment choice. DHE nasal spray is a more recently developed formulation that has been found to be safe and effective for acute migraine. It may be prescribed for patients with moderate to severe migraine and may be especially appropriate for patients unable to tolerate oral medications because of nausea and vomiting.

Other Medications for Acute Migraine

In studies reviewed by the US Headache Consortium,[72] isometheptene-containing compounds were found to be more effective than placebo, with a small but statistically significant difference. They are well-tolerated agents and may therefore be useful for patients with mild to moderate acute migraine headaches, even based on this relatively modest finding of efficacy.

Oral opiate combinations may be considered for use in acute migraine. However, sedation side effects must be taken into account, and the risk of opiate abuse must be addressed and minimized. Parenteral opiates may serve as "rescue" medications, but the same issues must be considered and risk to the patient prevented or minimized. Butorphanol nasal spray, a newer opiate formulation, represents a treatment option for some patients with migraine. However, its use must also be limited because of its established risk of overuse and dependence.

Two agents that may be used as adjunct therapy for treating acute migraine and considered individually as monotherapy—based on clinical evidence reviewed by the US Headache Consortium—are IV metoclopramide and IV, IM, or rectal prochlorperazine. Oral antiemetics may be used as adjunct therapy in the treatment of patients with acute migraine but are not used as monotherapy.[72]

Guidelines for Preventive Treatment

The goals of preventive treatment, according to the US Headache Consortium,[77] are to reduce the frequency, severity, and duration of migraine attacks; to improve the patient's responsiveness to acute medication; to improve function; and to reduce disability. Migraine prophylaxis may include either pharmacologic or nonpharmacologic treatment. It is indicated for migraine that has a substantial impact on a patient's life, when attacks do not respond to acute therapy or when the frequency of attacks is so high, ie, more than 2 attacks per week, that acute treatments would be overused, raising the risk of rebound headache. Prophylaxis is also indicated for conditions such as hemiplegic migraine, migraine with prolonged aura, basilar migraine, and migrainous infarction.

In general, migraine prophylaxis should be attempted using medications with the highest level of efficacy, based on evidence, at the lowest effective dosage. Prophylactic medication should be titrated until a benefit is apparent or until therapy must be curtailed because of adverse events. An adequate trial of medication is essential, since treatment benefits for most agents develop gradually over weeks to months. Many patients prematurely discontinue a prophylactic medication after the first instance of breakthrough headache. Therefore, patient expectations must be shaped so that patients will adhere to an adequate treatment trial. Use of long-acting formulations may help improve compliance (Table 6).[78]

TABLE 6

PREVENTIVE THERAPIES FOR MIGRAINE

	Clinical Impression of Effect* (0, +, ++, ++++)	Adverse Effects (Infrequent, Occasional, Frequent)
Antiepileptics		
Divalproex Sodium	+++	Occasional to frequent
Gabapentin	++	Occasional to frequent
Topiramate	++	Occasional
Antidepressants		
Amitriptyline	+++	Frequent
Fluoxetine	+	Occasional
β-Blockers		
Propranolol	+++	Infrequent
Atenolol, Timolol	++	Infrequent
Calcium Channel Blockers		
Diltiazem	0	Occasional
Verapamil	+	Occasional
NSAIDs		
Aspirin	+	Infrequent
Naproxen	++	Infrequent
Serotonin Antagonists		
Methysergide	+++	Frequent

Data from Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, and Frishberg B. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: http://www.aan.com.

***Clinical impression of effect**

0 Ineffective: most people get no improvement

\+ Somewhat effective: few people get clinically significant improvement

++ Effective: some people get clinically significant improvement

+++ Very effective: most people get clinically significant improvement

Patients should not be given medications that could interact with other drugs that are being taken for migraine or other disorders. The physician should monitor both the patient's tolerance to the prophylactic medication and the extent to which headache frequency is reduced. If headaches are adequately controlled, consider tapering and discontinuing the medication. Ideally, a preventive medication that treats both migraine and any existing comorbidities, and that is not contraindicated by the presence of comorbidities, should be selected. Careful attention should be paid to potential drug interactions and to the possibility of pregnancy in female patients of reproductive age.

Many of the migraine drugs now available and used to prevent headache were originally discovered through serendipity. For example, the efficacy of antidepressants in migraine prophylaxis was recognized consequent to their use in depressed patients who also had migraine headache. In the late 1960s, it was found that the β-blocker propranolol could be used not only for angina but also for the prevention of migraine. Additional therapeutic agents were discovered as the pathophysiology of migraine became better understood.

