The Cost of Migraine and Its Treatment

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Abstract

Migraine headache incurs estimated annual costs totaling as much as $17 billion in the United States. Most of the direct costs are for outpatient services: medications, office or clinic visits, emergency department visits, laboratory and diagnostic services, and management of treatment side effects. Indirect costs from lost productivity in the workplace add substantially to the total. The triptan class of drugs, used for abortive treatment, account for the greatest portion of medication costs. Because these agents are expensive, optimal use is critical. Research suggests that a stratified care strategy, with initial therapy based on the patient's score on the Migraine Disability Assessment Scale, is both clinically advantageous and more cost-effective than stepped-care strategies. Also, the triptans are not interchangeable, and costs as well as clinical outcomes may vary with different agents in this class. Migraine prophylaxis is aimed at preventing frequent attacks and the development of a long-term condition that often incurs heavy costs for abortive treatment, diagnostic services, and medical care. Agents approved for migraine prophylaxis include the antiepileptics divalproex and topiramate and the beta blockers propranolol and timolol. As with abortive therapy, costs vary widely among these prophylactic agents. A novel approach to migraine prophylaxis is injection of botulinum toxin. A cost-analysis model is presented to show the impact of utilizing botulinum toxin in a large managed care system.

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Migraine headache incurs estimated annual costs totaling $13 billion to $17 billion in the United States.[1] The main cost drivers for direct clinical care are medications, emergency department visits, hospitalization, physician services (primary care and specialty), laboratory and diagnostic services, and management of treatment side effects. Indirect costs result from lost productivity in the workplace.

Drug treatment for migraine is classified as abortive (aimed at relieving acute attacks) and prophylactic (aimed at preventing episodic migraine from becoming recurrent and preventing recurrences in patients with chronic migraine). Approved treatments for aborting acute attacks include the triptans or 5-HT_1 agonists (eg, sumatriptan, zolmitriptan, naratriptan) and the ergot alkaloids (eg, ergotamine, dihydroergotamine). Non-approved abortive treatments include opioid analgesics (eg, butorphanol, meperidine), nonsteroidal anti-inflammatory drugs, aspirin, barbiturates, and antiemetics (eg, prochlorperazine, metoclopramide).

Drugs approved for migraine prophylaxis include the beta blockers propranolol and timolol and the antiepileptic drugs divalproex and topiramate. Drugs used off-label for prophylaxis include other agents of the beta blocker and anticonvulsant classes, calcium channel blockers, and antidepressants (eg, tricyclics and selective serotonin reuptake inhibitors). Methysergide, a serotonin blocker, was formerly approved for this usage, but approval was withdrawn because of safety concerns.

Another approach to prophylaxis is the use of botulinum toxin, which incurs minimal systemic side effects and does not rely on daily patient compliance. Botulinum toxin was discovered to have a high affinity to the neuromuscular junction, inhibiting release of adenosine. As a result, botulinum toxin is a highly focused therapy, which has been used in the treatment of muscle-spasm–related and dystonia conditions since its approval by the US Food and Drug Administration in 1989.[2] The initial rationale for its use in migraine prevention was to suppress myofascial triggering of acute attacks; however, it is now believed that botulinum toxin has a direct antinociceptive effect on sensory nerves, independent of its effects on muscle contraction.[3]

Of the total annual cost associated with migraine and its treatment, roughly one

tenth ($1.5 billion) goes to medication, with triptans accounting for the majority of this amount ($1.18 billion).[4] These agents are highly effective, but with a mean cost per prescription of $160, they are also among the leading contributors to cost. When properly used, their clinical effectiveness justifies their cost. However, overall treatment costs can be needlessly elevated due to misuse of medication; overtreatment represents waste and a risk factor for increased toxicity, and undertreatment can result in additional visits to the physician's office, clinic, or emergency department to deal with persistent symptoms. A more complex issue is that chronicity can develop from frequent acute episodes or from excessive use of abortive medications to treat frequent headaches. The rationale for prophylaxis is to prevent transformation to a costly and disabling long-term condition.

Headache has been among the most common complaints reported by patients visiting the emergency department,[5,6] accounting for almost 3 million visits in 2000, and representing an annual cost that may range from $600 million to nearly $2 billion. In a retrospective chart review of patients who visited an urgent care or emergency department facility for headache over a 6-month period, 54 of 518 patients (10.4%) made 502 of 1004 visits (50.0%). Among these repeaters, 79.6% of all visits during the preceding year were headache-related.[7]

Similarly, headache was the primary diagnosis in more than 50 000 hospital discharges in 1996, for which costs totaled $278 million; migraine accounted for two thirds of these headache-related discharges and costs.[8] Headache has also been a leading reason for visiting a neurologist, with migraine diagnosed in a large number of these cases; specialized care may add to the treatment costs associated with migraine, but expert management is still cost-effective if it leads to better outcomes than would be achieved by nonspecialists.

