Specialty Healthcare Benefits Council
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Concepts in Acute Migraine Management: Clinical and Managed Care Perspectives

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ABSTRACT

Migraine is a chronic, prevalent, and disabling neurologic condition, affecting millions of adults in the United States. Inadequate management of and undertreatment of migraine impact patients, payers, providers, and employers and result in increased frequency of attacks, the need for additional medication, and spiraling costs. Although prevention is important, this article highlights treatment challenges in migraine management and explores unmet needs in acute treatment.

(Am J Pharm Benefits. 2012;4(5):201-206)

Migraine is one of the most prevalent neurologic conditions, affecting more than 29.5 million adults in the United States.[1] It is more prevalent than Alzheimer's disease (patients aged ≥65 years), Parkinson's disease (patients aged ≥65 years), stroke, and multiple sclerosis combined.[2] Despite its wide prevalence and debilitating nature, migraine is often misdiagnosed and poorly managed by both primary care providers (PCPs) and neurologists.[3-6]

The costs of migraine to managed care organizations (MCOs) can be substantial. Inappropriate use of both over-the-counter and prescription medications can lead to increased costs and poor patient outcomes by causing medication overuse headache and unnecessary emergency department (ED) visits. In the United States, total annual migraine-related costs in 2010 were $3.2 billion for outpatient visits, $700 million for ED visits, and $375 million for inpatient hospitalizations.[7] Sixteen percent of first presentations are in the ED.[8] The average total hospital costs are about $1800 per visit.[9] These costs can be substantially higher if imaging is ordered at an average cost of about $2500 for magnetic resonance imaging.[10] One prominent factor correlated with escalating utilization of the ED is opioid use (see clinical recommendations for opioid use in Table 1). A study showed that patients who were dependent on opioids used the ED almost 24 more times per year than those who were not.[15]

Few physicians are familiar with International Classification of Headache Disorders II diagnostic criteria (Figure), and although American Headache Society treatment guidelines exist, they are infrequently used by PCPs.[3,6] Inappropriate management of migraine can increase the potential progression from episodic (0 to 14 headache days per month) to chronic migraine (≥15 days a month lasting at least 4 hours without treatment),

Table 1. Clinical Recommendations for Classes of Acute Migraine Therapy

Drug Class	Clinical Recommendations
Triptans	Early use may prevent central sensitization Less effective after central sensitization develops Triptans contraindicated in patients with ischemic or vasospastic heart disease, stroke, uncontrolled hypertension, and basilar or hemiplegic migraine[11,12]
NSAIDs	Early use can inhibit neurogenic inflammation and peripheral sensitization Ability to interrupt established central sensitization when used during later stages of migraine progression Prevention or interruption of cutaneous allodynia Only 1 prescription NSAID (diclofenac potassium for oral solution) is approved by the FDA for acute therapy of migraine[13]
Opioids	Opioids are not FDA approved for acute therapy of migraine Even low-level use of opioids is associated with poor patient outcomes[14] Use of opioids should be limited or discontinued because of their abuse potential and sedative effects
Butalbital-containing combinations	Butalbital-containing combinations are not approved by the FDA for acute therapy of migraine and are controversial in this setting Efficacy in migraine has not been proved in placebo-controlled trials Propensity to cause MOH, dependence, and addiction The US Headache Consortium recommends limited use of these compounds and prescribing only with careful monitoring
Dihydroergotamine	Rapid-acting therapy that is effective at any stage of migraine Ability to interrupt established central sensitization when used during later stages of migraine progression

FDA indicates US Food and Drug Administration; MOH, medication overuse headache; NSAID, nonsteroidal anti-inflammatory drug.

with a pervasive and debilitating impact on quality of life and related increased costs to the payer.[17-19]

PATHOPHYSIOLOGY OF MIGRAINE PROGRESSION

The pathophysiology of migraine is not completely understood. One generally accepted pathway begins with the depolarization of meningeal perivascular trigeminal nerve endings, generally initiated by a wave of cortical spreading depression.[20]

Sensitization of central trigeminal pathways (central sensitization) occurs as a result of a barrage of impulses into the brainstem trigeminal nucleus caudalis via the first branch of the trigeminal nerve.[21] The ideal acute treatment of migraine should address both central and peripheral mechanisms of migraine to reduce the risk of developing cutaneous allodynia. A marker for central sensitization, cutaneous allodynia is characterized by pain that is precipitated by normally nonpainful stimuli.[22] Early treatment is a clinical priority, as central sensitization is associated with poor response to therapy and progression to chronic migraine.[22,23]

OVERCOMING CHALLENGES IN MIGRAINE TREATMENT

Current challenges to optimal migraine treatment include incomplete response to acute therapy (which may increase recurrence), intolerable side effects, medication overuse, poor patient compliance, and frequency of migraine.

