Recent Advances in Migraine Management

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Migraine periodically disables millions of Americans and thus has a significant economic impact on society. Successful treatment of migraine requires that the physician understand the pathophysiology underlying migraine and educate the migraineur in the management of this chronic pain syndrome. Recent advances in the receptor biochemistry of serotonin have given important insight into the mechanisms of migraine pain and treatment. An understanding of these mechanisms has resulted in treatment strategies that address the mechanism of headache control rather than just symptom control. Advances in pharmacologic therapy include a newly developed highly selective serotonin agonist called sumatriptan, which appears to be a promising addition to the armamentarium of abortive migraine treatments. Further data correlating the role of daily analgesics and ergotamines in transforming episodic migraine into chronic daily headache represent another significant advance in migraine management. Clinical trials of sumatriptan are reviewed, and the role of daily analgesic and ergotamine use is discussed in relation to advances in migraine pathophysiology and available demographic data on migraine.

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Migraine is a disabling condition afflicting millions of Americans, and its prevalence has increased more than 60% during the last decade.[1] Recent demographic data suggest that 17.6% of the adult female population and 5.7% of the adult male population suffer from migraine.[2] These figures reflect considerable personal suffering and substantial cost to society. The estimated annual cost of work absenteeism because of migraine is $5 to $7 billion.[3] Diagnostic tests, treatment, and decreased productivity of workers who suffer migraine attacks add billions more to this cost. Headaches account for 10 million office visits to physicians each year.[4] Family physicians are the specialists most commonly consulted by patients for headache care.[5]

Despite these impressive facts, migraine remains a significantly underdiagnosed and undertreated medical condition.[6] Only one third of migraineurs use prescription medication to treat their migraine, and almost one half will abandon these therapies once they are prescribed.[6] There is a high degree of dissatisfaction among the migraine population regarding their therapy. In a recent consumer survey of migraine sufferers, nearly three fourths of the patients expressed dissatisfaction with their medical encounters, mainly because of the ineffectiveness of prescribed therapy or perceived bias against these patients by physicians.[7]

Headache is a nearly universal human experience, and people often assume that their headaches are similar to those of the migraine sufferer. However, migraine is a systemic disorder quite different from the common headache. This confusion has led to many deeply ingrained biases regarding migraine. Migraineurs are frequently misunderstood by families, friends, and employers. Frequent, unpredictable attacks of migraine that result in absence from work or social functions can create feelings of isolation and inadequacy. Over time, migraineurs can experience loss of self-esteem, anxiety, and recurrent bouts of depression.[8] Society may reinforce these dynamics, as evidence suggests a downward socioeconomic stratification for the chronic migraine sufferer.[9] The stereotype of migraine being an illness of high-functioning, upwardly mobile women is clearly untrue. Migraine is more common in lower socioeconomic groups, is more prevalent in the prime working years of a person's life, and afflicts a significant percentage of both men and women.[9]

Natural History of Migraine

The course of a migraine attack can be divided into several distinct phases, which aids the clinical understanding of this disorder. In addition, there is an observed transformation of episodic migraine attacks into a

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more chronic headache pattern. Researchers now propose a "headache spectrum" with migraine and tension headache represented on opposite ends, but arising from a common biologic origin.[10]

Prodrome

The earliest clinical phase of migraine is called the *prodrome*. This phase consists of subtle changes in neurologic function that precede the onset of headache. Prodromes are observable in 50% to 80% of migraineurs during the 24-hour period prior to headache.[11(pp4–7)] It is believed that these subtle changes in neurologic functioning reflect the early neurochemical changes associated with the migraine process. The most commonly noted symptoms are decreased activity, changes in mood, depression, euphoria, food craving, repetitive yawning, and fluid retention.[11(pp4–7)] Patients are often reluctant to volunteer these symptoms to physicians, as they fear they may be viewed as having psychological problems.

