Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care

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For more than 10 years, Brandes has been involved in clinical trials as principal or coprincipal investigator, primarily examining issues in migraine such as acute treatment, prophylaxis, and menstrual migraine. She lectures on these subjects and others in grand rounds and symposia nationally and internationally. Brandes has written on such topics as migraine as a predictor for the presence of other serotoninergic disorders, postcraniotomy headache syndrome, and medical treatment of headache after suboccipital acoustic tumor removal. A contributor to the medical literature, her work has appeared in such journals as JAMA, Headache, American Surgeon, Laryngoscope, American Journal of Otology, and Virology. She also sits on the editorial board of Headache.

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ABSTRACT

OBJECTIVE: To provide managed care pharmacists with information regarding the prevalence and burden of migraine in the United States, approaches to diagnosing and managing migraine, and implications for managed care organizations.

SUMMARY: Migraine is a common chronic condition that imparts tremendous disability to those afflicted. Economic costs associated with migraine are staggering, with the majority of costs resulting from lost workdays. Barriers to the proper management of migraine patients include misdiagnosis and a limited understanding of available pharmacological and nonpharmacological treatment options. Use of screening tools in primary care may help diagnose migraine and point to appropriate treatment plans. The use of migraine-specific therapies is discussed, with special emphasis on triptans, which have demonstrated efficacy and modest side effects. Use of triptans has been shown to reduce migraine-associated disability and overall costs associated with migraine. Studies comparing the effectiveness and costs of individual triptans are also described.

CONCLUSIONS: Migraine-associated pain and disability can be significantly reduced with proper treatment. Use of diagnostic tools, such as ID Migraine, can facilitate the identification of migraine patients who need treatment. A stratified care approach with appropriate treatment can improve the lives of migraine sufferers as well as reduce migraine-associated costs for managed care organizations.

KEYWORDS: Migraine, Cost-effectiveness, IHS criteria, Triptans, ID Migraine

The Prevalence and Burden of Migraine in Relieving the Burden in Managed Care

Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care

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There are various aspects of the broad burden of migraine (Figure 2). Migraine creates a social burden, affecting relationships, family life, and the ability to participate in social engagements. More than 50% of patients with migraine report interference with social activities and nearly 60% report significant impact on relationships with family members. Migraine also hinders activities of daily living (e.g., the ability to do household chores) and work performance, causing work absenteeism and impacting career prospects. As expected, health care resources are also greatly burdened by migraine.7-9

The impact of migraine is greatest on the individual sufferer. Seventy-five percent of migraine sufferers report severe to extremely severe pain during migraine attacks; 92% report impairment with their migraines; and 53% report severe impairment in activities or that they require bed rest. This debilitation is reflected in the reduced work productivity of migraineurs. More than 90% of migraine sufferers miss 1 or more days of work per year because of their condition, and more than 50% of female migraine sufferers miss 6 or more total workday equivalents per year due to an attack.10

The Economics of Migraine

According to a 1999 study, the economic burden of migraine in the United States totaled $14 billion in 1998. Direct medical costs, such as inpatient, outpatient, and prescription drug costs, accounted for approximately $1 billion, while indirect costs accounted for the great majority of the economic burden. Indirect costs of migraine, attributable to missed workdays and reduced worker productivity, were estimated at $13 billion annually. Migraine-related missed workdays alone accounted for almost $8 billion (This figure did not take into account the large group of patients who continued to go to work while suffering with migraine. Working migraineurs are far less productive and, therefore, also contribute to economic losses for their employers.). The majority (57%) of direct costs of migraine were attributable to physician visits, while prescription costs accounted for 29% of direct costs.11

This 13 to 1 ratio of indirect to direct costs is not characteristic of most other disease states. It suggests that money spent on diagnosing and treating migraine, which can enable migraineurs to return to work and be productive while at work, will lead to much greater returns for the employer. Hence, the employer will get the “biggest bang for the buck” for funds spent on health care that will enable the migraineur to return to work.

In a comparison study enrolling 1,087 subjects who reported moderate or severe migraine and an equal number of migraine-free subjects, migraineurs were found to have significantly more visits to general practitioners, specialists, psychiatrists, and emergency rooms (ERs).12 The subjects completed a 12-page questionnaire regarding their health status, use of health care resources, and time lost from home or employment duties because of illness. In order to maximize recall accuracy, resource use and time lost were reported only for the previous 6 months. Subjects were geographically representative of the U.S. population. As would be expected, migraineurs incurred significantly higher direct and indirect costs as a result of their increased health care utilization. Over a span of 6 months, the mean total cost (direct medical costs and lost productivity) of migraineurs was $1,242 (direct medical costs, $522) compared with a mean total cost of $929 (direct medical costs, $415) for nonmigraineurs (P = .006). The direct health care costs were based on U.S. averages for 1992-1993 and lost productivity on mean personal income for full-time workers in 1995. The primary direct-cost drivers were outpatient and ER visits (P <.001). Compared with patients with moderate migraine, patients with severe migraine had higher indirect costs such as lost productivity ($1,021 versus $251, P <.001) and higher total direct and indirect costs ($1,656 versus $685, P <.001). Since migraine is an expensive illness, with the majority of financial burden linked to indirect costs, employers, insurance companies, and managed care organizations have an economic stake in reducing the migraine burden.

The Effectiveness and Costs of Migraine Treatment in Managed Care

Migraineurs have significantly more health care utilization and expenses than nonmigraineurs. A retrospective study that reviewed medical and pharmacy claims within a managed care organization over an 18-month period found that migraineurs have nearly twice the medical claims and nearly 2.5 times the pharmacy claims as nonmigraineurs. The study found that medical and pharmacy claims totaled $3.4 million for the migraine group (n = 1,336) compared with $2.1 million for the comparison group (n = 1,336). The cost of diagnostic procedures totaled $83,537 for the migraine group compared with only $13,140 for the comparison group. In the migraine group, 525 patients underwent 612 magnetic resonance imaging (MRI), computed tomography (CT), and X-ray diagnostic procedures.
compared with 101 comparison group patients who underwent 121 such procedures. And yet, according to Academy of Neurology guidelines, migraineurs with stable patterns of headache, no history of seizures, and normal neurologic exam do not need or require imaging.

