Clinical Approaches to Migraine Prophylaxis

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Abstract

Chronic migraine is a recognized complication of episodic migraine. A high frequency of attacks and frequent use of abortive medications are important risk factors associated with conversion to a chronic condition. Prophylaxis is therefore recommended for patients with frequent episodic migraine. The agents approved for migraine prophylaxis are the antiepileptic agents divalproex and topiramate, and the beta-adrenergic antagonists propranolol and timolol. However, a wide range of other systemic agents and local injections of botulinum toxin have also been used in migraine prophylaxis. The anticipated benefits must be weighed against the adverse effects associated with each agent in determining the optimal preventive regimen for individual patients.

(Am J Manag Care. 2005;11:S55-S61)

In 2003, the International Headache Society (IHS) issued revised diagnostic criteria for headache, including migraine with and without aura.[1] In a change from the 1988 criteria, chronic migraine is now recognized as a complication of episodic migraine (**Table**). The criteria for chronic migraine include attacks with migraine features on at least 15 days per month for at least 3 months, with no other condition present to which chronic migraine could be attributed, including overuse of abortive medication for acute migraine.[1,2]

The overall prevalence of migraine is approximately 11% among adults in western nations, with the highest rates reported in the age range 25 to 55 years; women account for the majority of patients with migraine.[3] A survey of migraine patients in the United States showed 1-year prevalence rates of 17.2% among women and 6.0% among men. More than 50% of the patients surveyed either had never seen a physician or had not seen one within the past year, which represents a modest improvement over the past decade.[4] The prevalence rates in America are consistent with rates reported in England (18.3% among women and 7.6% among men), with the highest rates seen among whites.[5]

Most migraineurs do not seek medical help and rely on nonprescription medications for headache pain; consequently, disability interfering with education and employment is common, and these indirect costs exceed the direct costs of medical intervention.[3] Similar findings were reported from a survey of healthcare utilization conducted among patients in the United States and England with headache that met the clinical criteria for migraine. The survey revealed that patients in England were significantly more likely than patients in the United States to have consulted a physician for headache (lifetime, 86% vs 69%, $P < .0001$), whereas patients in the United States who did see a physician were seen more often overall and more often by a specialist. In both countries, however, the majority of people with headaches relied on nonprescription medications, and disability rates were high among those who never consulted with a physician and never received a proper diagnosis and prescription medication, demonstrating that undiagnosed migraine remains a substantial health problem.[6]

In a subgroup of the migraine population, the condition progresses from episodic to chronic as defined by the 2003 IHS criteria. One of the main risk factors for conversion to a chronic migrainous state is a high frequency of episodic headache with associated high use of abortive medications (Note, however, that the formal criteria for chronic migraine exclude excessive use of medication as a cause, because chronicity caused

Table. Classification of Migraine (Migraine is *ICHD-II* classification 1; *ICD-10* classification G43)

ICHD-II code	*ICD-10* code	Type and subtypes
1.1	G43.0	Migraine without aura
1.2	G43.1	Migraine with aura
1.2.1	G43.10	Typical aura with migraine headache
1.2.2	G43.10	Typical aura with nonmigraine headache
1.2.3	G43.104	Typical aura without headache
1.2.4	G43.105	Familial hemiplegic migraine
1.2.5	G43.105	Sporadic hemiplegic migraine
1.2.6	G43.103	Basilar-type migraine
1.3	G43.82	Childhood periodic syndromes, commonly precursors of migraine
1.3.1	G43.82	
1.3.2	G43.820	Abdominal migraine
1.3.3	G43.821	Benign paroxysmal vertigo of childhood
1.4	G43.81	Retinal migraine
1.5	G43.3	Complications of migraine
1.5.1	G43.3	Chronic migraine
1.5.2	G43.2	Status migranosus
1.5.3	G43.3	Persistent aura without infarction
1.5.4	G43.3	Migrainous infarction
1.5.5	G43.3	Migraine triggered seizures
1.6	G43.83	Probable migraine
1.6.1	G43.83	Probable migraine without aura
1.6.2	G43.83	Probable migraine with aura
1.6.5	G43.83	Probable chronic migraine

ICHD-II indicates *International Classification of Headache Disorders, 2nd Edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.*

by medication overuse is now classified separately [see reference 1, page 31, section 1:51]).