Pain costs employers more than $60 billion annually, with diminished performance on the job accounting for a greater portion of this cost than absenteeism and medical expenses; headache is the most frequent pain-related complaint among workers.[9] Focusing specifically on migraine, another study found that the annual cost to employers exceeded $14.5 billion, of which $7.9 billion was due to absenteeism, $5.4 billion to diminished productivity, and $1.2 billion to medical costs.[10]

The Cost Effectiveness of Migraine Treatment

A number of recent studies have assessed the clinical and cost effectiveness of different approaches to abortive and preventive treatment of migraine. In abortive treatment, triptans provide rapid relief of acute attacks with minimal side effects, resulting in improved quality of life (**Table 1**). When used appropriately, triptans can decrease treatment costs, despite their relatively high acquisition cost, by reducing the need for rescue medication and follow-up visits.[11] An earlier pharmacoeconomic review also concluded that triptans can reduce the overall cost of migraine from the perspective of society, but notes that the effect on direct treatment costs from the perspective of payers would depend on whether reductions in other aspects of treatment would offset the high acquisition cost of these drugs.[12]

Sumatriptan was used in a study comparing early and late abortive treatment of migraine. Total treatment costs were sub-

Table 1. Abortive Antimigraine Medications

Drug category	Approved	Nonapproved
Triptans (5-HT_1 agonists)	Sumatriptan, zolmitriptan, naratriptan, etc	
Ergot alkaloids	Ergotamine, dihydroergotamine	
NSAIDs		Ibuprofen, naproxen, etc; aspirin
Opioids		Butorphanol, meperidine, etc
Barbiturates		Butabarbital, etc
Antiemetics		Prochlorperazine, metoclopramide, etc

NSAIDs indicates nonsteroidal anti-inflammatory drugs.

stantially lower with early treatment, when pain was mild, than with later treatment, when pain was moderate to severe. Compared with later treatment, early abortive treatment also reduced total time with headache pain, increased the proportion of patients who were pain-free at 4 hours, and decreased the need for subsequent physician and emergency department visits. Although outcomes were better with 100-mg doses of sumatriptan than with 50-mg doses, either dose used early was superior to either dose used later in the course of an attack.[13]

A large-scale, randomized, controlled trial involving 835 patients compared a stratified care strategy (initial therapy based on the patient's score on the Migraine Disability Assessment Scale) and 2 stepped-care strategies (initial therapy with a simple combination analgesic, and escalation as needed to zolmitriptan across attacks and within attacks). Cost-effectiveness analysis over 6 attacks, including treatment and worker-productivity costs, showed that stratified care was associated with higher mean health service costs (241% of the cost for stepped care across attacks, 122% of the cost for stepped care within attacks) but lower mean productivity costs (78% of the cost for stepped care across attacks, 88% of the cost for stepped care within attacks). Because productivity costs were at least 4 times as great as health service costs, the overall cost was lower in the stratified care group than in either of the stepped-care groups. Although these differences in total costs were not statistically significant, clinical response was significantly better with stratified care than with stepped care. Based on these findings, a stratified-care strategy including this triptan appears to be more cost-effective than a stepped-care strategy across or within attacks.[14]

The triptans are not interchangeable. Patient responses to the different agents in this class vary, and it may be necessary to try a few triptans to find the one that works best in a patient, which reflects not only individual differences between patients, but also that migraine is not a single diagnosis but a heterogeneous group of disorders with similar symptoms.

A population-based, retrospective cohort study looked at the costs of managing chest pain in 1390 migraine patients treated with either almotriptan or sumatriptan. The incidence of new diagnoses related to chest pain rose by 43.6% in the 5 months after taking sumatriptan compared with the preceding 5 months (P = .03); no such rise was seen in patients treated with almotriptan. Including all direct medical costs (hospital care, outpatient visits, and diagnostic tests, as well as drug therapy), the use of almotriptan instead of sumatriptan would be expected to yield an annual savings of $11 215 per 1000 patients.[15] Based on data from more than 9 million migraine patients treated with sumatriptan, it was estimated that more than $12.7 million could have been saved if almotriptan had been used instead, mainly from avoidance of chest symptoms requiring diagnostic assessment.[16]

Migraine prophylaxis is aimed at preventing acute attacks and also at preventing conversion from an episodic condition to a chronic condition (**Table 2**). Consequently, utilization of clinical resources and associated costs would be expected to decrease. A retrospective analysis of a large claims database confirmed this expectation; the addition of a prophylactic agent to overall migraine management resulted in meaningful reductions in the use of other medications, visits to physicians' offices and emergency departments, and the need for costly diagnostic scans.[17]

