Burden of Migraine and Impact of Emerging Therapies on Managed Care

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ABSTRACT

Migraine is a highly prevalent neurological condition with substantial impact on individuals through associated complications, comorbidities, and increased healthcare costs. The burden on society is likewise substantial via increased healthcare costs and greater indirect costs, such as lost productivity. Research about the pathophysiology of migraine has led to the introduction of a new class of drugs, calcitonin gene-related peptide (CGRP) inhibitors. Current drugs in this class are biologics, which are often accompanied by high prices. A highly competitive and rapidly evolving market landscape is being shaped by biopharmaceutical manufacturers and managed care payers. With an understanding of the societal impact of migraine and the potential impact of CGRP biologics, healthcare providers and managed care professionals should be prepared to develop policies and procedures to ensure appropriate patient access to new therapies.


For author information and disclosures, see end of text.

Burden of Migraine

Individual and Societal Burden

The burden of migraine takes many forms and, by several measures, makes a substantial global impact by causing considerable disability. Estimates on the annual direct costs of migraine in the United States range from $9 billion to $28 billion.1-3 The ranking of migraine in the Global Burden of Disease (GBD) survey in terms of years lived with disability (YLDs) has increased steadily from 19th in 2000 to sixth in 2013 and to second in 2016.4-6 When focusing on disability-adjusted life-years (DALYs) in people between the ages of 15 years and 49 years, migraine ranked as the third cause of disability in 2015 and first in 2016.5,7 The increase in global YLD ranking may be a result of better and more comprehensive data collection rather than an increase in prevalence; however, with improvements in data, the impact of migraine becomes more apparent. In 2016 alone, an estimated 1.04 billion people worldwide experienced migraine and contributed to 45.1 million YLDs.6,8

Results from the American Migraine Prevalence and Prevention (AMPP) Study and other surveys provide context about migraine in the United States. The AMPP study results determined that the 1-year prevalence of migraine in adults aged 15 years to 59 years was 11.7%, with a higher prevalence in women (17.1%) compared with men (5.6%).9 Other surveys, such as the National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey, the National Ambulatory Care Survey, and the National Hospital Ambulatory Medical Care Survey, combined migraine with severe headache data,10 which may overestimate the prevalence of migraine. A closer look at data within the various surveys can highlight certain trends. Women consistently exhibit higher prevalence of migraine and severe headache compared with men.3,9,10 Age is also a factor, with prevalence appearing to peak in middle age, particularly for women.3 The effect of socioeconomic status should also be considered when addressing the impact of migraine. Both the AMPP and the NHIS indicate that lower socioeconomic status coincides with an increased prevalence of migraine (AMPP)11 and migraine or severe headache (NHIS).10
**Direct and Indirect Costs**

As expected with a condition of such extensive prevalence, direct and indirect costs of migraine are substantial. In recently published papers, total direct annual costs per patient were estimated to be between $11,010 and $13,032, and both estimates were significantly greater than controls without migraine by $6575 to $9798. Bonafede et al compared their results to previously published data that used similar methods. Adjusting for inflation, Bonafede et al estimated a $6575 incremental direct cost due to migraine, which was 1.82 times greater than the previous estimate of $3609 by Hawkins et al. With the higher estimated direct costs, Bonafede et al estimated the annual direct costs of migraine in the United States to be at least $28 billion, which is greater than other estimates of annual direct healthcare costs that range from $9.20 billion to $11.07 billion. Direct costs may also be affected by chronic versus episodic migraine status. Patients with chronic migraine may incur $3238 more in annual direct costs compared with patients with episodic migraine, suggesting that individuals who experience chronic migraine drive the bulk of migraine costs. Although the estimates may vary, the impact of multibillion-dollar annual direct healthcare costs is staggering.

The indirect costs of migraine are also substantial, with annual estimates similarly in the billions of dollars. Hawkins et al acknowledged that their estimate of annual indirect cost of $12 billion is likely an underestimate primarily because presenteeism was excluded in their analysis. Annual indirect costs on a per-patient basis were similarly greater in the migraine cohorts versus controls by $2350, with $11,294 in indirect costs for patients with migraine compared with $8945 in indirect costs for control patients. The patient's status of chronic or episodic migraine also contributes to differences in indirect costs. A study by Munakata et al estimated that the costs of lost productivity per person per year was $5392 for patients with chronic migraine compared with $978 for patients with episodic migraine for an incremental cost of $4414. On the other hand, Messali et al reported a more modest difference, with $2357 in incremental annual indirect costs for patients with chronic migraine ($3300) compared with patients with episodic migraine ($943). Overall, Messali et al determined that total, direct, and indirect costs were all significantly greater in chronic migraine compared with episodic migraine.