In a survey of 532 consecutively seen patients with episodic migraine followed for 1 year, 64 of 450 patients (14%), who could be evaluated developed chronic headache, with the highest odds ratio (OR) for conversion to chronicity seen in patients with a high frequency of episodic headaches.[7] Other risk factors for conversion include psychiatric comorbidity, personality traits, stress, and physical disorders, such as hypertension, allergies, asthma, hypothyroidism, sleep disturbances, and overconsumption of caffeine.[8,9] The degree of risk associated with each of several somatic conditions and lifestyle factors has been assessed as follows (OR in patients with chronic migraine compared with patients with nonchronic migraine): hypothyroidism, 8.4 (P = .0004), hypertension, 6.9 (P <.0001), allergies, 3.5 (P = .0001), daily consumption of caffeine, 2.9 (P = .0008), asthma, 2.4 (P = .03); however, this study showed no correlation between smoking or alcohol use and the risk of chronicity.[9]

Diverse factors, such as high dietary fat intake, obesity, insulin resistance, vigorous exercise, hunger, oral contraceptives, and smoking, may also be implicated as increased levels of lipids and free fatty acids in circulation lead to increases in platelet aggregation and prostaglandin levels, which, in turn, trigger the cerebral vasodilation associated with migraine.[10] Any of these factors may therefore pose an added risk of conversion from episodic migraine to chronic migraine. Two other pathologic factors that have been associated with chronic migraine are Epstein-Barr virus[11] and white matter abnormalities detected on magnetic resonance imaging.[12,13] The latter suggest a possible kindling effect, as more attacks lead to more changes.

Chronic migraine, with or without medication use, is a common form of chronic daily headache (affecting 4% of the adult population and defined as headache of more than 4 hours duration occurring on at least 15 days per month for more than 6 months).[9,14] The transformation of episodic migraine to chronic migraine is marked by increasing frequency often in combination with decreasing severity until the condition stabilizes into a daily or even continuous pattern. The risk of chronicity is higher among patients with migraine than those with nonmigraine headaches (8% vs 5%, respectively; OR 1.6).[15] Demographic factors associated with the prevalence of chronic daily headache include female sex (adjusted OR 1.69 for women compared with men, P <.005), limited education (3.35 for patients who did not finish high school compared with college graduates), and a previous marriage (1.45 for those widowed, separated, or divorced compared with those currently married, P <.05).[14]

Clinical risk factors include obesity (1.34 for those with body mass index ≥30 kg/m^2 compared with normal, $P < .05$) and arthritis (2.41 for those with this diagnosis compared with no arthritis, $P < .005$),[15] as well as medication use, caffeine consumption, and snoring (independent of sleep disturbance).[15]

Apart from the risk of conversion to a chronic condition, frequent migraine (especially migraine with aura) is also associated with an increased risk of ischemic stroke, possibly caused by concomitant risk factors for cardiovascular disease. In a large-scale epidemiologic study from the Netherlands, migraineurs (in comparison with control patients) were more likely to smoke (OR 1.43) and less likely to consume alcohol (OR 0.58), while migraineurs with aura were more likely to have dyslipidemia (OR 1.43-1.64), hypertension (OR 1.76), and a history of coronary heart disease or stroke (OR 3.96).[16]

Prophylaxis is warranted in patients who have frequent episodic attacks. However, the decision to provide prophylaxis is a matter of clinical judgment based not only on frequency but also on the severity of attacks and the resulting degree of impairment and dysfunction in each individual patient. A common guideline is that prophylaxis should be considered in patients who have 3 or more acute attacks per month, but some patients may tolerate 3 attacks better than others tolerate 2 attacks per month. Although some clinicians will not generally start prophylaxis until patients have more frequent acute migraines (such as 6 per month), it is important to remember that the goal in prophylaxis is not only to prevent further acute attacks but also to prevent conversion to a chronic condition, because the risk of conversion increases with more frequent episodic attacks, apart from the frequency of medication use.

Drugs approved for prophylaxis include the antiepileptic agents topiramate and divalproex, and the beta-adrenergic blockers propranolol and timolol. Among these agents, divalproex has been associated with weight gain,[17] which may be a risk factor for conversion from episodic to chronic migraine. In contrast, topiramate has been associated with substantial weight loss, but paresthesias, cognitive effects, and metabolic acidosis secondary to bicarbonate loss have also been reported with this agent.[18] As with many drugs used in diverse clinical conditions, the agents used in migraine prophylaxis may be associated with sleep disturbances and numerous drug interactions. The serotonin blocker methysergide was formerly approved for this use; however, approval from the US Food and Drug Administration was withdrawn in 2003 for reasons of safety, including the rare but serious risk of retroperitoneal fibrosis.

Systemic agents used off-label for migraine prophylaxis include calcium channel blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), newer antidepressants (including venlafaxine, mirtazapine, and duloxetine), atypical antipsychotics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (including nonprescription formulations), the antiepileptic agents gabapentin and zonisamide, the antihistamine cyproheptadine, and magnesium supplements. In some cases, the benefits gained must be weighed against the risks incurred. For example, the tricyclic antidepressants may be useful in migraine patients with comorbid depression, but they are also associated with drowsiness and weight gain, which may increase the risk of conversion from episodic migraine to a chronic pattern.

