

In response to the expense of new migraine therapies, treatment practices aimed at controlling direct costs are now the norm.

Advances in Migraine Management: Implications for Managed Care Organizations

DAVID W. DODICK, MD

Department of Neurology, Mayo Clinic, Scottsdale, Ariz.

ROBERT J. LIPSY, PHARM D

Department of Pharmacy, University of Arizona, Tucson

ABSTRACT

Migraine headache is a disabling disease that poses a significant societal burden. Stratified care and early intervention are current strategies for migraine management. It has been shown that early treatment with triptans in select patients can improve treatment outcomes. Triptans are selective 5-HT receptor agonists that are specific and effective treatments in the management of migraine, and they meet the acute treatment goal of rapid relief with minimal side effects. Triptans are associated with improved quality of life. Factors such as speed of onset, need for a second triptan dose, and patient satisfaction should be considered in the selection of a specific triptan treatment. Appropriate treatment can decrease costs. The patient's migraine history and response to prior therapy should

be considered when selecting acute treatment. Cost-effectiveness models can be used to understand the effect of treatment choices on health care budgets. The direct cost per migraine episode, driven primarily by the need for rescue medications, is important to include in economic models. All aspects of effectiveness (efficacy, tolerability, and cost) should be considered to reduce overall managed care expenditures for migraine treatment. The improved clinical profiles of the triptans provide substantial value to managed care organizations.

INTRODUCTION

The treatment of migraine has progressed significantly in the last decade. Multiple new drug approvals and many developing investigational drugs reflect this improvement. Progress also has been made in devising strategies for migraine management and in strengthening the evidence base for the development of treatment guidelines. Despite these advances, migraine remains a common, disabling, and costly disorder that is underdiagnosed and undertreated. The recognition of migraine as a significant treatment priority will assist in increasing the level of awareness and reducing the clinical and economic burden associated with migraine.

Unmet needs

Migraine affects an estimated 28 million Americans (Lipton 2001).

The prevalence of migraine varies with age, having the greatest impact from ages 25 to 50, with peak prevalence at age 40. Migraine affects nearly three times as many women as men (Stewart 1992). Despite recent advances in understanding the mechanisms of migraine pathophysiology and improved treatment options, migraine remains underdiagnosed and undertreated. Almost half of patients with migraine do not seek treatment for their migraine symptoms (Lipton 1998). No objective markers or diagnostic tests for migraine have been identified, and patient assessments and perceptions of their condition are subjective. Lack of communication between physicians and patients regarding symptoms, and in particular the level of disability experienced, has also contributed to the undertreatment of migraine (Holmes 2001). Additionally, similarities among the clinical features of migraine and tension-type and sinus headache contribute to the misdiagnosis and undertreatment of migraine (Lipton 2002). Many professional organizations, including the World Health Organization, the American Medical Association, and the National Institutes of Health, have recognized migraine as a significant treatment priority. This recognition will increase health care professionals' awareness of migraine and help reduce the significant burden associated with the disease.

Migraine in pediatric and adoles-

Author correspondence:

David W. Dodick, MD

Department of Neurology
Mayo Clinic, Scottsdale
13400 East Shea Boulevard
Scottsdale, AZ 85259
Phone: (480) 301-8112
Fax: (480) 301-8451
Email: Dodick.David@mayo.edu

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cent patients is unquestionably an important issue. The purpose of this paper, however, is to provide a general review of diagnosis, treatment, and economic consequences in managed care. Additionally, the vast majority of patients are not children or adolescents, and migraine in these patients represents a unique body of knowledge.

Related disability

Severe migraine is rated along with quadriplegia, psychosis, and dementia as one of the most disabling chronic disorders (Goadsby 2002). More than 75 percent of patients report severe to extremely severe pain; 80 percent report photophobia; 76 percent report phonophobia; 73 percent report nausea; 44 percent report blurred vision; and 29 percent report vomiting (Lipton 2001). More than half of patients with migraine require bedrest during an attack. Approximately 70 percent of employed migraine sufferers lose work time, with an average loss of 1 day per month (Von Korff 1998). The loss in work time is concentrated among the most severely affected patients, with 40 percent of migraine sufferers accounting for 90 percent of lost workdays. In addition, productivity at work is reduced by an estimated 41 percent on days when migraine sufferers work during a migraine attack (Von Korff 1998). During an attack, more than 75 percent of patients report that they are unable to do household work, 59 percent report missing family and social events, and 51 percent report a reduction in school productivity (Lipton 2001). Studies designed to quantify the effect of migraine on quality of life demonstrate that patients with migraine have significantly lower quality of life scores compared with individuals without migraine (Lipton 2000).