The indirect costs of migraine have also been studied in a managed care population. Estimates of the annual indirect costs associated with migraine in a managed care population, including workplace and domestic productivity losses for persons employed outside the home, persons engaged in household production, and persons unable to work, averaged $4,548 per male migraine patient and $4,897 per female migraine patient (in 1990 dollars). This study also found that indirect costs increased with escalating headache severity.

### Migraine Cost Management in Managed Care

At Kaiser Permanente, Maizels and colleagues examined the impact of a group-based model of disease management for 264 patients with headache in a prospective, open-label, observational study. Key objectives of this approach were the identification of appropriate patients and proactive intervention. Patients who were identified or referred with headache attended a group education session and later had follow-up consultations. Triptan costs and headache-related visits were documented over the course of 6 months as were changes in the patients' headache frequency and severity. This approach resulted in a 49% reduction in headache-related ER visits, a 32% reduction in clinic visits, and significant clinical improvement. Although there was a 19% increase in pharmacy costs ($5,423)—most likely due to better diagnosis of patients and more appropriate use of triptans—overall, health care costs were reduced by $18,757 despite increased triptan costs. This demonstrates that increasing the diagnosis and management of migraine could lead to better outcomes for patients as well as potentially lower overall costs for a managed care organization.

This example of a cost-management approach demonstrated improved control of migraine suffering as well as the costs associated with this debilitating condition. Since migraine prevalence and associated disability affect more than 12% of the U.S. population and economic costs are billions of dollars annually, managed care organizations have a large stake in the identification and treatment of migraineurs.

### Simplifying the Diagnostic Process: A New, Validated Screening Tool for Migraine

**Underdiagnosis and Undertreatment of Migraine**

Proper diagnosis and treatment of migraine improves patients' lives and reduces the overall economic burden associated with migraine. However, despite the high prevalence and debilitating effects of migraine, many migraineurs do not receive adequate care. Possible reasons for this include reluctance of the migraineur to seek medical assistance, improper diagnosis by physicians, and ineffective prescribed treatments. Often, patients do not consult a physician because they believe that their headaches are simply an aspect of their lives they must endure, possibly because they have seen family members suffer without seeking treatment. Poor experiences with older drugs and lack of physician empathy are other reasons patients do not seek medical attention. A U.S. population-based study using self-administered questionnaires surveyed 14,000 households and found that 59% of men and 49% of women whose symptoms were consistent with the International Headache Society (IHS) diagnosis of migraine had never been diagnosed by a physician, even though they experienced frequent and disabling headaches. In fact, 61% of these subjects who were not consulting a physician reported severe or very severe pain, and 67% reported severe disability or the need for bed rest.

Among the migraine patients who do consult a physician, it is reported that 40% do not receive a diagnosis of migraine. In one study examining the prevalence and diagnosis of migraine in primary care settings, patients who presented to PCPs with headache were instructed to record the symptoms of their next 6 headache attacks in diaries, which were then reviewed by a panel of headache experts. Using IHS criteria, 94% of the patients diagnosed with migraine-type headache, 3% with episodic tension-type headache, and 3% were unclassifiable. This shows that the majority of patients presenting to PCPs with episodic disabling headache have migraine headaches. Tension-type headache, while more common in the population (lifetime prevalence is 66%), is an uncommon office complaint. The same study also looked at how accurately PCPs diagnosed their patients with headache. Of the patients diagnosed with migraine (n = 272), 98% had received an accurate diagnosis. But, 82% of the patients with a diagnosis of nonmigraine primary headache (n = 105) also had descriptions in their diaries consistent with migraine headache.

Studies have also demonstrated that many diagnosed migraineurs are undertreated. In one study, 23% of patients diagnosed with migraine received prescription medication, 49% received over-the-counter (OTC) medication, 23% received both prescription and OTC medication, and 5% received no medication. The high percentage of patients on OTC remedies parallels the finding that most patients with migraine have not been diagnosed by a physician. These patients are probably not receiving adequate treatment.

**The Patient Role in Migraine Management**

Even patients receiving prescription medication do not always adequately manage their migraine. In a multinational study examining the measures migraine patients use to supplement prescription medication, bed rest was found to be the most widely used, with 62% of patients reporting supplemental bed rest. This underscores the fact that, although they are medicated, many migraineurs are at times unable to function or work, suggesting that patients are not optimally using migraine-specific medications.

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Clearly, there is an opportunity for improved migraine management. When patients consult a physician but do not have success with prescribed treatment, they will often lapse and discontinue medical consultation, which could prevent them from receiving an alternative effective prescription. In addition, undiagnosed migraineurs often self-treat their condition. Although their prescription drug costs may be lower, these patients often incur greater costs through increased use of medical services, emergency department visits, and OTC medications.

These results highlight the need to educate the public about the effectiveness and availability of migraine treatments and to emphasize the importance of effectively communicating symptoms to their physicians. These studies also underscore the need for careful migraine screening in primary care. The diagnosis problem may be due, in part, to the limited time PCPs have with their patients or confusion with autonomic features or different presentations of migraine. Therefore, a simple and quick diagnostic procedure or screening tool for PCPs would be useful and valuable.

Understanding Triggers and Characteristics of Migraine Headaches

Acute episodes of migraine occur when there is a shift in the homeostatic equilibrium of the central nervous system. Headache is the most obvious manifestation of an acute attack, but sensory processing, cognition, gastrointestinal function, and autonomic reactions are also affected.

