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The Future of Migraine: Beyond Just Another Pill

In this issue of *Mayo Clinic Proceedings*, 2 excellent review articles[1,2] poignantly assert that migraine is a potentially chronic, progressive disease that substantially affects patients, families, workplaces, and society. Ironically, this is the springboard for renewed optimism of a more positive future for patients living with migraine.

Today, the concept of migraine is evolving from a traditional view as an episodic pain disorder to a potentially chronic, progressive, and pervasive disease that disrupts all aspects of an individual's life. Even though migraine has no obvious catastrophic end point, it has the potential to erode a person's daily quality of life during what should be productive years of life.

The evolution in understanding the chronic nature of migraine was only recently initiated. In 1988, the International Headache Society (IHS) proposed a classification system for headache and facial pain disorders.[3] The timing of these new criteria was in preparation for a new class of abortive therapy, the triptans. With the release of sumatriptan in the early 1990s, migraine was quickly legitimized as a treatable medical condition. Many published studies defined plausible scientific underpinnings of the event of migraine.[4-6] However, as illustrated in articles on migraine in the current issue of *Mayo Clinic Proceedings*, improvements in patients' quality of life have not kept pace with scientific advances.

The IHS diagnostic criteria for migraine were monumental steps forward in establishing migraine as a valid biological entity, although the chronic, progressive nature of the disease was not included in the 1988 criteria. Interestingly, in defining the other primary headache disorders, the IHS included diagnostic criteria for chronic forms of both cluster and tension-type headaches but not migraine.

In 2004, the IHS criteria were revised and included the diagnosis for chronic migraine.[7] Chronic migraine was defined as 15 or more days per month (for a period of at least 3 months) of headache. Bigal et al[8] asserted that this definition was not operational and would seriously inhibit or prevent future research of chronic migraine.

See also pages 422 and 436

Consequently, in 2006 the IHS nomenclature committee published an appendix definition for chronic migraine characterized by a pattern of headaches experienced by a patient, rather than focusing on symptoms of individual headache attacks.[9] The potential progressive nature of migraine was addressed, such that episodic migraine was considered a precursor to chronic migraine. The spectrum of clinical phenotypes of primary headache observed in the patient with chronic migraine ranged from IHS migraine to IHS tension-type headache. Furthermore, it was an acknowledgment that this spectrum of IHS primary headaches in the patient with migraine responds to migraine-specific (triptan) treatment. This supported earlier suggestions that the different clinical phenotypes of primary headache witnessed in a patient with migraine might share common biological mechanisms.[10] This change in classification is arguably one of the most important recent advances in migraine and provides an opportunity to improve the clinical outcomes for patients with migraine.

Translating these new diagnostic criteria into optimal patient care will require professionals to think beyond traditional health care models of migraine management. Understanding migraine as a potentially chronic disease

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mandates a collaborative health care model with patients and health care professionals working in partnership toward common therapeutic goals. Although the need for these models is becoming increasingly evident in many chronic disease states, migraine presents a unique opportunity to the medical community. As alluded to earlier, the goal of migraine is more about prevention of day-to-day attrition from disease rather than a remote catastrophic consequence. This implies a need for models of care that encourage partnership and evaluation beyond the physician simply asking "How are your migraines?" to an invitation to comprehend and address all migraine-related health issues and comorbidities facing this patient population. The integration of assessment tools and relevant patient education, as suggested in the articles by Buse et al[1] and Burton et al,[2] highlights new opportunities for patients and health care professionals to improve communication and understanding of the disease of migraine. In addition, the recognition of "stages" in the evolution from episodic to chronic migraine provides the opportunity to develop therapeutic strategies that individualize and personalize care on the basis of disease progression.[11] In the future, successful management of migraine will ideally be measured not by attack termination but by prevention or reversal of disease progression. Thus, the role of preventive therapy will likely become more central to migraine management.

Pharmacologically, the past decade has brought relatively few innovations for the treatment of acute migraine. An important treatment paradigm called *early intervention*, or administering treatment early in the attack of migraine while the headache is mild, was introduced and studied and has been associated with improving pain-free efficacy and limiting attack-related disability.[12] Recently, a combination of sumatriptan and naproxen was approved by the Food and Drug Administration (FDA) and may decrease migraine recurrence and need for rescue medication in some patients.[13] Another novel approach was introduced for treatment of menstrually related migraine with frovatriptan. This forward-thinking strategy initiated treatment in anticipation of migraine associated with menses, ie, before the onset of headache. Although the efficacy and tolerability of this approach were demonstrated in a large clinical trial, the FDA did not approve frovatriptan for this indication, presumably because patient selection for the study did not demonstrate menstrually related migraine as a unique biological entity that required specific treatment needs.[14]

Calcitonin gene-related peptide (CGRP) receptor antagonist, a promising new class of abortive medication, is being developed for acute intervention. Clinical trials of 2 CGRP receptor antagonists, olcegepant and telcagepant, have been published, and both demonstrate efficacy for acute migraine.[15,16] This class of drug is interesting because its mechanism of action does not include vasoconstriction. Whether this provides therapeutic or safety advantages over the triptans remains to be determined, but its lack of vasoconstrictive effect is already expanding our understanding of pathophysiologic models of migraine and pharmacological mechanisms of acute intervention.

Additional work is under way analyzing adenosine receptors as a target for acute therapy. These compounds may inhibit trigeminal nociceptive transmission as well as inhibit CGRP release. Older drugs such as dihydroergotamine are being reexamined with novel delivery systems and a clearer understanding of their pharmacology.

Perhaps the greatest opportunity to advance migraine pharmacology will be in prevention. The antiepileptic drugs (AEDs) topiramate and divalproate sodium, both approved by the FDA as migraine prophylactic medications, have substantially altered physician and patient acceptance of preventive migraine therapy. The mechanism by which AEDs prevent migraine is still not fully understood because other AEDs such as carisbamate, although efficacious for epilepsy, appear to be ineffective as migraine preventive medications.[17]

On the positive side of the ledger, botulinum toxin type A was reported effective in reducing the number of headache days in patients with chronic migraine.[18] If these findings are substantiated, it would be the first preventive therapy found effective for chronic migraine. The overriding issue is to determine whether preventive medications alter disease progression. To date, no studies have demonstrated effectiveness in this regard.

Beyond pharmacological targets specific to pathophysiology in migraine is the possibility of pharmacology that addresses the many comorbid diseases associated with migraine. Over time, many leaders in the headache field have suggested that comorbidities may in fact occur because of shared biological mechanisms, rather than as simple linear consequences. Although little has been accomplished to date, further mechanistic understanding of migraine and comorbid disease may open entirely new models and biochemical pathways of treatment. There is also the possibility that the neurobiology of headache (and pain) may cosensitize the emotional or limbic pathways, resulting in a more pervasive neurologic disease.[19] This too expands the horizon of understanding patients and not simply their headaches.

The understanding of migraine as potentially a chronic disease offers many challenges and rewards in the future. Today, the focus of care is changing from the event of migraine to the patient with migraine. Treating patients

with migraine in the future will place greater emphasis on collaborative partnerships between patients and health care professionals that emphasize education and prevention of disease burden. These changes offer new hope for patients and health care professionals alike, brightening the future of patients with migraine. With these advances, migraine will become more effectively managed, and diagnostic and therapeutic interventions will reduce the impact of this potentially devastating disease.

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