β-blockers

β-adrenergic blocking agents have long been used in migraine prophylaxis. They are well-studied medications that have shown consistent efficacy for more than 30 years. Propranolol and timolol are first-tier migraine-preventive med-

ications that have demonstrated the highest level of efficacy among β-blockers in controlled trials. All lack partial agonist activity. Other β-blockers, including atenolol, metoprolol, and nadolol, have been shown to be effective, though evidence from controlled trials is less rigorous.[78]

β-blockers are particularly useful for patients with a cardiovascular indication for β-blockers as well as those with anxiety disorders. Propranolol may have a carryover effect for the prevention of migraines that can extend after drug discontinuation. Disadvantages of β-blockers include adverse events such as fatigue, depression, sleep disturbances, and decreased exercise tolerance; therefore β-blockers may not be optimal drugs for athletes. They are contraindicated for patients with comorbid depression, diabetes mellitus, and asthma.[78]

Calcium Channel Blockers

Verapamil is the best-studied calcium channel blocker available in the United States and has been shown to be mildly effective. Calcium channel blockers are a good alternative for patients with contraindications to β-blockers and are useful for patients with comorbid cardiovascular disease. Verapamil is less effective than β-blockers or amitriptyline.

Nicardipine and nifedipine are not effective for migraine prophylaxis, and nimodipine is cost-prohibitive. Flunarizine, an effective calcium channel blocker for migraine prophylaxis, is not available in the United States. Constipation is an adverse effect of verapamil; the adverse events most commonly associated with flunarizine are sedation, weight gain, abdominal pain, and depression.[78]

Antidepressants

TCAs. Amitriptyline is one of the most widely studied and used TCAs in migraine, with efficacy comparable to that of propranolol. Dosage of TCAs for migraine prophylaxis is generally lower than that needed to treat depression. This may help improve tolerability and patient compliance. The main disadvantage of TCAs is their potential for significant adverse events due to their anticholinergic, antihistaminic, and α-adrenergic properties. Adverse events include weight gain, dry mouth, mental clouding, reflex tachycardia, orthostatic hypotension, sedation, and blurred vision. Understanding the differences in the pharmacology of the various TCAs is important for optimal patient management.[78]

Selective Serotonin Reuptake Inhibitors (SSRIs). The SSRIs, including fluoxetine, have been studied for migraine prophylaxis with mixed results. Their widespread use for this purpose may stem from their superior tolerability compared with TCAs and the frequency of their use for psychiatric disorders in general practice. There is little or no evidence, however, that SSRIs are effective in migraine prophylaxis in placebo-controlled trials.[77,78,79]

Serotonin Antagonists (Methysergide)

Methysergide has been demonstrated to be effective for migraine prophylaxis in clinical trials. However, it is associated with a number of adverse events and carries a risk of retroperitoneal, cardiac, and pulmonary fibrosis after continuous use for more than 6 months. As a consequence, methysergide is restricted primarily to patients with refractory migraine, episodic cluster headache, and menstrual migraine. In these situations, it is used primarily on a short-term basis.[80]

NSAIDs

NSAIDs, including aspirin, may be given as preventives, in addition to their common use as therapy for acute migraine. Their efficacy in prevention is comparable to that of β-blockers. They may be effective as interval therapy in menstrual migraine, and they are useful for patients with comorbid arthritis and in the prevention of cardiovascular disease. Despite this advantage, their use in migraine has been limited by their potential for inducing gastrointestinal bleeding and renal or hepatic dysfunction with long-term use.[78]

Anticonvulsants

The following information discusses both current and emerging, novel treatments in the management of migraine. The results of ongoing trials are promising in establishing these agents as first-line choices in migraine prophylaxis.

Divalproex sodium. Divalproex sodium is a 1:1 mix of sodium valproate and valproic acid. Its mechanism of action in treating headache is unknown but is presumed to be a function of its influence on γ-aminobutyric acid (GABA). This substance is known to increase GABA synthesis and decrease GABA degradation. Accordingly, it may have an inhibitory influence on brain sensitivity or excitability. Divalproex has been available in the United States since 1983, initially as an anticonvulsant and then as a treatment for mania. It was approved for migraine prophylaxis in 1996.