Poor Response to Acute Therapy

Efficacy of acute migraine therapy depends on individual patient response, drug class(es) used, stage of the attack at the time of treatment, time to peak plasma concentrations, and side effects. Poor response may also be due to delayed treatment. Almost half of migraineurs delay taking their medication: reasons include mild pain at the onset of a migraine attack, avoidance of side effects, and fear of expending a limited supply of medications before the end of the month.[24] Compounding the impact of this delay are 2 additional factors: (1) tablet formulations may take 60 minutes or longer to work and (2) gastroparesis, which occurs in the majority of migraineurs, impairs absorption or reduces bioavailability of tablet formulations, resulting in further delay of therapeutic efficacy.[18,25,26] Triptans, due to their specific activity on 5-hydroxytryptamine 1 (5-HT_1) receptors, can further exacerbate this problem by delaying gastric emptying times. Liquid preparations and those that act like liquids, on the other hand, are thought to be unaffected by gastroparesis.[27]

Intolerance to Triptan Therapy and Headache Recurrence

Side effects are a major treatment challenge and may occur in up to 89% of patients taking triptans.[23,28] Although these are often innocuous "triptan sensations," their prevalence underscores the need for additional treatment options. Migraine recurrence can result in medication overuse and increased utilization costs, which should be a consideration for both prescribers and payers.[23] The average rate of recurrence for oral sumatriptan is approximately 30%, while it may be as high as 39% for sumatriptan subcutaneous injection.[23,28-30] Diclofenac potassium for oral solution has one of the lowest 24-hour recurrence rates, reported at 14%.[18]

Medication Overuse and Medication Overuse Headache

Medication overuse headache may occur with overuse of several classes of drugs but is commonly associated with over-the-counter medications, triptans, opioids, and butalbital-containing combinations.[15,31] In March 2012, the US Food and Drug Administration issued a label change for several triptans, highlighting their potential to contribute to medication overuse headache.[32-34] Additional concerns with opioids are tolerance, dependence, and addiction; patients should restrict their use of opioids or avoid them completely.[14]

Figure. International Classification of Headache Disorders II Criteria for Migraine Without Aura[16]

A. At least 5 headache attacks fulfilling criteria B through D
B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following characteristics:
- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache, at least 1 of the following characteristics:
- Nausea and/or vomiting
- Photophobia and/or phonophobia

E. Headache cannot be attributed to another disorder

Progression to Chronic Migraine

The transformation from episodic to chronic migraine can be costly for MCOs. In one study, patients who developed chronic migraine had significantly more outpatient, pain clinic, and ED visits compared with those whose migraine remained episodic.[35,36] While overuse of acute medications (particularly opioids, butalbital-containing combinations, and triptans) is strongly associated with migraine recurrence and the transformation to chronic migraine, about 3% of migraineurs develop chronic migraine each year without medication overuse.[18,28,37]

Benefits of Early Treatment With Rapid-Acting Therapy

Interrupting migraine progression is a key goal of treatment. Once central sensitization and its clinical correlate cutaneous allodynia occur, the efficacy of triptans is reduced.[22,23] Benefits of early treatment include potentially improved patient outcomes, reduced use of medications, and reduced risk of developing chronic migraine. While triptans and other acute therapies are effective early in the course of migraine, nonsteroidal anti-inflammatory drugs (NSAIDs) or dihydroergotamine are preferred therapies in later stages, as they can prevent or reverse central sensitization and cutaneous allodynia.[38–40] Clinical recommendations for classes of migraine drugs are shown in Table 1.

THERAPEUTIC AND FORMULARY CONSIDERATIONS

Availability of generic triptans and new formulations of migraine drugs may prompt formulary reviews of the migraine category. Products in development include a sumatriptan transdermal patch (Zelrix), a dihydroergotamine mesylate inhalation aerosol (Levadex), a sumatriptan nasal powder device (OptiNose), and calcitonin gene-related peptide (CGRP) antagonists. Existing products, available since the 7 triptan tablets were approved, include a sumatriptan–naproxen sodium fixed-combination tablet (Treximet), a sumatriptan injection needle-free delivery system (Sumavel DosePro), diclofenac potassium for oral solution (Cambia), and onabotulinum toxin A injections (Botox) for prevention of chronic migraine.