A single migraine attack may be divided into 4 different phases. First is the preheadache phase (or prodrome), in which many patients experience premonitory symptoms (e.g., food cravings, thirst, euphoria, photophobia, phonophobia, lethargy, or mood changes). This phase can begin anywhere from 48 hours to just a few minutes prior to the onset of headache. The second phase is the aura phase, which occurs in about 15% of migraine attacks and is characterized by focal neurologic symptoms that reflect cortical dysfunction. Aura usually precedes a migraine headache, but it may occur during the headache. An aura may also occur and not lead to headache (a condition termed “acephalgic migraine” or “migraine equivalent”). The third phase is the actual headache phase, which is represented by increasing severity of pain (from mild to moderate to severe) followed by a gradual decrease in pain until the headache subsides. The headache phase generally lasts 4 to 72 hours. The final phase is the postheadache phase, which occurs after pain relief is achieved. In some patients, postheadache symptoms (lethargy, irritability, and other symptoms) extend the “migraine-related disability” that is often associated with the headache phase, but is not associated with the actual headache pain.

Many factors may trigger a migraine attack, including internal stimuli such as hormonal changes, and external stimuli such as stress, changes in sleep habits, a change in weather, dietary factors such as alcohol, or flickering light. Clearly, some of these triggering events may be controllable, such as alcohol consumption, while other factors are unavoidable, such as weather changes. Some authors believe that anyone can have a migraine attack under the right circumstances. It is not the attack that is abnormal—it is the recurrence of the attack that is abnormal.

Food cravings associated with the prodrome phase are often mistaken for headache triggers. If patients are able to recognize the prodrome and get treatment (e.g., naproxen sodium, triptans, or dopamine agonists) at this phase, the actual headache phase may be averted. Stopping a migraine attack before it becomes debilitating can result in significant savings in terms of cost and suffering. The sooner the migraine pathway is shut down, the more likely the headache pain will be avoided or stopped.

The pathophysiology of migraine involves irritation of peripheral pain fibers, which leads to throbbing head pain, and sensitization of central neurons that process information arising from the scalp and facial skin, termed “central sensitization.” Sensitization of the central neurons may begin shortly after the onset of pain and causes a condition termed “cutaneous allodynia” in which ordinarily nonpainful stimuli evoke pain. Up to 79% of migraine patients experience allodynia, and most triptans are less effective or ineffective after allodynia has occurred. Patients who report that they “failed” triptan therapy may have been treated at this allodynic stage, without recognizing the presence of allodynia. The likelihood of therapy being successful is increased by using triptans prior to the development of allodynia.


diagnosis of migraine

Two widely used approaches for diagnosing migraine are (1) a symptom-based approach, using IHS criteria, which distinguishes headache types by differences in symptoms, and (2) an impact-based approach, which emphasizes impact as the most consistent migraine feature. IHS criteria differentiate among different types of headaches. With an impact-based approach, physicians base their diagnosis and treatment on a patient’s answers to a series of questions asked about their headache.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Symptom-Based Approach to Diagnosing Migraine: International Headache Society Criteria for Migraine Without Aura</th>
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<tbody>
<tr>
<td>• At least 5 attacks</td>
<td></td>
</tr>
<tr>
<td>• Pain (2 of 4)</td>
<td></td>
</tr>
<tr>
<td>• Unilateral</td>
<td></td>
</tr>
<tr>
<td>• Throbbing</td>
<td></td>
</tr>
<tr>
<td>• Moderate to severe</td>
<td></td>
</tr>
<tr>
<td>• Aggravated with activity</td>
<td></td>
</tr>
<tr>
<td>• In addition (1 of 2)</td>
<td></td>
</tr>
<tr>
<td>• Nausea and/or vomiting</td>
<td></td>
</tr>
<tr>
<td>• Photophobia and phonophobia</td>
<td></td>
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<tr>
<td>• No evidence of organic disease</td>
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</tbody>
</table>
frequency and headache-associated disability. These 2 approaches are illustrated in Table 1 and Table 2.

When migraine is misdiagnosed, it is often thought to be sinus headache, or, less often, tension headache. Both migraine and sinus headaches can be triggered by changes in the weather due to changes in barometric pressure. For both, pain can be bilateral and in the areas of the sinuses. Sinus medication may relieve the symptoms of migraine, which often prompts a diagnosis of sinus headache. When the headaches continue, these patients are often referred to allergists and may receive full allergy workups. After finding that they have no allergies, the patients may be referred to ear, nose, and throat specialists. If imaging studies are performed, they may include CT scans and MRIs of the sinuses. In extreme cases, patients may even undergo sinus surgery in the hope that it will alleviate their headaches. Obviously, the costs associated with these procedures and medications can be enormous, and the patient may continue to suffer from debilitating headache.

This hypothetical scenario has support from studies that examined patients with either self-described sinus headache or physician-diagnosed sinus headache. In one prospective, multicenter study of 3,038 patients with either self-described or physician-diagnosed sinus headache, IHS criteria were used to rere diagnose the patients. Eighty percent of these patients met the IHS criteria for migraine with or without aura, and an additional 8% met IHS criteria for “migrainous” headache, which is a headache that has all but 1 characteristic of a true migraine headache. A second study found that 69% of subjects with self-described and/or physician-diagnosed sinus headache obtained pain relief with a migraine medication (sumatriptan 50 mg) compared with 43% of patients treated with placebo (P<0.001).

Migraine is also often confused with tension-type headache (sometimes referred to as stress, tension, or muscle contraction headache). Differentiating between these headache types is complicated because of their overlapping symptoms. Some tension-type headache sufferers experience migraine-like symptoms such as throbbing or unilateral pain, visual disturbances, or nausea, while many migraineurs experience muscle tension and associated neck pain, which are often wrongly thought to be a unique feature of tension-type headache. Therefore, headache sufferers complaining of neck pain are often diagnosed with tension-type headache when, in fact, they have migraine. One study of 144 migraineurs found that 75% experienced neck pain. In another study, 83% of individuals with headaches meeting IHS criteria for migraine also had headaches meeting IHS criteria for tension-type headache. These findings reinforce the need for improved accuracy of migraine diagnosis in primary care.