**Work Productivity: Absenteeism and Presenteeism**

Loss of work productivity in the forms of absenteeism and presenteeism (working while sick/impaired) represents the indirect costs of an illness. As described previously, indirect costs due to migraine are upwards of $12 billion, excluding presenteeism concerns. Presenteeism, however, can contribute substantially to indirect costs of migraine. Another annual estimated indirect cost (in 1999 USD) of $13.3 billion attributed $7.9 billion to absenteeism and $5.4 billion to diminished productivity. In a survey study, respondents indicated that 64% of migraines occurred during weekdays and, of those weekday migraines, 68% interfered with work productivity in absenteeism, presenteeism, or both. Study results also suggest that presenteeism accounted for more work-hours lost (1470 work-hour equivalents) compared with absenteeism (1169 work-hours). Individuals with migraine may miss an additional 4 to 8 workdays per year, but appropriate treatment may reduce the losses in worker productivity. The relative contribution of presenteeism versus absenteeism may be an important factor in addressing certain impacts of migraine, but the overall magnitude of indirect costs may be more important to consider.

**Personal Life Impact**

Per the GBD, migraine ranked second in YLDs in 2016 and contributed to 45.1 million YLDs. With that magnitude of disability, the impact on the lives of individuals can be difficult to overestimate. Health-related quality-of-life (HRQOL) surveys, including headache-specific tools (eg, the Migraine-Specific Quality of Life Questionnaire Version 2.1 [MSQ]), serve to help frame the effect of migraine on individuals. Individuals with migraine scored lower on HRQOL surveys compared with the control participants, and patients with chronic migraine tended to score lower on HRQOL parameters compared with patients with episodic migraine. Researchers are also becoming interested in the impact of the condition on family members of individuals with migraine as well as the effect of treatment modalities on HRQOL.

Employment issues may also be considered a component of the personal life impact due to migraine. In their study of direct and indirect costs, Messali et al observed that a lower percentage of individuals with chronic migraine are employed (full- or part-time) compared with patients with episodic migraine (49.5% for chronic vs 60.5% for episodic). The authors acknowledge that the opportunity cost of unemployment is not adequately captured in indirect cost analysis and they suggest that this opportunity cost may be substantial. Considering the role of work life in modern society, the opportunity cost may extend beyond economic costs to impact an individual’s personal life. Whether employment costs, healthcare costs, quality of life, or comorbidities, the effects of migraine on an individual’s life can be substantial, and healthcare providers should be mindful of the myriad ways that migraine impacts patients.

**Comorbidities**

In addition to QOL issues, a number of comorbidities can accompany migraine. Psychiatric conditions that often occur along with migraine include depression, anxiety disorder, and bipolar disorder. Other comorbidities include fibromyalgia, restless legs syndrome, and epilepsy, among others. The issue of chronic...
versus episodic migraine also relates to comorbidities, with individuals with chronic migraine more likely to have a comorbidity, including depression and anxiety; higher healthcare costs also correspond with the presence of a comorbidity. There is also mounting evidence that migraine is associated with increased risk of cardiovascular and cerebrovascular events, such as stroke and myocardial infarction.

Impact of Emerging Therapies on Managed Care

Historic Review of the Last Major Change in Migraine Management: Introduction of Triptans

With the advent of CGRP-targeted biologics, migraine therapy appears to be poised for another revolutionary change. Such advances in treatment have not been seen in the 20 years since the last major evolution of migraine therapy occurred with the introduction of triptans, which were considered to be the most important breakthrough in 50 years.

Triptans became a first-line therapy per evidence-based treatment guidelines based on their efficacy and safety. Several studies, many of which were sponsored by pharmaceutical companies, have analyzed the pharmacoeconomics of triptans as well as their effect on overall healthcare costs. Given different methodologies, efficacies, and outcomes, identifying a single best triptan is neither practical nor feasible. For example, the same research group found opposite effects of triptan use on healthcare costs based on differences in patient populations.

Availability of generic versions of triptans subsequent to the analyses also may impact economic conclusions. Variability in costs and patient response to triptans may warrant the inclusion of multiple triptans in formularies. Payers have managed costs associated with triptan therapy through common methods, such as step therapy, by potentially requiring other therapies (eg, nonsteroidal anti-inflammatory drugs or preventive rather than abortive treatments) as a prerequisite before triptan use and monthly quantity limits. Payers have also included triptans with different dosage forms (injectable, oral, nasal) in formularies. As a result, insurance coverage, access barriers to triptans, and quantity limits vary widely across both government and private insurance plans.

In addition, access to triptans may be affected by socioeconomic status either alone or as a result of the type and extent of health insurance coverage. Although triptans are effective both therapeutically and economically, the drugs are not appropriate for a substantial portion of the population with migraine due to cardiovascular complications and contraindications; thus, the role of new therapies in managed care may be impacted. The experience with triptans provides context for managed care approaches to new migraine therapies, and pharmacoeconomic and health economic studies with the new drugs will be needed to help determine the best approach to provide quality medical care to individuals with migraine.