Associated costs

Patients and insurance providers share the direct cost of a patient's

medical care. Direct medical costs of migraine are estimated at over \$1 billion annually with indirect costs exceeding \$13 billion (Hu 1999). Physician-office visits account for approximately 60 percent of the direct costs of treating migraine, with annual migraine-per-patient costs for medical-resource use ranging from \$200 to \$5,000 per patient each year (Hu 1999). Indirect costs (incurred by employers, other institutions, or individuals) are difficult to quantify but generally are considered to be much higher than direct costs. One study has estimated that the ratio for indirect-to-direct costs is as high as 10:1 (Hu 1999).

Diagnosis

Despite the recent advances in understanding the mechanisms of migraine pathophysiology and improved treatment options, migraine remains underdiagnosed and undertreated. Diagnosis is hampered because objective markers or diagnostic tests for migraine are limited and patient perceptions of their condition are subjective. Low diagnosis rates are compounded by low treatment rates. Lack of communication between physicians and patients regarding headache symptoms and the level of disability experienced contribute to undertreatment. The overlapping clinical features of migraine with episodic tension-type headache (ETTH) and sinus headache also contribute to the misdiagnosis and undertreatment of migraine (Lipton 2002). In one study, approximately 42 percent of misdiagnosed migraine sufferers received a diagnosis of sinus headache, whereas 32 percent of patients received a diagnosis of ETTH (Lipton 2002).

The 1988 Headache Information Society (HIS) classification of migraine forms the basis for the system used by the International Classification of Diseases (ICD) version 10b. In this system, migraine is characterized by recurrent episodes of headache,

with various combinations of nausea, vomiting, photophobia, phonophobia, and aura (i.e., focal neurologic symptoms, usually visual, that are reported in approximately 20 percent of attacks), although characteristics vary between patients and between attacks in an individual patient (Silberstein 2000). The coexistence of primary headache such as ETTH should be determined. Secondary causes of headache should be excluded. Neuroimaging is the only form of diagnostic testing supported by the literature and is recommended only if there is evidence for a significant intracranial abnormality. Neuroimaging should be avoided if it will not lead to some alteration in planned treatment (Silberstein 2000).

The Spectrum Study was designed to compare the initial diagnosis of migraine made in a clinical trial to a subsequent diagnosis made by a neurologist via patient diary review (Lipton 2002). Using the Migraine Disability Assessment (MIDAS) and Headache Impact Test, the study targeted only the most disabled half of migraine sufferers. Patients were classified as having three different kinds of headache attacks: migraine, migrainous, or ETTH. Investigators sought to determine if the classification of headache type, the attack characteristics, or both would be most predictive of outcome for a particular patient.

This study demonstrated that disabling ETTH was difficult to find, whereas 90 percent of subjects reporting a disabling headache had a form of migraine. The Spectrum Study also demonstrated that a diagnosis of migraine usually can be confirmed on the basis of diary data for patients with disabling headache. Diary review by neurologists resulted in a diagnosis of migraine in 32 percent of patients originally diagnosed with ETTH during study enrollment. Triptan therapy, which is highly specific for pain caused by migraine (Goadsby 2002), was found to be ef-

fective in this patient cohort, further supporting the author's rediagnosis of migraine (Williams 2001).

MANAGEMENT OF MIGRAINE

Principles for migraine management include patient education and development of individualized treatment plans (Silberstein 2000). Migraine therapy can be acute or preventive. Acute therapy is initiated after an attack has begun and is designed to relieve pain and disability, stop attack progression, and restore functioning. Preventive therapy is administered daily to reduce attack frequency, severity, and disability. Preventive therapy also minimizes reliance on poorly tolerated, ineffective acute therapies, thus avoiding acute headache medication escalation.

Preventive care should be considered for patients who have more than 4 attacks per month and whose migraine condition has a substantial impact on their lives (Goadsby 2002). To prevent neurologic damage, preventive care also should be considered in patients who experience adverse events with acute therapy and who would prefer preventive intervention and in those patients who present with uncommon migraine conditions (hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction) (Silberstein 2000).

PHARMACOTHERAPY

For patients with moderate or severe migraine symptoms, initial treatment uses more specific agents such as triptans (Williams 2001). The stratified care approach is appropriate for acute treatment across attacks and within an ongoing attack (Silberstein 2000).