In 4 large-scale clinical trials of divalproex for the prophylaxis of episodic migraine, a positive effect for divalproex compared with placebo was consistently found.[81,82] Forty-three percent to 50% of patients will achieve a 50% or greater reduction in the frequency of headaches. The presence or absence of aura is not helpful in predicting the effectiveness of divalproex therapy for an individual patient.[81]

Three doses of divalproex have been demonstrated to be effective for migraine prophylaxis in clinical trials: 250, 500, and 750 mg, all given BID. No clear dose-response relationship was noted. Clinical experience, however, suggests that a partial response to a low dose of divalproex may be improved if the dose is increased. Drug response is usually evident within 4 to 6 weeks of initiation of therapy. Relatively few patients who fail to show even partial response during that period will report improvement if the treatment is continued, even at a higher dose.[83] (See also *PDR, 2001*).

Approximately 20% of patients discontinue therapy because of intolerance.[83] The side effect most commonly reported in the first few weeks after initiating treatment with divalproex is nausea. Alopecia, tremor, and weight gain are other adverse events that may lead to discontinuation of therapy. Rare, serious adverse events that can occur with divalproex include hepatotoxicity and pancreatitis.[83]

In summary, divalproex is an effective option in the treatment and prevention of migraine. Patients with only a partial response to divalproex may benefit if the dose is increased, but those unresponsive to treatment may not improve at higher doses. As with all medications, the adverse-event profile of divalproex should be factored into its therapeutic utility in migraine prevention.

Gabapentin. Gabapentin is an antiepileptic approved for the treatment of partial seizures. Currently, gabapentin's label does not include an indication for migraine. Gabapentin structurally resembles GABA but is not a GABA mimetic and does not exert any action at GABA receptors. It is known to enhance the conversion of glutamate to GABA in the brain; unlike GABA, gabapentin crosses the blood-brain barrier.[84]

Gabapentin has 2 properties relevant to the treatment of migraine: It is an anticonvulsant and it is antinociceptive. The mechanisms of its antinociceptive effect are unclear. Gabapentin binds to a membrane-associated protein, now believed to be an alpha (2) delta subunit of a voltage-dependent calcium channel. Gabapentin therefore may inhibit neurotransmitter release and total cellular calcium content in neurons.[84]

A 12-week double-blind study of gabapentin and migraine, involving 7 US study centers, was conducted. The dosage of gabapentin was initiated at 300 mg per day and titrated up to 1800 or 2400 mg per day. A total of 110 patients completed the study; 74 were treated with gabapentin and 36 received placebo.[85]

A modified intent-to-treat analysis showed that 46.4% of patients receiving a stable dose of 2400 mg/day of gabapentin had at least a 50% reduction in the 4-week migraine headache rate compared with 16.1% of patients receiving placebo (P=0.008). The most common adverse events reported in patients receiving gabapentin were somnolence (24.5%), dizziness (25.5%), and asthenia (22.4%). A total of 13 patients in the gabapentin group and 3 in the placebo group discontinued the trial because of adverse events. One patient in each group withdrew because of treatment failure.[85]

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, with few drug interactions.

Topiramate. Topiramate is indicated as adjunctive treatment for partial onset seizures and primary, generalized tonic-clonic seizures in adults and children over 2 years of age. At the time of this publication, topiramate was not FDA approved for the treatment of migraine. Topiramate has multiple mechanisms of action. It blocks voltage-activated sodium and L-type calcium channels, enhances the activity of the inhibitory neurotransmitter GABA, inhibits the excitatory neurotransmitter glutamate at AMPA/kainate receptors, and inhibits some isoenzymes of carbonic anhydrase.[86]

The efficacy and safety of topiramate for migraine were evaluated in 2 randomized, placebo-controlled, double-blind trials with patients who had migraine with or without aura.[87,88] Topiramate was started at 25 mg/day and titrated up to a target dosage of 200 mg/day, or the highest tolerated dose.

In the first study, involving 30 patients,[87] 47% of patients taking topiramate experienced a 50% or greater reduction in migraine frequency compared with 7% in the placebo group (P=0.035). The most frequently reported adverse events with topiramate were paresthesias (60%), diarrhea (27%), altered taste (20%), and somnolence (20%). Topiramate-treated patients also experienced a mean weight loss of 6.2 pounds. Four patients in the topiramate group discontinued the study prematurely because of adverse events.[87]

In the second study, 40 patients were enrolled.[88] Twenty-six percent of the topiramate treated patients and 10% of patients who received placebo experienced a reduction of at least 50% in headache frequency (P=0.226). Adverse events were generally mild. Paresthesias (68%), altered taste (37%), anorexia (21%), and memory impairment (21%) were the most commonly reported adverse events in the topiramate group. Weight loss was observed in 53% of patients taking topiramate (n=10). Patients lost an average of 4.9 pounds.[88] Two patients in the topiramate group withdrew from the study because of adverse events.