In contrast to systemic agents, botulinum toxin, given as low-dose local injections (usually at 3-month intervals), avoids compliance problems and is generally well tolerated. The mechanism of action of botulinum toxin in migraine prophylaxis is uncertain, but it appears to block pain impulses apart from its ability to eliminate tension in the muscles of the head and neck.[19] Specifically, botulinum toxin is believed to inhibit the release of neurotransmitters from nociceptive nerve terminals to block pain impulses, just as it inhibits the release of acetylcholine at the neuromuscular junction to block motor impulses.[20] However, this approach is not successful in all migraine patients, and finding a means of identifying patients who are likely to respond to botulinum toxin is a high-priority goal of research.

A variety of nonpharmacologic approaches have been employed to reduce the incidence of acute attacks and the conversion from episodic acute migraine to chronic migraine. These approaches focus on lifestyle adjustment (such as weight correction, smoking cessation, and stress reduction) and avoidance of known triggers of acute attacks (such as glaring or flickering lights, perfume or other strongly aromatic substances, rapid changes in atmospheric temperature or pressure, and various foods including chocolate, coffee, and other caffeinated beverages, wines and other products containing sulfites, and products containing large amounts of salt or preservatives, MSG, and aspartame). The remainder of this article is a review of representative published reports that provide a perspective on the clinical experience to date with pharmacologic approaches to migraine prophylaxis.

Antiepileptic Drugs

The utility of anticonvulsants in migraine prophylaxis was discovered because both epilepsy and migraine are episodic disorders of the central nervous system that are often comorbid and share certain symptoms.[21] However, when used for migraine prophylaxis, these agents may be more properly described as neurostabilizers. The mechanism of action of divalproex in migraine prophylaxis is unknown, but increased levels of brain gamma-aminobutyric acid (GABA) has been suggested as a mechanism of its anticonvulsive activity.[17] Topiramate, like divalproex, may exert its clinical activity through augmentation of GABA activity, but other possible mechanisms include blockade of voltage-dependent sodium channels and decreases in carbonic anhydrase activity and certain types of glutamate activity.[18]

A recent review of the literature confirmed the effectiveness of divalproex and topiramate in this role.[22] A Cochrane Database review of 15 published studies involving 2024 patients concluded that anticonvulsants are generally safe and effective in migraine prophylaxis, although the weight of evidence varies considerably among the different agents of this class.[23]

Two large-scale randomized trials of virtually identical design yielded similar positive results for the use of topiramate as prophylaxis in more than 900 patients with chronic migraine (3-12 attacks per month). Topiramate at 100 and 200 mg/day produced significant reductions in mean headache frequency over a 6-month period, and the proportion of patients who achieved at least a 50% reduction in migraine frequency was significantly higher with topiramate than with placebo. Topiramate was less effective at 50 mg/day than at 100 mg/day, whereas topiramate at 200 mg/day offered no advantage over the 100-mg dose.[24,25] A review of the clinical evidence to date, including these 2 trials, concluded that topiramate at 100 mg/day is safe and effective in migraine prophylaxis.[26]

A comprehensive review of open-label and controlled trials of divalproex concluded that the various formulations of this agent are safe and effective for the prevention of migraine, chronic daily headache, and cluster headache, apart from its utility in intravenous form as an abortive treatment for acute migraine attacks.[27] A trial of an extended-release formulation of divalproex demonstrated efficacy similar to that of the delayed-release formulation that had been in use as prophylaxis.[28]

An open-label study in patients with treatment-resistant migraine assessed the combination of sodium valproate and a beta blocker (ie, propranolol or nadolol). Among 52 patients, 29 (56%) showed a 50% or greater reduction in migraine days, 15 (29%) had lesser or no response, and 8 (15%) discontinued because of adverse events. These findings suggest that the combination regimen may be effective as prophylaxis in some patients with resistant migraine.[29]

Other Systemic Drugs

A Cochrane Database analysis of 58 trials of propranolol as migraine prophylaxis in 5072 patients found numerous methodological shortcomings in the published literature (especially, involving high dropout rates). Nevertheless, the analysis showed clear evidence of short-term effectiveness in preventing migraine, inadequate evidence on long-term effectiveness, and no clear clinical distinctions in comparisons with calci-

um antagonists, other beta blockers, and other drugs.[30]

A meta-analysis of 38 English-language, randomized, placebo-controlled trials of antidepressants as prophylaxis for chronic headache (including 25 studies that focused on migraine) showed comparable effectiveness with tricyclic antidepressants, serotonin antagonists, and SSRIs; however, it was not possible to determine if these benefits were independent of effects on depression.[31] A recent review of antidepressants used in migraine prophylaxis confirms support for the tricyclic agent amitriptyline as well as for SSRIs, such as fluoxetine.[32]