### Diagnostic Tools to Assess and Identify Migraine

Several diagnostic tools and questionnaires have been designed to assess the impact and severity of migraine. From a primary care standpoint, however, some are too lengthy or complex to be practical, and others are not validated for use in a primary care setting. The Migraine Disability Assessment Scale (MIDAS) and the Headache Impact Test (HIT-6) are 2 tools appropriate for use in primary care. They assess time lost from work and other activities to measure the impact of migraine, and they allow patients to be followed over the course of months or years to track treatment successes and failures. These tools also help stimulate discussions between patients and doctors.

#### ID Migraine

In order to improve diagnosis of migraine in primary care settings, the U.S. Headache Consortium Guidelines recommend the use of screening or case-finding instruments. Given the need for a practical diagnostic tool to support the needs of both physicians and patients, a new diagnostic tool called ID Migraine was recently developed by Richard Lipton in collaboration with Pfizer Inc.

ID Migraine was developed to help physicians quickly identify migraine among their headache patients even when migraine is obscured by comorbidities or other types of headache. ID Migraine also provides patients with a means of quickly and clearly communicating their symptoms to their physicians. This migraine screener was tested in a study of 563 patients in a primary care setting, and headache experts using IHS criteria confirmed its validity and reliability. The sensitivity and specificity of 9 screening items (nausea, disability, photophobia, pain on 1 side, phonophobia, pain exacerbated by activity, moderate to severe pain, throbbing pain, and aura symptoms) were calculated. Although all the items were associated with migraine, the combination of 3—nausea, disability, and photophobia—was the most predictive of the presence of migraine, and therefore they were chosen for inclusion on the screener. Nausea was found to have an odds ratio of 3.97 (i.e., a headache patient with nausea is 3.97 times more likely to have migraine than a patient without...
symptoms of nausea), disability had an odds ratio of 3.82, and photophobia had an odds ratio of 3.30.

The questions of ID Migraine are shown in Figure 3. Empirical testing of combinations of these 3 individual items found that the optimal scoring method is to regard 2 "yes" answers as indicating a positive diagnosis of migraine. This 2-out-of-3 scoring yielded a 3-item screening tool with a sensitivity of 81% (95% confidence interval [CI], 77%-85%; i.e., 81% of patients who did have migraine were identified as having migraine), a specificity of 75% (95% CI, 64%-84%; i.e., 75% of patients who did not have migraine were identified as not having migraine), and a positive predictive value of 93% (95% CI, 89.9%-95.8%; i.e., 93% of patients identified as positive for migraine on the screener actually had migraine). The reliability of ID Migraine is comparable with that of other screening tools used in primary care medicine, for example, the prostate-specific antigen (PSA) test for prostate cancer (sensitivity, 75%; specificity, 74%) and the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) for major depression (sensitivity, 75%; specificity, 90%). ID Migraine is an easy-to-use, validated tool, which should prove valuable for identifying migraine among patients with headache.

It is hoped that an increased emphasis on diagnosing migraine in primary care and effective screening tools such as ID Migraine will increase the proportion of migraineurs who receive a proper diagnosis and can, in turn, receive adequate treatment. These advances will not only improve the lives of migraine sufferers but also will reduce the enormous economic burden migraine places on employers and managed care organizations.

### Matching Patient Profiles with Effective Treatment: A Comprehensive Review of Triptan Therapy

Once the hurdles of recognizing and diagnosing migraine have been met, the question of how best to treat the migraine patient arises. Although there are several pharmacologic options available, too often there is a gap between the medications available and the patient in need; the hope is that this gap can be bridged with individualized treatment plans.

#### Triptans

The triptans are a class of selective serotonin (5-HT1B/1D) agonists for the treatment of migraine. Seven triptans are clinically available: sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan. Triptans have several advantages over ergot derivatives, which were previously the only relatively specific treatments for migraine attacks. Triptans have a more selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescribing instructions, well-established efficacy, modest side effects, and well-established safety records. They are, however, contraindicated in the presence of cardiovascular disease and are more expensive than many older, oral ergots and OTC medications.

#### Step Care Versus Stratified Care

Traditionally, headache treatment strategies have followed a “step-care approach” in which treatment is initiated at the lower end of the therapeutic armamentarium (e.g., acetaminophen or aspirin) and then escalated if treatment fails. The process continues until an effective treatment is identified. This process may take place over the course of several attacks (“step care across attacks,” e.g., aspirin → acetaminophen combination → isometheptene combination → butalbital combination → triptan), or within the course of 1 attack (“step care within attacks,” e.g., naproxen sodium → second dose naproxen sodium → rescue medication). In contrast, “stratified care” consists of an initial treatment based on measurement of the severity of the illness. For example, choosing a treatment based on a MIDAS score, which indicates the level of migraine-associated disability. A patient with a low level of migraine-related disability may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), for example, whereas a patient with a high level of disability may be prescribed triptans alone or in combination with preventive treatments.

The Disability in Strategies of Care (DISC) trial was one of the first studies that looked at management strategies in migraine, comparing step care within attacks, step care across attacks, and
stratified care. The main outcome measures were headache response and disability time per treated attack (for 6 attacks). Results of the study demonstrated that stratified care provided significantly better clinical outcomes than either step-care approach.44

It is now recognized that successful treatment relies on matching the appropriate treatment to the severity and disability of migraine, as well as to the migraine stage. Many patients fare better if they are treated with a triptan at the beginning of their attack, when the triptan is most effective.45,46 In addition to patients faring better with a stratified treatment approach, this approach may be less costly. Step-care approaches require patients to return for additional office visits and prescriptions if the initial treatment fails. Failed prescriptions, increased use of rescue medication, and return office visits are all associated with increased direct costs for migraine care. In addition, patients may experience several attacks before finding the correct treatment, which could cause decreased work productivity and, therefore, increase the indirect costs of migraine as well.