These pilot studies suggest the safety and efficacy of topiramate for the prevention of migraine. Multicenter placebo-controlled trials are under way for further evaluation.

Behavioral and Physical Therapies

Relaxation therapies and biofeedback reduce sympathetic neural outflow and muscle activity in patients with migraine. Neurofeedback is being used increasingly to control neuronal hyperresponsiveness. These techniques also provide migraine patients with a sense of control over their disorder.[71,89]

Cognitive behavior, or stress-management therapies, are largely directed at reducing self-generated stress, which may precipitate or aggravate migraines or impair the patient's coping skills between migraines. These alternative techniques have been found to result in a 30% to 50% reduction of migraine attacks. In addition, investigators found that thermal-biofeedback methods have an efficacy comparable to that of propranolol (plus analgesics) in the prevention of migraine.[71]

Chronic Migraine

Chronic daily headache is an umbrella term that encompasses the disorders of CM, chronic tension-type headache, new persistent daily headache, and hemicrania continua. The IHS has recently agreed to consider validating by future studies the above subclassification of chronic daily headaches. The daily pain of CM is generally of moderate intensity, but superimposed acute migraine attacks are common. CM affects approximately 4% of the general population and up to 80% of headache clinic populations.[90]

In most patients with CM, the headache gradually evolves from a progressive pattern of intermittent or episodic migraine that first presents at 20 to 30 years of age to the full-blown syndrome. This consists of daily or almost-daily mild to moderate headache and neck or face pain accompanied by episodes of acute migraine.

The pathophysiology of this progression is largely unknown. There may be a genetic component involved, and environmental stressors may have an impact on the pathologic mechanism of the disorder within the brain. This mechanism most likely involves a cortical input to the brainstem nociceptive system.

Diagnosis of CM

The history is an essential part of the workup for CM. Typically, the patient interview will often elicit a positive family history of headache, depression, anxiety, panic disorders, or alcoholism.[91] CM shares many comorbidities with migraine, including depression, anxiety, panic disorder, obsessive-compulsive disorder, bipolar disease, irritable bowel syndrome, sleep disturbances, and fibromyalgia. Medication overuse is present in up to 80% of cases and may result in secondary complications, including gastritis and renal insufficiency from NSAID overuse.[91] Very rarely, fibrotic disease of the retroperitoneum occurs as a result of ergot overuse (Table 7).[91]

TABLE 7

TYPICAL FEATURES OF CHRONIC MIGRAINE

- Comorbidities
  - – Depression, anxiety, panic disorder
  - – Psychophysiologic sleep disturbance
  - – Irritable bowel syndrome, fibromyalgia
- Potential secondary illnesses
  - – Gastritis
  - – Renal insufficiency
  - – Other
- Family history of headache
  - – Depression
  - – Anxiety
  - – Alcoholism
- Medication overuse in 30% to 80%
  - – 30% in population sampler of chronic daily headache
  - – 80% in subspecialty clinic
  - – Cause or effect?
  - – Predictable, unavoidable need for medication
  - – Withholding/delay of medication worsens headache
- Decreased health-related quality of life

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

No diagnostic studies specifically establish a diagnosis of CM, but since it is an atypical form of headache, structural neurologic abnormalities should be ruled out. Neuroimaging may be used to exclude pathology such as cerebral vein thrombosis, Arnold-Chiari malformation, cervical disease, and meningioma.[92]

Treatment of CM

Patient management should take into account the need for treatment of rebound headache due to medication overuse as well as any comorbid neuropsychiatric disorders that may be present.[91] Rebound headaches consist of increasingly frequent headaches followed by escalating medication use. Before the patient can be expected to respond to more appropriate therapy, the rebound cycle must be ended by discontinuing the medication with adequate preparation for adverse events related to withdrawal. Alternate treatments should be substituted during the period of withdrawal.

CM should be treated primarily with prophylactic therapy.[91] However, until the overused medications have been tapered, preventive therapy may not be effective.[93] Preventive treatments include antidepressants, β-blockers, anticonvulsants, calcium channel blockers, methysergide, and other medications, alone or in combination.