Aura

As central dysmodulation proceeds, abnormalities in cerebral blood flow may precipitate focal neurologic disturbances. This can result in a so-called aura. The commonly quoted occurrence of aura is 10% to 15%, but this may be a misleading underestimation of neurologic disturbances associated with migraine.[11(pp4–7)] Earlier theories suggested that the aura was the result of focal areas of cerebral ischemia.[12] However, recently it has been proposed that aura results from a spreading wave of cortical neuronal depression secondary to oligemia (a subischemic decrease in blood flow).[13] This neuronal depression begins in the posterior aspect of the brain and advances anteriorly at a rate of about 3 mm per minute.[14,15] Preceding this wave of depression is a wave of excitation that may excite certain "perturbable" neurons, thus giving rise to the aura. Auras are most commonly visual, consisting of scotoma, loss or distortion of visual fields, or alternating light and dark lines in the visual field called the *fortification spectra*. Paresthesia of the face or hand is common. Occasionally, profound disturbances in central nervous system activity occur such as hemiparesis or hallucination. Usually lasting less than an hour, an aura typically resolves before or shortly after the headache phase of migraine begins.[16]

Headache

As the migraine process continues, the vascular regulation of the brain and surrounding structures changes. Pain-sensitive vascular structures, especially in the dura mater, dilate, causing extravasation of plasma into the surrounding neurovascular tissue. Various vasoactive peptides, such as substance P, neurokinin A, and calcitonin-gene-related peptide, are released from the surrounding trigeminal afferents, initiating a vascular inflammatory response.[17] As blood pulses through these inflamed vascular beds, the characteristic throbbing pain of migraine emerges. This phase of migraine lasts from 4 to 72 hours,[16] and is accompanied by other symptoms such as anorexia, nausea, vomiting, photophobia, phonophobia, and tenderness of muscles in the head and neck. Headache pain is unilateral and throbbing in about two thirds of cases and typically made more intense by routine activities. During this phase, migraineurs seek rest and avoid stimulation of the nervous system. They tend to seek an isolated, dark, quiet room.

Recovery

The biochemical events leading to recovery from migraine are poorly understood. Recovery typically occurs during rest or sleep, although the episode may resolve during a period of intense emotion or with vomiting. Subsequent to headache resolution, migraineurs experience a "postdrome" for up to 24 hours. This is characterized by food intolerance, impaired concentration, fatigue, and generalized myalgia.[11(pp16,17)]

Migraine Transformation

Important observations on the natural history of migraine suggest an interrelationship between episodic migraine and tension headache. Recently it has been suggested that migraine and tension headache may share a common biologic origin with clinical distinctions determined by activation of differing trigeminal pain pathways.[18] It has been noted that many migraineurs who had well-defined migraine attacks during their late teenage years and 20s experience daily or almost daily headache activity with intermittent superimposed episodes of more migraine-like symptomatology by their 30s and 40s. This phenomenon has been termed *transformed migraine*[19] and adds evidence to the concept of a "headache spectrum."

Mathew and others have observed that daily use of analgesics, anxiolytics, sedative-caffeine-analgesic combinations, and/or ergotamines is a potent catalyst for this transformation in many chronic headache sufferers.[20,21] The over-the-counter simple analgesics such as acetaminophen, aspirin, and analgesic-caffeine–containing products are also widely implicated in this transformation.

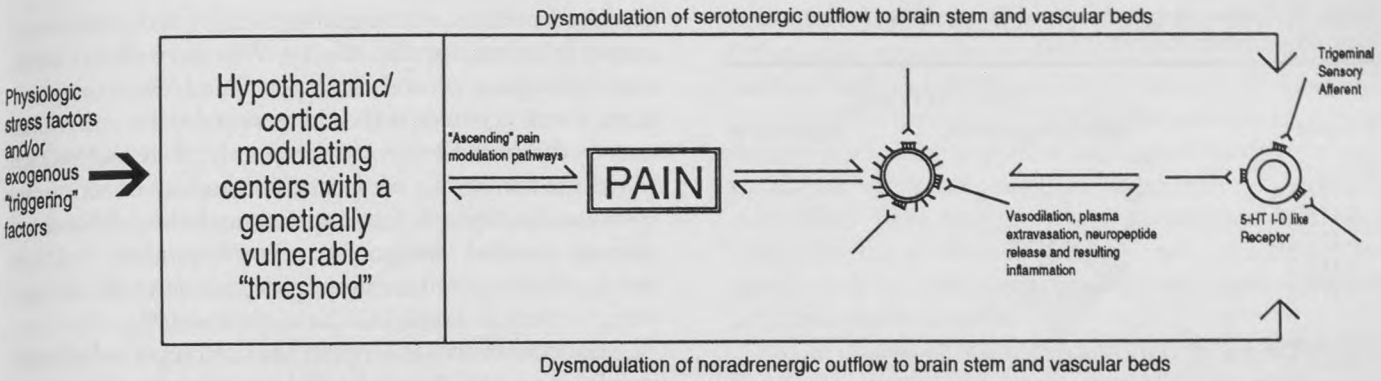

Figure 1. Proposed overview of migraine pathophysiology.