**Treating Migraine Early and When Mild**

Clinical trials designed to evaluate migraine therapies typically require patients to wait until their headaches are moderate or severe in intensity before administering the study medication. The argument for early intervention, however, gained support from a post hoc analysis of the Spectrum Study, a large, randomized, placebo-controlled study of patients with disabling headaches.47 The subjects of this post hoc analysis were a subgroup of patients who violated protocol by treating their headaches while pain was mild to severe before finding the correct treatment, which could cause decreased work productivity and, therefore, increase the indirect costs of migraine as well.

An analysis of zolmitriptan showed similar results: 80% of headaches of mild pain intensity treated with zolmitriptan 5 mg achieved a pain-free response compared with 57% of headaches of moderate pain intensity and 35% of headaches of severe pain intensity.48 Similarly, in studies with eletriptan, pain-free responses were higher among patients who received eletriptan 40 mg while their headaches were mild compared with those who received it when headaches were moderate to severe (68% versus 39%; see Figure 4).49 Sustained pain-free rates were also higher among those who received eletriptan when pain was mild compared with those who received it when headaches were moderate to severe (56% versus 30%). In addition, recurrence of headache pain was lower among patients who treated mild headaches versus those who treated moderate-to-severe headaches (6% versus 21%).50 Results favoring the early treatment of migraine headaches with rizatriptan51 and almotriptan52 have also been reported. Therefore, studies consistently show that treating migraine patients early in the course of the attack or when the pain intensity is mild results in better outcomes, including higher rates of early pain-free response, higher sustained pain-free rates, and less recurrence. There is also speculation that effective early treatment from an early age (or in a patient’s early migraine experiences) may prevent escalation to more frequent and severe headaches or chronic headache.53 Thus, in clinical practice, the trend is now toward early aggressive treatment of migraine.

**Comorbidities**

Many migraine patients have additional medical conditions that can add to the pain and physical disability associated with migraine. Studies have demonstrated that major depression and panic disorder are the conditions having the strongest associations with migraine.54 Therefore, psychiatric, neurologic, and other medical disorders should be considered when designing a treatment plan for migraine.

**Migraine Management**

When designing the best migraine treatment plan, several factors need to be considered. Management should be individualized and stratified, such that the severity of the illness is assessed and treatment assigned accordingly. Choice of treatment should be based on an overall assessment of attack frequency and severity, presence and degree of disability, associated symptoms such as nausea or vomiting, prior response to medication and patient preferences, and comorbid or coexisting conditions.

It is also important to engage patients in their own management. Migraine patients should understand that migraine is a genetic, biological disorder, and it is not their “fault.” They should be educated on the basic mechanisms involved in migraine, including hyperexcitability of the brain, susceptibility to triggers, and phases of an attack. Patients should know how to recognize triggers of migraine, if present, and how to evaluate
changes in their condition in order to ensure that medications or doses are adjusted when needed.

The importance of headache diaries, disability questionnaires (e.g., MIDAS), and regular follow-up care as well as the advantages of early treatment and the possibility of illness progression should also be discussed. In addition, limits on dosing should be established to prevent medication overuse and “rebound headaches,” which may occur from excessive (more than 2 days per week) or frequent use of short-acting headache medications. The U.S. Headache Consortium published evidence-based guidelines for migraine headache in 2000. Their goals for long-term migraine treatment are to reduce headache frequency, severity, and disability; reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; improve quality of life; avoid acute headache medication escalation; educate and enable patients to manage their disease to enhance personal control of their migraine; and reduce headache-related distress and psychological symptoms. To meet these goals, the consortium recommends using migraine-specific agents (triptans, DHE) in patients with moderate or severe migraine or whose mild-to-moderate headaches respond poorly to NSAIDs or combinations such as aspirin plus acetaminophen plus caffeine. Of the migraine-specific medications, triptans are considered effective for the acute treatment of migraine headaches and are an appropriate initial treatment choice in patients with moderate-to-severe migraine who have no contraindications for their use. Initial treatment with any triptan is also a reasonable choice when the headache is moderate to severe or in migraine of any severity when nonspecific medication has failed to provide adequate relief in the past.

### Specific and Nonspecific Migraine Treatments

Several medications are available to treat migraine. Specific migraine treatments include ergotamine-containing compounds/dihydroergotamine (DHE) and triptans in oral, nasal spray, and subcutaneous formulations. Nonspecific treatments include NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, combination analgesics, opioids, neuroleptics/antiemetics, and corticosteroids.

Ferrari and colleagues performed a meta-analysis of 53 double-blind, randomized, controlled clinical trials of oral triptans in migraine. The efficacy and tolerability of 6 triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, and almotriptan) were compared, as described earlier. Two-hour data were not available for frovatriptan. The placebo response was subtracted from the active response to control for differences in study designs among the trials. As expected, all oral triptans were more effective than placebo; between 79% and 89% of patient responded in at least 1 of 3 treated attacks. Efficacy comparisons were based on rates of 2-hour headache response, 2-hour pain-free response, sustained pain-free response, and consistency of response. Tolerability comparisons were based on proportions of patients with at least 1 adverse event (AE), patients with at least 1 central nervous system AE, and for at least 1 chest AE. Comparisons of the main efficacy and tolerability measures for the oral triptans versus sumatriptan 100 mg are summarized in Table 4.

Three compounds showed favorable results compared with sumatriptan 100 mg; rizatriptan 10 mg had better efficacy and consistency, eletriptan 80 mg showed better efficacy, and almotriptan 12.5 mg showed better consistency and tolerability. Individual patient characteristics and preference vary, however, as does their response to a particular triptan. Therefore, finding the best triptan may require trial and error; failure of one triptan does not preclude success of another.