In addition to pharmacotherapy, supportive and behavioral psychotherapy, patient education, and lifestyle changes such as improvement of diet, exercise, and sleep patterns are important for an optimal outcome. For acute, severe CM exacerbations, outpatient therapy with sumatriptan and DHE may be useful for patients who do not overuse medication. Hospitalization may be considered for patients with refractory CM.

CM is a disorder that is difficult to treat. With the best of care, approximately 75% of patients show a prolonged benefit. Continuity of care and frequent physician visits are important in preventing relapse.

CLUSTER HEADACHE

Cluster headache is widely considered to be the most painful headache disorder. The term "cluster" is used to describe the way in which the attacks recur on a daily basis for a period of weeks or months ("cluster periods"), with attack-free remission periods lasting for months to years in between.[60]

The prevalence of cluster headache in the general population is between 0.1% and 0.4%.[94] Unlike migraine, it is a predominantly male disorder with a male-to-female ratio of approximately 4:1. The mean age of onset is 27 to 31 years, and research suggests that genetics may play a role. Individuals with first-degree relatives who suffer from cluster headaches have a 14-fold increased risk of developing the disorder compared with the general population.[95]

Clinical Characteristics of Cluster Headache

Perhaps the most singular feature of cluster headache is its circadian and "circannual" periodicity. Cluster periods usually last about 2 months but may have a duration of between 4 and 16 weeks, with 1 to 2 cluster periods per year. Approximately one third of patients have peak incidences occurring most often within 2 weeks of the summer and winter solstices. The incidence is typically decreased within 2 weeks after the start of Daylight Savings Time, suggesting that headaches are related to the amount of daylight exposure.[94]

Most patients suffer between 1 and 3 attacks, up to as many as 8 attacks per day, and have consistent periods when attacks usually occur. Cluster headaches have a predilection for occurring during sleep. Most patients have almost exclusively unilateral attacks, although attacks may alternate sides between cluster periods or even within the same period. In contrast to migraine, peak intensity is usually maximal at 5 to 15 minutes, and the duration of the headache is about 60 minutes. Unlike migraine patients, who prefer to remain motionless, patients with cluster headache are usually very agitated.[94,96]

Pathophysiology

Premonitory symptoms such as nausea, photophobia, phonophobia, and even visual aura have been reported to precede cluster headache, suggesting a shared underlying pathobiology with migraine or a common final pathway for expression of these disorders. Most patients have autonomic signs such as conjunctival lacrimation, nasal congestion and rhinorrhea, or a partial Horner's syndrome during attacks. These autonomic signs are invariably confined to a trigeminal distribution. Growing evidence suggests that the pain and autonomic symptoms result from dual activation of the trigeminal and cranial parasympathetic systems.[94]

The circadian and rhythmic periodicity of these headaches suggests that they may be due to a disorder of the hypothalamic pacemaker—the suprachiasmatic nucleus located in the hypothalamus. This hypothesis is supported by the finding of altered circadian rhythm of hypophyseal-pituitary hormone release in patients with cluster headaches. Furthermore, the secretory rhythm of melatonin has been shown to be dysregulated in patients with cluster headache. This rhythm is regulated by the suprachiasmatic nucleus, which controls the synthesis and secretion of melatonin from the pineal gland. In addition, positron emission tomography studies have demonstrated ipsilateral hypothalamic activation during cluster attacks.[97]

Treatment of Cluster Headache

Successful treatment of cluster headache follows many of the same principles that apply to most headache disorders. However, the rapidity of onset and the short latency-to-peak intensity warrant rapid-acting therapy. Ergotamine and intranasal lidocaine are inconsistently effective and do not provide sufficiently rapid pain relief to most patients. Zolmitriptan has been investigated for these patients but does not appear to provide strong evidence of efficacy.

Oxygen is the standard recommended therapy for cluster headache, with 7 to 10 L/min of 100% oxygen administered for 15 minutes achieving pain relief in approximately 70% of patients.[98,99] Oxygen appears to be most effective when the headache is at maximal intensity but may delay rather than abort the attack in some patients and is not readily accessible.