Amitriptyline and venlafaxine were compared in a randomized, double-blind, crossover study (12 weeks receiving each treatment separated by a 4-week washout period), which showed that both drugs offered significant benefit in migraine prophylaxis, but venlafaxine incurred fewer side effects.[33]

Prophylaxis is also used in children with migraine. In a review of 250 children and adolescents, (mean age 12 years, range 3-18), 126 (50%) were placed on prophylaxis. The most commonly used agent was amitriptyline, especially among older children; headache frequency was reduced by 62% and the overall positive response rate was 89%. Cyproheptadine, used more often in younger children, produced a 55% reduction in headache frequency and an 83% overall positive response rate. Smaller numbers of patients received propranolol, valproic acid, naproxen, nimodipine, imipramine, or topiramate.[34] An earlier study in 10 children showed that valproate was effective and well tolerated in migraine prophylaxis.[35]

Among novel regimens tried for migraine prophylaxis, the combination of riboflavin 400 mg, magnesium 300 mg, and the herbal product feverfew (*Chrysanthemum* or *Tanacetum parthenium*) 100 mg was compared with an active placebo (containing 25 mg riboflavin) in a randomized, double-blind trial. All 3 substances have been suggested as effective treatments although definitive evidence is scant. After 3 months of treatment, both groups showed significant improvement from baseline, but there were no between-group differences in the proportion of patients who achieved a 50% or greater reduction in migraines (42%, 44%) or in reductions in migraine days, migraine severity, or use of triptans to abort acute attacks. These findings may suggest that even at the low dose used in the placebo group, riboflavin was as effective as the combination regimen,[36] which complements the findings of an earlier study showing that riboflavin at 400 mg/day was effective and well tolerated in migraine prophylaxis.[37]

Botulinum Toxin Injections

Most of the clinical data available on the use of botulinum toxin in migraine prophylaxis relates to use in patients who have already been diagnosed with chronic migraine. A recent review of the literature has concluded that botulinum neurotoxin is an effective and well-tolerated approach to headache prevention.[20] A single treatment, consisting of carefully placed low-dose injections, has an effective duration that may exceed 4 months, although treatments are usually scheduled at 3-month intervals. Although this form of migraine prophylaxis is still considered investigational, it appears to be relatively safe, incurring no systemic or serious adverse effects. Nevertheless, its use in migraine prophylaxis is not an extension of its use for cosmetic purposes, and should therefore be reserved for headache specialists who have experience in the exact placement of injections based on the pattern of headache pain.[38]

A review of 4 trials involving a total of 167 patients treated for at least 12 weeks concluded that a treatment of botulinum toxin injections reduces migraine frequency by 57% (range among the studies, 38%-75%), and that an improvement of this magnitude could be cost-effective, in that reduced need for acute treatment offsets the cost of providing this form of prophylaxis.[39]

In a recently published randomized, double-blind clinical trial, 355 patients with chronic daily headache received botulinum toxin or placebo every 3 months for 9 months (after a 1-month, single-blind, placebo run-in phase to identify patients who respond to placebo). At the 6-month assess-

ment among the 279 patients identified as placebo-nonresponders, botulinum toxin showed significant advantages over placebo in terms of the proportion of patients achieving at least a 50% reduction from baseline in the number of headache days per month (32.7% vs 15.0%, $P = .027$) and reduction in the mean number of headaches per month (–6.1 vs –3.1, $P = .013$); the mean change in number of headache-free days per month was greater with botulinum toxin than placebo (6.7 vs 5.2), but this difference was not statistically significant.[40] Likewise, a subgroup analysis of the 228 patients who were taking no other prophylactic medications showed significantly greater reductions in the mean number of headaches per month with botulinum toxin than with placebo at 6 and 9 months.[41]

The Cost Effectiveness of Prophylaxis

A detailed assessment of the cost effectiveness of migraine prophylaxis is beyond the scope of this paper. However, prophylaxis is warranted in patients with frequent episodic attacks and at risk for conversion to chronic migraine because it can substantially reduce the cost of acute treatment,[42,43] and, in particular, the cost of medication for acute episodes.[39] A double-blind, placebo-controlled trial of anticonvulsive medications in prophylaxis showed that gabapentin, divalproex, and topiramate were all clinically effective, but cost effectiveness was evident only in patients with frequent episodic attacks or comorbid disease.[44]

Conclusion

Although additional well-designed clinical trials are needed to confirm and expand our current knowledge, the evidence now available demonstrates that prophylaxis is clinically warranted and potentially cost effective in patients with frequent episodic migraine. It has not yet been clearly established that any one class of agent is notably superior to any other in this usage. Also lacking at present are clear guidelines based on individual patient characteristics for determining the optimal prophylactic regimen—selection of specific agents to be used at specific dose levels, singly or in combination, for a specific duration.

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