Many patients need more than one triptan, and sometimes more than one formulation, for effective migraine relief. For example, patients suffering from the nausea associated with migraine may only tolerate an inhaled or injectable formulation. Use of more than one triptan within 24 hours, however, is contraindicated. Physicians need more than one triptan in their repertoire to best treat patients with migraine. It should also be

### Triptans for Migraine Management

In order to aid in the selection of the most appropriate triptan, Ferrari and colleagues performed a meta-analysis of 53 double-blind, randomized, controlled clinical trials of oral triptans in migraine. The efficacy and tolerability of 6 triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, and almotriptan) were compared, as described earlier. Two-hour data were not available for frovatriptan. The placebo response was subtracted from the active response to control for differences in study designs among the trials. As expected, all oral triptans were more effective than placebo; between 79% and 89% of patient responded in at least 1 of 3 treated attacks. Efficacy comparisons were based on rates of 2-hour headache response, 2-hour pain-free response, sustained pain-free response, and consistency of response. Tolerability comparisons were based on proportions of patients with at least 1 adverse event (AE), patients with at least 1 central nervous system AE, and for at least 1 chest AE. Comparisons of the main efficacy and tolerability measures for the oral triptans versus sumatriptan 100 mg are summarized in Table 4.

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### Table 3 General Principles of Migraine Management

- Individualize management (stratified care)
- Treatment choice depends on
  - Attack frequency and severity
  - Presence and degree of disability
  - Associated symptoms
  - Prior response to medications
  - Patient preferences
  - Comorbid and coexistent conditions
  - Triggers (environmental/lifestyle and biological)
- Involve patients in their own management
- Establish dosing limits (2 days/week)

### Table 4 Comparison of the Main Efficacy and Tolerability Measures for the Oral Triptan Versus Sumatriptan 100 mg

<table>
<thead>
<tr>
<th>Oral Triptans Versus Sumatriptan 100 mg</th>
<th>Initial 2-Hour Relief</th>
<th>Sustained Pain Free</th>
<th>Consistency (2-3 Attacks)</th>
<th>Tolerability</th>
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<tr>
<td>Sumatriptan 50 mg</td>
<td>=</td>
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<td>Zolmitriptan 2.5 mg</td>
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<td>Naratriptan 2.5 mg</td>
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<td>Rizatriptan 10 mg</td>
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<td>Eletriptan 80 mg</td>
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<tr>
<td>Almotriptan 12.5 mg</td>
<td>=</td>
<td>+</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>

= indicates no difference, + indicates better, - indicates inferior when compared with sumatriptan.
Cost to Attain 100 Sustained Pain-Free Patients Without AEs

Cost-Effectiveness of Triptans in Migraine Management

Decisions regarding which drugs to include on a formulary should be based on the best available evidence of their clinical efficacy and AEs. Costs of the drugs should also be considered. In studies assessing the economic impact of triptan therapy for migraine on employers and health maintenance organizations (HMOs), triptan therapy resulted in improved work productivity and net benefits for employers and HMOs. For example, in an open-label study enrolling HMO patients (N = 148) receiving sumatriptan subcutaneously for 12 months, reductions were reported in migraine-related health care utilization (general outpatient services, urgent care services, telephone calls, and emergency department visits), in comparison with the previous 12 months prior to sumatriptan therapy (P<.05). In addition, a work productivity outcomes assessment conducted among employed sumatriptan users (N = 164) in an HMO population found a 10-fold difference between the productivity benefits ($435 per employee per month) gained via sumatriptan treatment and the sumatriptan costs ($44 per employee per month). These results demonstrate that a marginal expense on the direct side (through prescription costs) can lead to a huge return for the employer, via the increased productivity of medicated workers.

Studies have also been designed to examine the cost-effectiveness of different individual triptans in migraine management. One cost-effectiveness study that compared oral eletriptan 40 mg and 80 mg with the older formulation of oral sumatriptan 50 mg and 100 mg used 2 composite measures of treatment outcome. Achieving one of these outcome measures required a patient to be free of headache pain 2 hours after dosing, have no recurrence within 24 hours of the first dosing, and have no need for rescue medication; this measure has been called “sustained pain free” elsewhere. The second, more demanding measure required a positive headache response at 1 hour, pain-free status by 2 hours and sustained at 4 hours, and the absence of headache recurrence within 24 hours of the first dose. In this randomized, double-blind, placebo-controlled clinical trial, drug cost for initial dosing, second dosing for nonresponse, recurrence, and rescue medication were taken into account. The study found that eletriptan resulted in lower costs per successfully treated attack than sumatriptan under both outcome measures. Using the sustained pain-free measure, the cost per successfully treated attack with eletriptan 40 mg was 27% of that for sumatriptan 50 mg; with eletriptan 80 mg, 39% of the cost of successful treatment with sumatriptan 100 mg. Using the second measure, the cost of successful treatment with eletriptan 40 mg was 31% that of sumatriptan 50 mg; eletriptan 80 mg, 39% the cost of sumatriptan 100 mg.

Comparisons among the oral triptans are complicated by the fact that there are few published head-to-head trials. There are, however, numerous randomized, placebo-controlled clinical trials, and meta-analyses of these trials have been used to indirectly compare the efficacy, tolerability, and cost-effectiveness of oral triptans. A 2001 meta-analysis of 53 trials found that all oral triptans were effective and well tolerated at marketed doses and that rizatriptan 10 mg, eletriptan 80 mg, and almotriptan 12.5 mg provided the highest likelihood of consistent success, which may be important from a managed care perspective. When the results of this meta-analysis were combined with medication costs to identify the best overall economic value among 5 oral triptans (almotriptan 12.5 mg, naratriptan 2.5 mg, rizatriptan 10 mg, sumatriptan 100 mg, and zolmitriptan 5 mg, eletriptan was not available at the time of this study), almotriptan 12.5 mg had the lowest cost to attain 100 sustained pain-free patients without AEs. By this measure, other triptans were 1.7 to 2.8 times more costly than almotriptan. This is important for the managed care community because AEs may need to be managed as well, which incurs additional costs for additional prescriptions, OTC remedies, and physician visits. Excluding the cost of AEs, the other triptans were 1.5 to 2.7 times more costly than almotriptan. Naratriptan 2.5 mg had the highest cost of the agents studied although the increase in cost to attain pain-free patients was slight (<$500) (Figure 5).