SC sumatriptan is the most effective of the self-administered acute treatments for cluster headache. It is effective in both episodic and chronic cluster headache, although patients with the episodic disorder respond more quickly. Most patients respond to this medication within 15 minutes.[100-102]

The importance of an effective preventive regimen for cluster headache cannot be overstated. The primary goals of preventive therapy are to produce rapid suppression of attacks (transitional therapy) and to maintain suppression over the expected duration of the attack (maintenance therapy).

Prednisone will quickly suppress headaches while a maintenance prophylactic agent is initiated and allowed to take effect. A large, open-label study reported marked relief in 77%, and partial relief in 12% of patients treated with prednisone.[94] Verapamil is considered by many to be the agent of choice for preventive therapy over the expected duration of the cluster period. Significant improvement has been demonstrated in both open-label and double-blind placebo-controlled trials.[103,104]

In more than 28 studies examining lithium as prophylaxis, efficacy was observed in approximately 78% of patients with chronic cluster headache but in fewer patients (approximately 63%) with episodic cluster.[100] Divalproex, with an observed response rate of 73% in patients with cluster headache, is being used with increasing frequency, since some of the other available agents may limit the use of sumatriptan because of the potential for drug interactions. For example, methysergide it often not used in combination with sumatriptan.[96] Melatonin and topiramate have both shown promise in this setting, but additional corroborative data are needed.

Methysergide is an effective prophylactic drug for the treatment of cluster headache, but because of the potential for fibrotic complications, it is not commonly used for more than 3 months.[96]

Combination therapy may be necessary in refractory cluster headache. The most effective combinations, according to the consensus reached at the 9th International Headache Research seminar in Copenhagen, Denmark, are (in order of efficacy) lithium and verapamil, methysergide and verapamil, methysergide and valproate, or methysergide and lithium. Verapamil and valproic acid or verapamil and topiramate are also potentially effective combination treatments (personal communication, D.W. Dodick, MD, June 2000).

If these treatments fail, patients may be referred to a tertiary center where they may be treated with IV DHE or IV methylprednisolone. Surgery may be considered as a last resort for patients who have genuinely intractable headaches, or who develop intolerable side effects. However, surgery, most often consisting of radiofrequency trigeminal rhizotomy is only an option in patients with unilateral disease.

CONCLUSIONS

One in 4 US households has a migraine sufferer. The disorder affects patients in their most productive years and costs American employers about $13 billion per year because of missed work and decreased productivity.

A number of psychiatric and neurologic disorders are commonly found to be associated with migraine, including major depression, personality and anxiety disorders, epilepsy, and sleep disturbances. Some of these conditions share similar characteristics with migraine; for example, both migraine and epilepsy can cause headache and alterations in mental status. Some ischemic strokes may be caused by prolongation of the pathophysiologic event associated with ongoing migraine.

Migraine is underdiagnosed and undertreated in the United States and around the world. Keys to improving diagnosis and treatment include (1) encouraging more disabled migraine sufferers to seek medical care; (2) improving communications between clinicians and patients; and (3) treating more disabled migraine sufferers more aggressively.

The development of a migraine headache appears to be based on a cascade of events occurring in susceptible individuals. Cortical spreading depression and/or trigeminal activation seem to result in a migrainous episode that can last for hours. Researchers are only beginning to understand and investigate the potential opportunities for interrupting these events to prevent or end an episode of migraine.

Studies of the *CACNA1A* gene and familial hemiplegic migraine suggest that migraine may be a channelopathy with dysfunction of the P/Q-type calcium channel. However, other genetic links remain to be investigated.

The IHS classification system and diagnostic criteria represent a useful basis for standardizing descriptions of and references to different types of migraine and for unequivocally diagnosing migraine that may or may not manifest itself with classic signs and symptoms.

The management of migraine includes the use of both acute and prophylactic treatment. Acute treatment is used to alleviate pain and, ideally, abort the migraine attack. Therapeutic targets of acute drug treatments include meningeal blood vessels and central or peripheral neuronal pathways by which migraine is stimulated and propagated.

Preventive treatment for migraine is intended not only to reduce the frequency, severity, and duration of migraine attacks but also to improve the patient's function and to reduce disability. In addition, the use of an effective preventive treatment may increase the patient's responsiveness to acute therapy. A better understanding of the mechanisms of prophylactic migraine drugs should help us learn more about the details of migraine pathogenesis.

Cluster headache is a severe, episodic disorder widely considered the most painful type of headache. Oxygen, the standard recommended acute therapy, is not readily accessible to most patients; other acute drug therapy may be used as an alternative. Prophylactic therapy is very important in the management of cluster headache.