Overuse and dependence are concerns with opiate analgesics, and use of these agents should be considered only after sedation and abuse risks have been addressed. Nasal butorphanol is an effective treatment op-

tion for some patients with migraine when other medications cannot be used, or it can be used as a rescue medication if sedation will not jeopardize the patient's safety. Parenteral opiates also are effective as rescue medication when sedation is not an issue (Silberstein 2000).

Non-oral administration routes should be used for patients with migraine associated with severe nausea or vomiting. Care should be taken to guard against medication overuse (rebound) headache that is associated with frequent use (>3 days per week) of acute medications. Consequently, many experts limit the use of acute therapy to 2 headache days per week. Patients with a history of overusing medication should be considered for preventive therapy (Silberstein 2000). Preventive care also should be considered in patients whose attack frequency causes overreliance on acute care medications (Silberstein 2000) and in patients who have 4 or more attacks per month (Goadsby 2002).

Several drug classes are useful for migraine prevention. Preventive pharmacotherapy may take up to 2 to 6 months, with dosing titrated gradually until therapeutic benefit or intolerance curtails further titration. Beta-blockers are the most widely used medication for migraine prophylaxis; atenolol and nadolol are effective agents due to their long half-lives and favorable side effect profiles. Beta-blockers with intrinsic sympathomimetic activity do not appear to be beneficial in migraine prevention. Divalproex sodium is as effective as propranolol in migraine prophylaxis and may be used when beta-blockers are contraindicated. Divalproex and topiramate are especially attractive in migraine patients with epilepsy, anxiety disorders, or bipolar disease (Silberstein 2000).

Tricyclic antidepressants and methysergide have proved effective in migraine prophylaxis. A recent randomized, placebo-controlled

study has shown that angiotensin-converting enzyme inhibitors also may be effective in preventing migraines (Schrader 2001). Selective serotonin reuptake inhibitors (SSRIs) and calcium-channel blockers that are available in the United States have not been as extensively studied for use as migraine prophylaxis.

PHARMACOLOGY OF TRIPTANS

The current understanding of the pathophysiology of migraine suggests that most antimigraine agents constrict dilated large cranial vessels, inhibit activated peripheral trigeminal nerve terminals, or reduce neuronal activity in central trigeminal neurons. Triptans are 5-HT_{1B} and 5-HT_{1D} selective agonists with weaker affinity for 5-HT_{1A} and 5-HT_{1F} and have no significant activity at other serotonin receptors. Significant expression of vasoconstrictor 5-HT_{1B} receptors in the smooth muscle of meningeal blood vessels makes these receptors an attractive target to reverse the abnormal vasodilatation that may occur during migraine. These receptors are expressed on both the peripheral and the central terminals of the trigeminal nerve fibers arising from the trigeminal ganglia and in the nucleus of the tractus solitarius, which mediates the nausea and vomiting associated with central pain transmission, a clinically important aspect of migraine (Goadsby 2000).

THERAPEUTIC INTERVENTION WITH TRIPTANS

Currently accepted guidelines for triptan therapy recommend their use in patients with migraine who are unresponsive to other therapies or in patients who have substantial migraine-related disability. In the Disability in Strategies of Care (DISC) study, only 25 percent of patients with MIDAS grade IV (highest disability grade) migraine responded to aspirin plus metoclopramide. This study demonstrated that treatment outcomes, as measured by headache re-

sponse and disability time, improve when the most highly disabled patients are treated with triptans (Lipton 2002).

Triptans are contraindicated in patients with ischemic heart disease, coronary vasospasm, multiple risk factors for coronary artery disease, hemiplegic or basilar migraine, uncontrolled hypertension, concomitant use of monoamine oxidase inhibitors, and in patients who have used an ergot within the past 24 hours (Goadsby 2002). Various triptans have slightly different affinities for different serotonin receptors that may influence side-effect profiles. Side effects that are commonly experienced with triptans include tingling, warmth, flushing, chest discomfort, sensations of pressure, and dizziness (Goadsby 2002).

At the dosages studied, triptans show a similar performance for the outcome "headache response at 2 hours after dosing." Approximately 60 to 70 percent of patients report reduced headache symptomology within 2 hours with sumatriptan, rizatriptan, zolmitriptan, and eletriptan. Naratriptan, almotriptan, and frovatriptan have somewhat lower response rates (30 to 40 percent). Approximately 30 to 40 percent of patients taking sumatriptan, rizatriptan, zolmitriptan, eletriptan, and almotriptan are pain free at 2 hours, while only 15 to 25 percent of patients taking naratriptan and frovatriptan are pain free at 2 hours (Dahlof 2002).