A second meta-analysis used efficacy data from 27 oral triptan trials and per-dose costs (from July 2002) to determine the cost-effectiveness of 6 triptans (eletriptan was not included in this analysis). This study used the end point of pain-free status within 2 hours after dosing as the indicator of efficacy. Efficacy data were used to determine the number needed to treat (NNT) to achieve pain-free status in 1 patient within 2 hours postdose, and per-dose costs for each triptan were applied to the NNT values. Rizatriptan 10 mg and almotriptan 12.5 mg were found to be the most cost effective of the triptans, costing $48.34 and $48.57, respectively.

Note that not all patients can use triptans. Those suffering from coronary artery disease, angina, peripheral or vascular disease, or uncontrolled hypertension should not use triptans. Note that not all patients can use triptans. Those suffering from coronary artery disease, angina, peripheral or vascular disease, or uncontrolled hypertension should not use triptans.
to achieve pain-free status in 1 patient within 2 hours postdose. The other triptans in decreasing order of cost-effectiveness were zolmitriptan 5 mg ($65.18), sumatriptan 100 mg ($70.83), sumatriptan 50 mg ($75.67), zolmitriptan 2.5 mg ($78.74), naratriptan 2.5 mg ($141.43), and frovatriptan 2.5 mg ($162.49).61

There are several limitations of these analyses that are relevant to a clinical setting. The use of pain-free response at 2 hours postdose as a measure of efficacy impacts naratriptan and frovatriptan negatively, as both are slower-acting triptans with much greater half-lives than the faster-onset triptans (sumatriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan). Because of their slower onset and longer duration of action, naratriptan and frovatriptan are not used interchangeably with the other triptans in a real-life setting and, therefore, comparisons may be misleading. It is also important to note that the cost of almotriptan has increased disproportionately to the other triptans since the publication of these cost-effectiveness studies. Compared with the 2002 prices used, the per-dose cost of almotriptan has increased more than 60% whereas the per-dose costs of the other triptans increased between approximately 4% and 13% (based on July 2004 prices).64 The results of cost-effectiveness studies, therefore, should be considered as one factor of many when selecting among the available triptans, and data from these studies needs to be updated frequently.

As previously described, the selection of triptan therapy for a migraine patient should be based on the patient's individual situation, preferences, and history. The choice of triptan also depends upon the stratification of the patient's migraine attack by peak intensity, time to peak intensity, level of associated symptoms such as nausea, time to associated symptoms, comorbid diseases, and concomitant treatment that may cause drug-drug interactions.65 Each formulary for migraineurs should include triptans of multiple formulations, including injectable triptans, nasal spray triptans, rapid-onset oral triptans, and long-acting oral triptans, with good safety and tolerability profiles.

Conclusions

Migraine is one of the most common diseases encountered in primary care, yet only a fraction of sufferers are diagnosed. Even among those diagnosed, less than half receive prescription medication, and most report migraine-associated pain and disability. Migraine impacts sufferers during the most productive years of their life, causing significant personal, social, and economic burdens. The economic burden of migraine now exceeds $14 billion annually, more than half of which is attributed to lost work days. These statistics and others make migraine a condition that warrants examination from a managed care and employer perspective.

Problems of underdiagnosis and misdiagnosis of migraine may be reduced with increased awareness of migraine and the use of screening tools in primary care. Employment of individual, stratified treatment plans; patient education; appropriate use of triptans; and follow-up care can lead to better migraine control for patients and reduced overall costs for managed care organizations.

DISCLOSURES

This article is based on proceedings from the unsanctioned symposium, Migraine Matters: Relieving the Burden in Managed Care, presented in conjunction with the Academy of Managed Care Pharmacy’s 16th Annual Meeting, April 1, 2004, in San Francisco, California, and supported by an unrestricted educational grant from Pfizer Inc. The authors received an honorarium from Pfizer Inc. for participation in the symposium upon which this article is based. Author Diana I. Brixner discloses no conflict of interest or potential bias regarding this article; author Jan Lewis Brandes discloses that she has received grants and research support from, participates in the speaker's bureaus of, and is a consultant to numerous pharmaceutical companies.

REFERENCES

Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care

32. Ishkanian G. Poster presented at: Headache Update 2002; July 16, 2002; Orlando, FL.
Continuing Education

Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care

Date: __________________________

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Last name: ___________________________  First name: ___________________________

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Address: ________________________________________________________________

City: ___________________________  State: ___________________________  ZIP: ______

Daytime phone: ___________________________  Social Security no.: __________________

Fax number: ___________________________  E-mail: ___________________________

Member Type:  ❑ Active  ❑ Supporting Associate  ❑ Student  ❑ Nonmember

Posttest Answers:

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**POSTTEST**

**Continuing Education**

**Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care**

Please indicate the correct answers on the Record of Completion.

1. Migraine affects approximately what percentage of the U.S. population?
   - a. 6%
   - b. 10%
   - c. 12%
   - d. 18%

2. More than 90% of migraine sufferers report impairment with their migraines.
   - a. True
   - b. False

3. Which of the following statements regarding the economic burden of migraine is true?
   - a. Indirect costs of migraine total approximately $1 billion.
   - b. Indirect costs of migraine total approximately $13 billion.
   - c. The majority of indirect costs are attributed to prescription drug costs.
   - d. The majority of direct costs are attributed to prescription drug costs.