Implication of Emerging Therapies on Migraine Treatment

When new drug therapies are introduced for a condition or disease, 2 concerns remain paramount: (1) the efficacy/safety in a particular patient population and (2) the costs of the new drugs. Although the efficacy and safety parameters are evaluated by the FDA before drug approval, real-world efficacy and safety data will emerge as a broader population uses the new drug. The cost of the drug, whether to the patient, insurer, or payer, can become a complicated matter. Before the introduction of CGRP inhibitors and 5-HT1F agents in migraine therapy, managed care professionals incorporated triptans and onabotulinum toxin onto formularies to various extents, typically with step-therapy procedures, prior authorization requirements, and/or monthly quantity limits. Similar approaches would be expected for emerging migraine therapies. As injectable biologics, the current CGRP inhibitors are expected to come with higher costs and different administration concerns. Therefore, to evaluate the potential impact of the costs of CGRP inhibitors on managed care decision making, the historical examples of hepatitis C drugs and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors as well as the current pricing and marketing strategies employed for CGRP inhibitors will be reviewed.

Presentation of an Analogue Case (Similar Number of Patients Affected, Similar Costs) to Demonstrate Potential Impact of a New Biologic

As managed care professionals and clinicians prepare for new migraine drugs, 2 previous examples of costly, novel drugs may provide perspective. In the first instance, the introduction of antiviral drugs for hepatitis C created extraordinary financial pressures on the US healthcare system. Focusing on Medicare Part D, spending on hepatitis C drugs increased more than 15-fold from $283 million in 2013 to $4.5 billion in 2014. The out-of-pocket spending for a Medicare Part D patient with hepatitis C (without a subsidy) ranged from $6297 to $10,889 for a course of treatment. Such large drug costs are becoming increasingly common and cost shifting to higher co-payments and deductibles has become commonplace.

The PCSK9 inhibitors represent a new class of monoclonal antibody drugs for hyperlipidemia. Patients hoping to obtain access to PCSK9 inhibitors have encountered hurdles of more cumbersome prior authorization requirements and high prior authorization rejection rates. Because the drugs’ high price tags may have negatively affected market growth, pharmaceutical companies marketing one of the PCSK9 inhibitors, alirocumab, struck a deal in 2018 with a major pharmacy benefit manager to lower the price via rebates. In response to lagging sales apparently due to the high costs and lack of payer coverage, the manufacturer of evolocumab decreased the list price of that drug in October 2018 by approximately 60% from over $14,000 annually to $5850 annually.
patient access issues for new migraine drugs may not mirror those of hepatitis C drugs or PCSK9 inhibitors, but these examples serve to illustrate the impact of drug cost, appropriate utilization, and the role of payers in managing costs and access.

**Forward-looking Strategic Planning Using Analogue Biologics and Historic Data**
The prevalence of migraine contributes to the heightened interest in finding novel and effective therapies for preventing and treating the condition. As new migraine treatments become commercially available, the big questions of cost and access come to the forefront. A complex interplay among manufacturers, payers, pharmacy benefit managers, clinicians, and patients creates an atmosphere of uncertainty regarding the availability of new migraine drugs. Managed care professionals can apply historical experience with hepatitis C therapies and PCSK9 inhibitors for hyperlipidemia (which is still evolving) to new migraine drugs, but those examples may not be relevant as numerous competitive products have come to market almost simultaneously. As these new agents jockey for market share position and acceptance by managed care, manufacturers have been taking the novel approach of providing the migraine drugs to commercially insured patients initially at no cost or using an outcome-based pricing strategy. Based on anecdotal reports, it appears that these programs may be in place for up to 1 year of therapy. The manufacturers may be hedging their bets by gaining patient acceptance before insurer acceptance, thereby hoping to add pressure to payers to cover or authorize therapy for a patient if their migraine therapy is producing the expected results.

Recent reports suggest that the approach may have mixed results as 1 major pharmacy benefit manager announced that it would cover new migraine drugs from 2 of the manufacturers but not from the third. With the 3 CGRP inhibitor products similarly priced at approximately $6900, market differentiation may depend on ease of administration, patient support services, and patient preference, in addition to efficacy and safety. Appropriately determining which patients would most benefit from CGRP inhibitor treatment will also be critical to the uptake of these products and to the potential reduction of the use of acute migraine treatments. At least 1 pharmacy benefit manager company has publicly announced a specific approach to managing access to CGRP inhibitors. Given the hypercompetitive, multibillion–dollar biopharmaceutical market, rapid changes and surprising efforts to gain market share for new migraine therapies can be expected.

**Conclusions**
The economic impact of migraine (both via direct and indirect costs) puts a substantial burden on patients and on society. New biologic therapies that inhibit CGRP may provide relief to patients with migraine but concerns about costs may limit patient access. Biopharmaceutical manufacturers are competing for market share and inclusion in payer formularies through a variety of approaches. As demand for CGRP inhibitors increases, managed care professionals may anticipate a range of payer mechanisms that will ideally balance patient access concerns with budgetary issues.

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**Funding source:** This activity is supported by educational funding provided by Teva Pharmaceuticals.

**Author disclosure:** Dr. Rich has no relevant financial relationships with commercial interests to disclose.

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**Medical writing and editorial support provided by:** Thomas J. Cook, PhD, KPhP.

**REFERENCES**