MIGRAINE MANAGEMENT STEPPED VS. STRATIFIED CARE

Migraine management with triptans has been evaluated in both stepped care and stratified care algorithms. Stepped care requires initial treatment of acute migraine with a nonspecific agent. If treatment fails, therapy is stepped up to include a migraine-specific therapy. Stepped care can delay effective treatment and increase direct costs due to frequent of-

fice visits for medication adjustment. Indirect costs also may be increased due to disability during the earlier stages of the algorithm (Pascual 2002). In addition, it is now considered inappropriate to administer an ineffective or poorly tolerated medication in a sequential and arbitrary manner.

Stratified care matches therapy with severity. For patients with severe migraine, specific agents such as triptans should be administered initially (Silberstein 2000). Stratified care is appropriate for acute treatment across attacks and within an ongoing attack (Silberstein 2000). Stratified care results in fewer physician consultations and increased clinical response rates. In a study that used a decision analytic model to simulate a controlled clinical trial, the model estimated that 71 percent of migraine attacks would be responsive to treatment with stratified care, whereas only 40 percent would be responsive with stepped care (Williams 2001). In the same study, stratified care lowered total medical costs by 3.4 percent and cost per successfully treated event by 46.2 percent compared with stepped care (Williams 2001).

Stratified care has been compared to stepped care across attacks using a two-hour headache response score as an outcome measure. Stratified care applied over six successive attacks was considered successful in 53 percent of patients compared with 41 percent of patients treated with stepped care (Lipton 2000). Stratified care also has been compared with stepped care within attacks using headache response scores at one, two, and four hours and was significantly more effective than stepped care after one hour and two hours (Lipton 2000).

Acute treatment should be initiated at the first sign of pain and before progression to moderate or severe levels. Many patients request early treatment, and clinical experience suggests that better outcomes

and higher pain-free rates are achieved with early treatment. One study reported that 84 percent of patients with migraine were pain free within two hours if treatment with almotriptan was initiated when the pain was considered mild. In contrast, only 53 percent of patients were pain free at two hours if treatment was initiated when pain was moderate or severe (Pascual 2002). Another study found that 69 percent of patients were pain free at two hours if treatment was initiated early, compared with 39 percent of patients considered pain free if treatment was initiated when pain had progressed to moderate or severe levels (Cady 2000). The outcome of pain free at two hours strongly correlates with patient satisfaction rates and quality of life (Davies 2000). A review of all the evidence indicates that the benefits of early treatment of migraine include increased pain-free rates, more rapid restoration of function, lower recurrence rates, reduced need for multiple doses, and reduced need for rescue medication.

PHARMACOECONOMICS OF TRIPTAN THERAPY

Several studies have been done to quantify treatment costs with the different available triptans, including studies focusing on direct and indirect costs, costs of adverse events, and quality of life. Several studies have examined the impact of triptans on expenditures for migraine treatment. One study investigated the cost effectiveness and cost benefit of switching from non-triptan treatment to triptan treatment (Lofland 2001). Direct medical costs decreased from a mean of \$147 per patient before triptan treatment to \$103 per patient after triptan treatment was initiated. During the same time, migraine-related pharmacy costs increased from \$124 per patient for 6 months to \$420 for 6 months. Nevertheless, 6 months of triptan therapy averted 1898 migraine disability days, resulting in an

overall net savings of \$1249 per patient per 6 months of treatment and a benefit-to-cost ratio of \$5.67 gained for each health care dollar spent when indirect costs were taken into account (Lofland 2001).

In another study, patients recorded the number of sumatriptan or zolmitriptan tablets consumed for pain relief during an acute migraine. More sumatriptan tablets were taken per attack than zolmitriptan, suggesting that pain relief was achieved with fewer zolmitriptan tablets. This finding could have significant cost implications (Tepper 1998). A second, similar study reviewed clinical trial data to compare the cost per attack for sumatriptan versus zolmitriptan. The cost per attack for zolmitriptan was \$23.03, whereas the cost for sumatriptan was \$26.06. Assuming an average of 20 attacks per year per patient, this would result in a cost savings of \$60.60 per patient per year and a potential cost savings of \$181,800 per year for an MCO with 3,000 migraine sufferers (Vreeland 1998).