4. Migraineurs have nearly ____________ the medical claims and nearly ____________ the pharmacy claims as nonmigraineurs.
   - a. equal, twice
   - b. twice, 2.5 times
   - c. twice, 5 times
   - d. 5 times, twice

5. Which of the following statements regarding triptans is true?
   - a. Triptans are the only available specific treatment for migraine attacks.
   - b. Triptans are safe for all migraine patients.
   - c. Triptans are less expensive than ergots.
   - d. Triptans are serotonin agonists.

6. A study examining the cost-effectiveness of triptan use in managed care found that productivity benefits gained with triptan use exceeded the costs of the triptans by how much?
   - a. 2-fold
   - b. 10-fold
   - c. 20-fold
   - d. 40-fold

7. A study by Reeder and colleagues that evaluated the cost-effectiveness of the triptans almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan found which triptan to have the lowest cost to attain 100 sustained pain-free patients without adverse events?
   - a. Almotriptan
   - b. Naratriptan
   - c. Rizatriptan
   - d. Zolmitriptan

8. What percentage of migraine sufferers have never been diagnosed by a physician?
   - a. 5% to 10%
   - b. 10% to 20%
   - c. 20% to 40%
   - d. 40% to 60%

9. The majority of patients presenting to primary care physicians with episodic disabling headache are suffering from what type of headache?
   - a. Tension-type
   - b. Sinus
   - c. Migraine
   - d. Unclassifiable

10. What approximate percentage of patients diagnosed with migraine receive prescription medication?
    - a. 10%
    - b. 25%
    - c. 50%
    - d. 75%
11. Migraineurs taking prescription medication are most likely to supplement their treatment with which of the following non-medicinal approaches?
   a. Herbal remedies
   b. Stress management
   c. Bed rest
   d. Avoidance of trigger factors

12. Approximately 50% of migraine patients experience aura.
   a. True
   b. False

13. Which of the following migraine-associated symptoms are the most predictive of the presence of migraine?
   a. Nausea, disability, and photophobia
   b. Nausea, aura symptoms, and pain on 1 side
   c. Disability, aura symptoms, and photophobia
   d. Nausea, photophobia, and phonophobia

14. Which of the following statements regarding the ID Migraine screening tool is true?
   a. Answering “yes” to 2 of the 3 questions indicates a positive result.
   b. The reliability is comparable to that of the prostate-specific antigen (PSA) test.
   c. It provides a means for patients to quickly communicate their symptoms to a physician.
   d. All the above

15. Which of the following statements is true regarding stratified care?
   a. Treatment is initiated at the lower end of the therapeutic armamentarium.
   b. Initial treatment is based on measurement of the severity of the illness.
   c. It is more expensive than step care.
   d. All the above

16. The Disability in Strategies of Care (DISC) trial found which of the following to be true?
   a. Step care within attacks results in better clinical outcomes for patients.
   b. Step care across attacks results in better clinical outcomes for patients.
   c. Stratified care results in better clinical outcomes for patients.
   d. There are no significant differences in clinical outcomes among the 3 management strategies.

17. Treating migraine patients early in the course of an attack has been shown to result in which of the following?
   a. Higher rates of pain-free response and higher risk of developing chronic headache
   b. Higher rates of pain-free response and more use of rescue medication
   c. Less disability and more need for multiple doses
   d. Higher rates of pain-free response and less need for multiple doses and rescue medication

18. Education for migraine patients should include which of the following topics?
   a. The phases of a migraine attack and how to control migraine triggers
   b. The use of headache diaries and disability questionnaires
   c. Advantages of early treatment and warning about rebound headaches
   d. All the above

19. A meta-analysis of trials of oral triptans in migraine found which triptan(s) to have favorable efficacy compared with sumatriptan 100 mg?
   a. Rizatriptan 10 mg and eletriptan 80 mg
   b. Naratriptan 2.5 mg
   c. Zolmitriptan 5 mg
   d. All the above

20. A meta-analysis of trials of oral triptans in migraine found which triptan to have favorable tolerability compared with sumatriptan 100 mg?
   a. Almotriptan 12.5 mg
   b. Zolmitriptan 5 mg
   c. Rizatriptan 5 mg
   d. Eletriptan 80 mg
Migraine Matters: The Role of Triptans in Relieving the Burden in Managed Care

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

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<thead>
<tr>
<th>Scale For Questions 1–5</th>
<th>Scale For Questions 6 and 7</th>
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<tbody>
<tr>
<td>1 = Not at all</td>
<td>1 = Poor</td>
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<td>2 = Not very well</td>
<td>2 = Fair</td>
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<tr>
<td>3 = Somewhat well</td>
<td>3 = Good</td>
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<td>4 = Well</td>
<td>4 = Very good</td>
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<tr>
<td>5 = Very well</td>
<td>5 = Excellent</td>
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Using the scale above for questions 1–5, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

**Objectives:**

1. Discuss the prevalence of migraine and migraine-associated disability;

2. Review the economic burden of migraine, including direct and indirect costs, as it relates to managed care;

3. Describe the barriers to diagnosing migraine and how the use of simple screening tools can lead to improved diagnosis and treatment of migraine patients;

4. Discuss the different approaches to managing migraine and the need for patient education; and

5. Understand the cost-effectiveness of triptans in managed care.

6. What is your overall rating of this program? ____________

7. How would you rate the pertinence of this program material to your practice? ____________

8. To what degree was there promotional bias? (check one)
   a. Not at all ____________
   b. Somewhat ____________
   c. A great deal ____________

9. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
   1 = No change
   2 = 1
   3 = 2
   4 = 3
   5 = 4
   6 = Significant change

10. Please indicate the length of time it took to complete this program. (circle selection(s))
    Hours: 1 2 3
    Minutes: 0 15 30 45

11. Please rate the difficulty factor for completing this CE program. (circle selection)
    Easy Moderate Difficult

12. Please rate your willingness to recommend this program to colleagues. (circle selection)
    Very willing Willing Not willing

13. Please indicate which venue you prefer for obtaining continuing education. (circle selection)
    Written monograph Slides Videos Internet-based

    Live sessions Other: ____________________________