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21st CENTURY PREVENTION AND MANAGEMENT OF MIGRAINE HEADACHES

POSTTEST/EVALUATION FORM

If you wish to receive CME credit for your participation in this program, you must complete both the posttest and evaluation form. You can do this by reviewing the learning objectives to determine if the newsletter's content relates to your individual learning needs. Read the newsletter carefully, and pay 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 along with a check for $15.00 made payable to Jefferson Medical College to: **21st Century Prevention and Management of Migraine Headaches, Jefferson Medical College of Thomas Jefferson University, Office of Continuing Medical Education (NEGN02XNIH-NEWS) Jefferson Alumni Hall, Suite M32, 1020 Locust Street, Philadelphia, PA 19107-6799.** Be sure to mail the CME Registration Form and the Answer Sheet on or before August 2003. After this date, the newsletter will no longer be designated for credit. CME Registration Forms received after the date listed cannot be processed. For questions regarding this posttest and/or evaluation, please call 888-JEFF-CME.

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POSTTEST ASSESSMENT

1. Within the United States, migraine affects nearly 1 in every ___ households.
   a. 20 b. 10
   c. 4 d. 2
2. With respect to gender prevalence and migraine:
   a. More men than women are affected by the disorder, with a ratio of 3 to 1
   b. A roughly equal prevalence is found between men and women
   c. More men suffer from the disorder, but more women seek medical attention for it
   d. More women than men are affected by the disorder, with a ratio of 3 to 1
3. After the onset of migraine, more than one third of sufferers experience:
   a. Hospitalization and inpatient treatment until the attack subsides
   b. Panic attacks
   c. Severe functional disability, including imposed bed rest
   d. Severe pain with essentially no decrease in productivity
4. What percentage of patients with migraine experience aura?
   a. 15% b. 50%
   c. 30% d. 75%
5. Familial hemiplegic migraine is a rare, inherited subtype of migraine that:
   a. Clearly demonstrates the typical course of migraine
   b. Has been linked to mutations in the *CACNA1A* gene on chromosome 19
   c. Refutes the idea that migraine may be associated with abnormalities in ion channels within the central nervous system
   d. Is usually confused with cluster headache
6. Typically, migraine aura:
   a. Affects only 1 side of a patient's body
   b. Involves symptoms that begin at 1 point and spread out gradually
   c. Does not last longer than about 1 hour, with headache often following
   d. a and b e. All of the above
7. Agents with proven efficacy that have been recommended by the US Headache Consortium for migraine prophylaxis include:
   a. Amitriptyline b. Divalproex
   c. Propranolol d. a and c
   e. All of the above
8. Which of the following is characterized by increasingly frequent headaches followed by escalating medication use?
   a. Episodic migraine b. Rebound headache
   c. Episodic cluster headache d. Chronic cluster headache
9. Topiramate is being studied for its effectiveness in:
   a. Episodic migraine with and without aura
   b. Chronic daily headache
   c. Depression and anxiety that are co-morbid with migraine
   d. a and b
   e. All of the above
10. Which of the following are properties of gabapentin that are relevant to its use in the treatment of migraine?
    a. It is an anticonvulsant b. It inhibits GABA synthesis
    c. It is an antinociceptive d. a and b
    e. a and c

PLEASE RECORD YOUR POSTTEST ANSWERS:

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

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

EVALUATION

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 the 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 1 of the following best describes a change you might consider making in your practice as a result of this activity? Pleases circle only 1 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 (highest) to 1 (lowest), how committed are you to making the changes?
   5 (highest) 4 3 2 1 (lowest)
10. What comments do you have and/or improvements, if any, would you recommend?
    _____
    _____
11. How would you like to receive continuing medical education information? On a scale of 5 to 1, please score each of the following: 5 = very useful; 3 = somewhat useful; 1 = don't use:
    _____ a. Newsletter _____ d. Monograph/Journal Supplement
    _____ b. Videotape _____ e. Symposium/Conference
    _____ c. Audiotape _____ f. CD-ROM/Computer-Based
12. Do you believe such materials, sponsored by educational grants from industry, are:
    _____ 10 very appropriate/useful, 0 not appropriate/useful?
13. Actual amount of time I spent in this activity: ____ 1-hour ____1.5 hour ____2 hours

Name (please print) _____ Degree _____

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I attest to having completed this CME activity.

_____
Signature (required)

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