When simple analgesics are taken on a daily or almost daily basis in quantities greater than 50 g per month or greater than 100 tablets of simple analgesic-caffeine combination products per month, they can cause migraine to transform into chronic daily headache.[16] In addition, persons caught in the medication rebound cycle are less sensitive to prophylactic medications and other available abortive regimens.[22]

Protocols using parenteral dihydroergotamine (DHE) given several times per day over several days can successfully break this headache pattern.[23] The DHE is then generally weaned over a period of several weeks. Chronic daily headache is often difficult to treat. It may require management in an interdisciplinary setting, where nonpharmacologic measures such as biofeedback and counseling can be instituted. These efforts greatly increase the long-term success in treatment outcome.

Migraine Pathogenesis

Earlier theorists on migraine pathogenesis debated whether migraine was a vascular or a neurogenic phenomenon. Both theories contributed many important observations about migraine, but in themselves were incomplete. Recently, the "unifying theory" merges these divergent concepts, suggesting that migraine results from overloading a genetically vulnerable, centrally regulated migraine threshold (Figure 1).[24] Many different precipitating factors can have an impact on this threshold, until at some point the system can no longer accommodate the sum of these stressors (Table 1). The resulting overload of this migraine threshold disrupts normal neurologic function, resulting in vascular changes and an ensuing neuropeptide-mediated vascular inflammatory process. Trigeminal afferents innervating these vessels become sensitized, and as pain signals proceed centrally, they are modulated by several different central nuclei. Neuronal interconnections from these nuclei to the brain stem, midbrain, and visual cortex may account for much of the associated migraine symptomatology. This process eventually culminates clinically as migraine.

Serotonin and Migraine

Central to the understanding of migraine pathogenesis is the neurochemical serotonin. Historically implicated in the etiology of migraine, serotonin's role in pathogenesis

Table 1. Triggering Factors Supporting the Concept of a Migraine Threshold

Common Precipitating Factors
Menstruation
Estrogen (oral contraceptives or replacement therapy)
Emotional stressors
Physical exertion
Fatigue
Lack of or poor quality of sleep
Hunger
Glaring artificial lights or sunlight
Weather changes
Analgesic overuse
Change in routine
Less Common Precipitating Factors
High humidity
Excessive sleep
Excessive vitamin A
Cold beverages or food
Pungent odors
Fluorescent lights
Allergies
Excessive heat
Dietary Factors
MSG—monosodium glutamate (hydrolyzed vegetable protein, natural flavor, sodium caseinate, autolyzed yeast, flavoring, seasoning, kombu extract)
Tyramine (aged cheese)
Caffeine
Theobromine (chocolate)
Alcohol (small quantities unrelated to "hangover" headache)
Nitrates/nitrites (sausage, prepared meats)
Wine (especially red)

Table 2. Dihydroergotamine and Sumatriptan Activity at Neurotransmitter Receptor Sites

Receptor	Degree of Activity*	
	Dihydroergotamine	Sumatriptan
Serotoninergic		
5-HT-1A	++++	+
5-HT-1C	++	–
5-HT-1D	++++	++++
5-HT-2	+	–
5-HT-3	–	–
Adrenergic		
Alpha-1	++++	–
Alpha-2	++++	–
Beta	–	–
Dopaminergic		
Dopamine-1	–	–
Dopamine-2	+	–

**The plus signs indicate degree of activity: ++++ = very strong; +++ = strong; ++ = moderate; + = weak; and the minus sign indicates no activity.*
Data adapted from Peroutka SJ.[39]

has been largely supported by indirect evidence.[25–27] Recently, considerable interest has been directed at characterizing serotonin receptors in the human brain. To date, four classes of serotonin or 5-hydroxytriptamine (5-HT) receptors have been described.[28] These are 5-HT-1, 5-HT-2, 5-HT-3, and 5-HT-4. For each of these receptor classes there can exist several distinct subclasses. For example, the 5-HT-1 receptor has subtypes A, B, C, and D. Each of these subreceptors modulates specific physiologic responses. This intricate array of receptor interactions is perhaps why serotonin has been implicated in so many human disorders (migraine, depression, alcoholism, suicide, sleep disorders, panic disorders, obsessive-compulsive disorder, and schizophrenia).[29,30]