Among the antiepileptic drugs, divalproex and topiramate are approved for use in migraine prophylaxis. A cost-effectiveness analysis using data from 3 double-blind, placebo-controlled clinical trials focused on the cost per headache prevented and the monthly number of headaches prevented that would define cost-effectiveness. The cost per migraine prevented was $138 with gabapentin, $115 with topiramate, and $48 with divalproex. Thus, divalproex became cost-effective with prevention of 10 migraines per month, whereas gabapentin and topiramate would become cost effective only when the frequency of migraines prevented was considerably higher. This analysis demonstrates that the antiepileptic drugs are cost-effective only for those patients who have

frequent migraines, and the cost per migraine prevented is an important determinant of the actual number of headaches per month that must be prevented for an agent to be cost-effective.[18] (This measure has been called the cost-equivalent number—the monthly number of headaches at which the cost of acute management, including, but not limited to, abortive medications, would surpass the monthly cost of prophylaxis. If this number is lower than the actual number of headaches that typically occur in 1 month, a preventive agent would be considered cost-effective.[19]) Compared with the antiepileptics, the beta blocker propranolol offers effective prophylaxis at low cost.[20]

A small open-label trial of botulinum toxin was conducted in 5 patients with migraine that was unresponsive to conventional antimigraine medications. After 1 year of injections at 3-month intervals, the use of other migraine medications had decreased from pretreatment levels, as measured by the change in annual costs for other medications. These costs declined from the $1002 to $3524 range before botulinum toxin treatment to the $0 to $1285 range after treatment. When the cost of the botulinum treatment itself was included, the total change in annual medication cost ranged from an increase of $648 to a decrease of $2717. All of the patients showed substantial clinical improvement with no reported adverse events; migraine symptoms typically decreased within a few days after each injection, and maximal effects were noted over the 2 months after treatment.[21] Since then, a number of controlled studies have assessed the tolerability and effectiveness of botulinum toxin as prophylaxis in patients with migraine.[22-28]

High-dose riboflavin (typically, 400 mg/day) has been reported to be an effective approach to migraine prophylaxis since 1994. Several trials indicate that it is significantly better than placebo and generally well tolerated.[29-32] In addition, the low cost of riboflavin suggests that it should be cost-effective; however, there have been no well-designed clinical trials providing a direct comparison between this novel approach and standard migraine prevention drugs.

Table 2. Prophylactic Antimigraine Medications

Drug category	Approved	Nonapproved
Beta blockers	Propranolol, timolol	Atenolol, etc
Antiepileptics	Divalproex, topiramate	Gabapentin, etc
Other		Calcium channel blockers, antidepressants

A Budget Management Model

A budgetary model provides a theoretical basis for predicting the cost outcome of selecting a given approach to migraine management. This model focuses on the use of botulinum toxin for prophylaxis in chronic migraine patients enrolled in a commercial managed care plan. The goal is to assess the impact of a decision to allow the use of botulinum toxin, in terms of cost effect for the plan as a whole.

Certain assumptions about the target population are made. Prophylaxis will be given to migraine patients who seek treatment and are determined to have a chronic condition based on experiencing headache on at least 15 days each month. It is estimated that 12% of the population has migraine, that 40% of migraine patients seek treatment, that 25% of patients who seek treatment have chronic migraine (at least 15 episodes per month), and that 2% of patients with chronic migraine receive botulinum toxin as prophylaxis. Thus, in a population of 1 million patients, 240 will receive botulinum toxin as prophylaxis for chronic migraine:

$$1\,000\,000 \times 0.12 \times 0.40 \times 0.25 \times 0.02 = 240$$

In calculating the cost of prophylaxis with botulinum toxin, treatment at a standard interval of 3 months means that patients would receive 4 treatments per year. With the cost of each treatment given as $521.25, the yearly cost per patient is $2085, and the total yearly cost for 240 patients is $500 400.

Offsetting these costs, prophylaxis is expected to reduce the amount of headache medication (abortive treatment) required.[28,33] For example, a 65% reduction in the overall use of triptans represents a decrease of

$576 760 for headache-related medications over the course of 1 year; $576 760 minus $500 400 acquisition cost for botulinum toxin yields a net annual savings of $76 360. Thus, in a plan with 1 million members, the savings associated with migraine prophylaxis using botulinum toxin represents a change of less than 1 cent in overall cost per member per month ($76 360 divided by 12 million member months is a reduction of approximately $0.006 per member per month). The point, however, is not the insignificant change in cost, but that superior clinical outcomes in migraine management can be obtained with no increase in cost.

Not counted in this model, a decrease in emergency department visits and hospitalization as a result of effective migraine prophylaxis would be expected to augment these savings. This expectation is consistent with the findings of a prospective, open-label, observational study in which patients with headache, referred by physicians or identified from emergency department records, attended a group session led by a registered nurse practitioner, followed by individual consultation. The goal was to assess the cost of triptan drugs and headache-related visits for 6 months before and after the intervention. Among 264 patients, the 6-month cost for triptan costs increased by $5423 (19%), but headache-related visits to the office and emergency department were reduced by 32% and 49%, respectively. These reductions in headache-related visits resulted in a net savings of $18 757, despite the increase in costs for triptans. The greatest clinical improvements were seen in patients whose conditions were most severe at baseline.[32] In summary, it is reasonable to expect improved management to yield meaningful cost savings despite increased expenditures for antimigraine medications.

These types of analyses can provide a rational basis for managed care to make appropriate decisions about treatment and coverage for patients with migraine.

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