Economic modeling has been used to compare total drug and overall costs per patient per migraine attack. Model outputs of a comparison between zolmitriptan and sumatriptan indicate the total overall cost per patient per attack was estimated to be \$56.13 for zolmitriptan and \$58.75 for sumatriptan. If a patient has 20 migraine attacks per year, the estimated per attack cost savings translates into \$52.40 in cost saving per patient per year for zolmitriptan. Based on these estimates, a managed care group with 3000 patients with migraine in its covered population would realize a cost savings of \$157,200 per year (Trotter 1998).

The direct cost per episode also is affected by costs incurred for diagnosing and treating adverse events. Side effect profiles vary among triptans, providing a way to differentiate these agents.

A 2-year postmarketing survey re-

ports that 41 percent of patients with migraine receiving oral sumatriptan experienced chest symptoms, and 10 percent of patients discontinued sumatriptan treatment as a result (Visser 1996). A retrospective, open-label study found that almotriptan had an overall incidence of chest pain of less than 1 percent (Wang 2002). The study used a pre-post design, with baseline and treatment periods of 5 months, before and after receiving sumatriptan. Data were obtained from an employer-based, fee-for-service data medical and pharmacy claims database, and an assumption of the incidence of chest-pain related to sumatriptan and almotriptan (2.2 percent and 0.3 percent, respectively) was based on a previous study comparing the two drugs. An economic model was designed to estimate the expenditures for chest pain-related care associated with use of almotriptan and sumatriptan. The model projected that the percentage of patients with chest pain-related diagnoses was 44 percent higher with sumatriptan and aggregate costs increased by 33 percent. This cost differential translated to an estimated \$11.22 per patient year in cost avoidance, using almotriptan instead of sumatriptan (Wang 2002).

Therapies that improve quality of life, increase patient satisfaction, and favorably affect daily activities have a significant impact on overall disease costs. Survey results indicate that use of zolmitriptan decreased the average time absent from work (3.86 days vs. 0.61 days), reduced attack severity, and resulted in less incapacitation when performing work, school, social, and household activities (Baker 2000). Another study assessed direct and indirect costs for 12 months before and after conversion to triptan therapy, which resulted in significant reductions in use of general outpatient services, urgent care services, and emergency department visits. Pharmacy costs and total direct costs increased, however. An overall eco-

nomie benefit was evident only when quality of life and indirect costs were considered. Triptan therapy improves quality of life, attendance at work, and patient satisfaction scores compared with usual therapy (Cohen 1999).

These studies indicate that all aspects of treatment effectiveness — including efficacy, tolerability, and cost — are important to consider in reducing overall managed care expenditures for migraine. Additionally, the improved tolerability profiles of triptans provide real value to MCOs by minimizing direct costs associated with diagnosing and treating adverse events.

MANAGED CARE CONCERNS

The costs of treating migraine are a concern to many health care payers, including MCOs. Because of the high costs associated with migraine, MCOs have developed a number of treatment practices aimed at containing migraine-related direct costs. Stratified care lowered direct costs, improved response rates to therapy, and decreased the cost per successfully treated event (Williams 2001). One component of the stratified care strategy is to select efficacious and well-tolerated therapies. In addition, using evidence-based treatment algorithms, protocols, and guidelines minimizes variability and decreases costs associated with diagnosis and treatment. Educational programs that empower patients to take responsibility for their condition are cost effective.

SUMMARY

Migraine headache is a common disabling disease that presents a significant health care burden. Utilization of appropriate treatments can decrease use of rescue medication, improve quality of life, and minimize medical resource use. Accepted strategies today include stratified care and early intervention. Triptans are selective 5-HT receptor agonists that

are specific and effective treatments in the management of migraine. Triptans provide rapid, complete relief of pain with minimal side effects and are associated with improved quality of life. Treatment with triptans early in a migraine attack improves treatment outcomes. Factors such as speed of onset, need for second dose, and patient satisfaction should be considered in the selection of a specific triptan. Cost-effectiveness models can be used to understand the effect of treatment choices. An important variable in economic models of migraine attacks is direct cost per migraine episode, driven primarily by the need for second dosages and rescue medications. All aspects of effectiveness (efficacy, tolerability, and cost) are important to consider to reduce overall managed care expenditures for migraine treatment. Triptans offer a significant value to managed care organizations.

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