In migraine, interest has focused on the 5-HT-1 receptor. This receptor is found in high concentrations in several central pain-regulating centers of the brain, such as the hippocampus, dorsal raphe, and substantia nigra,[31] which are integral parts of an "ascending" pain-modulating system. The 5-HT-1 receptor is also found in high concentrations in the cranial and pericranial neurovascular system, especially in the dura mater.[32,33] Stimulation of these receptors results in vasoconstriction, inhibition of neuropeptide-induced inflammation, and elevation of the sensory afferent firing threshold.[34,35] Drugs active at the 5-HT-1 receptor are effective at relieving migraine. The most studied of these drugs are dihydroergotamine and a newly developed antimigraine drug, sumatriptan.[34,36,37] Sumatriptan is highly selective for the 5-HT-1 receptor, whereas dihydroergotamine is less specific, stimulating many other serotonin and adrenergic receptor sites (Table 2). This distinction has allowed researchers to hypothesize that the relief of migraine pain is mediated primarily through the 5-HT-1 receptor, where sumatriptan has specific affinity. Whether relief is mediated through a central or a peripheral mechanism, or both, is still debated. It should be noted that sumatriptan crosses the blood-brain barrier poorly, if at all,[38] which favors the theory of a peripheral mechanism of action. By contrast, most prophylactic agents, including β-blockers, calcium channel antagonists, cyproheptadine, tricyclic antidepressants, and methysergide, act through antagonistic activity at the 5-HT-2 receptor site.[39]

Subcutaneous sumatriptan has been reported effective in relieving cluster headache.[40] Approximately 70% of individuals experienced relief of pain, resolution of associated autonomic dysfunction, and improvement in functional ability within 15 minutes of receiving sumatriptan. As cluster headache is a syndrome distinct from migraine, this observation adds support to the theory that a trigeminally mediated pain pathway involving the 5-HT-1 receptor is common to both headache syndromes.

Sumatriptan for the Treatment of Migraine

Sumatriptan, a promising treatment for migraine, has undergone extensive worldwide clinical trials. Recently the results of two large multicenter, double-blind, placebo-controlled studies have been reported.[41,42] The effect of a single subcutaneous dose (6 mg) of sumatriptan administered to migraineurs with moderate to severe migraine demonstrated reduction of pain to mild or no pain levels for approximately 50% of subjects within 30 minutes and 70% of subjects within 60 minutes. Placebo response was 9% and 22%, respectively. Nausea and photophobia resolved in 78% of the sumatriptan group compared with 37% of the placebo group. Data also suggested that sumatriptan is effective at relieving migraine at all phases of headache activity. Additionally, approximately 45% of individuals experience return to normal function within 1 hour and 75% within 90 minutes.[43]

Adverse events were three times more common with sumatriptan than with placebo and typically consisted of flushing, generalized tingling, warmth, lightheadedness, and burning at the site of injection. These adverse events were noted to generally occur within 10 minutes of injection and resolve spontaneously within 1 hour. Cardiovascular safety has been assessed in clinical trials with electrocardiogram monitoring in more than 1200 patients during or shortly after dosing with subcutaneous sumatriptan, and about the same number of patients after taking oral sumatriptan. The data demonstrate no relationship between the various types of chest symptoms reported as adverse events (about 3% to 5% of patients compared with 1% to 2% after placebo), and electrocardiogram changes[44]; in some cases these chest symptoms

have mimicked angina pectoris. Rare cardiovascular adverse events have been reported in patients with preexisting structural or ischemic heart disease.[45] Theoretically, there would appear to be the potential for coronary vasospasm to accompany sumatriptan administration in predisposed patients. There have been no reports of hypertensive crisis associated with the use of sumatriptan, but this must also be a theoretical concern. As with any other vasoconstrictor drug, sumatriptan should be used with great caution, if at all, in patients with a history of ischemic heart disease, other structural heart disease, cerebrovascular disease, or uncontrolled hypertension.

There are a few questions remaining concerning sumatriptan's clinical role in headache management. Return of headache has been noted in approximately 40% of treated patients.[37] The recurrence occurs from 14 to 20 hours after subcutaneous injection.[43] Because the half-life of subcutaneous sumatriptan is less than 2 hours,[37] the return of headache is not unexpected. If those factors that precipitate the migraine persist, then headache would likely return as sumatriptan is cleared from the 5-HT-1 receptors. Further studies treating headache recurrence with repeated doses of sumatriptan are currently underway. Whether drugs such as nonsteroidal antiinflammatory drugs used in conjunction with sumatriptan diminish or prevent recurrence has yet to be determined. The effectiveness of sumatriptan when administered by self-injection system and by oral tablet has also been studied. Both forms were noted to have similar efficacy to the physician-administered subcutaneous injection, ie, 70% of patients experienced relief within 1 hour after using the self-injection system[46] and within 4 hours after taking the oral tablet.[47]

Another question concerns the cost of sumatriptan. Until the drug is approved for use in the United States, the exact cost of sumatriptan to patients is unknown. Based on costs outside the United States, sumatriptan is likely to cost $30 to $40 per injection. If self-injection decreases the number of office or emergency department visits for acute treatment, or decreases the use of daily prophylactic medication, sumatriptan will be relatively cost-effective. Also, if migraineurs are able to return to normal levels of function sooner, work absenteeism will decrease, thus making sumatriptan very cost-effective.

Role of Sumatriptan and Other Therapies

Sumatriptan's role as a pharmacologic agent for headache has not been fully defined. Whether it has value in treatment of chronic daily headache, analgesic rebound headache, tension headache, pediatric migraine, or other headache syndromes remains open for investigation. Other acute treatments currently exist that are efficacious and used successfully by many patients. How sumatriptan should be used relative to these treatments is open to debate. If a headache patient has been inadequately controlled on other treatments or experiencing significant side effects from therapy, then sumatriptan will be a logical treatment alternative. Conversely, if a patient responds well to other therapy, then sumatriptan will add little therapeutic benefit.

The course of migraine can often be unpredictable. For those attacks that begin abruptly with severe pain, disability, and nausea, sumatriptan may represent an excellent first-line therapy. However, migraine often begins as a mild headache that may be amenable to or aborted effectively by other first-line therapies. For those attacks not controlled by these agents, having sumatriptan available may minimize disability or the need for physician-directed treatment. The reassurance of a readily available backup therapy will likely alleviate much of the anticipatory fear and anxiety of treatment failure. As a well-tolerated drug that maintains treatment efficacy through the later stages of the headache cycle, sumatriptan appears well suited for this role. This self-injection system may avoid the stigma of utilizing needles and syringes required with some therapies. Sumatriptan's rapid onset of action and ability to return many to normal or near-normal levels of function will reduce headache or treatment disability.

Nonpharmacologic approaches, such as biofeedback and relaxation therapy, may provide benefit for many chronic headache sufferers. Biofeedback therapy, used by skilled psychologists, is easy to learn and safe, and has a long-term prophylactic efficacy of 65% to 84%.[8,48] Biofeedback is the process of changing body function by supplying the body with new directions. Information regarding body performance is then "fed back" to the individual. For the treatment of headache, thermal biofeedback trains the person to alter internal physiology resulting from a stress response. Properly trained psychologists can assist headache patients to expand coping strategies and reduce anticipatory fears, anxiety, and depression.

Physicians can help patients establish reasonable therapeutic goals that emphasize headaches as a manageable rather than curable disorder. Patient participation in and responsibility for headache management are crucial. Encouraging lifestyle changes to avoid known precipitating factors, such as using tobacco or eating certain foods, are important. Headache should be managed like other chronic illnesses, with adequate patient education and regularly scheduled follow-up visits.

Guided by dramatic advances in neurobiology, med-

icine appears to be entering a new era in the understanding of headache. The importance of these advances extends far beyond the impressive accomplishments in pharmacology. Medications, while important, are not a panacea for headache. Headache is a multifactorial disorder and requires treatment strategies that address it as such.

Family physicians play a sentinel role in headache care. Through early identification of patients who are at risk for chronic headache, appropriate patient education, and logical pharmacologic interventions, much of the suffering and disability of headache can be alleviated. Helping patients avoid overusing medications that can transform episodic headache into chronic headache is an essential part of this education. Family physicians are ideally suited to provide the ongoing care required by the vast majority of headache patients. With a better understanding of headache pathophysiology, family physicians can redefine the treatment of headache.

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