Sumatriptan–Naproxen Sodium Fixed-Combination Tablets. Sumatriptan–naproxen sodium fixed-combination tablets are meant to stop migraine in its initial stages and thereby prevent central sensitization.[11,39] The combination is only modestly superior to sumatriptan or naproxen alone, and both components are available generically at a lower price.[39]

Sumatriptan Injection Needle-Free Delivery System. The sumatriptan injection needle-free delivery system uses pressurized nitrogen to propel the drug through the skin and into the subcutaneous tissue. Benefits include fast onset of action, even in the presence of gastroparesis.[12] It is bioequivalent to generic sumatriptan injections but is priced higher.

Diclofenac Potassium for Oral Solution. Diclofenac potassium for oral solution is a buffered powder that rapidly dissolves in 2 ounces of water and is the only prescription NSAID approved in the United States for the acute treatment of migraine. With demonstrated plasma levels within 5 minutes, it achieves initial analgesic relief within 15 minutes (compared with 60 minutes for tablet diclofenac), delivering peak plasma levels 2 to 4 times higher than those delivered by the tablet. The oral solution was significantly superior in time to onset, efficacy, and duration of response compared with the same dose in tablet formulation. It interrupts the progression

Table 2. **Assessment of Acute Migraine Medication Efficacy**[44]

Factor to Assess	End Point
Rapidity of relief	Meaningful onset within 1 hour
Partial vs total pain relief	Total relief within 2 hours
Relief of associated symptoms	No nausea, vomiting, photophobia, or phonophobia
Return to normal function	Within 2 hours without sedation
Headache recurrence	Prevented due to total relief with 1 dose of medication
Consistency of response	Relief for every headache
Adverse effects	None or minimal
Preference/convenience of formulation	Ease of use, acceptable pain or taste considerations, convenience
Cost	Reasonable, with good efficacy and return to functionality with minimal disability

of peripheral and central sensitization, and is not impacted by gastroparesis. There is no generic equivalent for this formulation, but it is priced higher than generic NSAIDs.[18,41]

Onabotulinum Toxin A. Onabotulinum toxin A is indicated for the prevention of chronic migraine and costs an estimated $1000 to $2000 per treatment, including physician fees.[42,43] A recent study on chronic migraine found onabotulinum toxin A has a small to modest benefit in reducing the number of headache days per month but was not associated with fewer migraine attacks per month.[42]

Formulary Management of Acute Migraine Medications

When reviewing a product or class of migraine drugs, clinical considerations such as efficacy, safety, tolerability, mechanism of action, formulation, and onset of analgesic effect are paramount. Efficacy parameters should be specific to the migraine category, including data across multiple end points (Table 2). Various formulary management strategies are utilized for migraine therapies (Table 3).

Economic considerations include the relative cost of care, currently available therapeutic options, appropriate use/place in therapy, and the potential for abuse or overutilization. Appropriate pharmacologic management of migraine can reduce outpatient visits, ED visits, diagnostic scans, and hospitalizations.

Table 3. **Formulary Management Provisions for Acute Migraine Therapies**

Tiered copayments	Generic triptans placed on tier 1 More expensive, branded triptans on a higher copayment tier Brands without generic equivalents on tier 2 or tier 3 with ancillary fees applied
Step-therapy edits	Depends on perceived benefits of therapy and appropriate use Step edits that require a patient to fail the same class of drug more than once may be a hindrance to successfully managing migraine
Quantity limits	Can help control the overuse of medications, including triptans, barbiturates, and opioids May lead some patients to hoard prescription medications and overuse OTCs, potentially increasing ED utilization and costs
Prior authorizations	Meant to ensure appropriate diagnosis or prior use of therapy based on formulary policy Often required for high-cost treatments or therapy with questionable clinical efficacy

ED indicates emergency department; OTC, over the counter.

Proactive Case Management Plan

To proactively manage migraine, healthcare providers should do the following:

- Review the American Headache Society guidelines.
- Initiate an effective treatment plan that recommends the right treatment the first time and deters medication overuse and hoarding, as well as the use of less effective medications.
- Consider the complementary use of a generic triptan and migraine-indicated NSAID to attack both peripheral and central components of migraine.
- Consider fast-acting medicines to reduce the need for rescue therapy.
- Educate patients to help them discover and avoid migraine triggers.
- Refer patients not responding to their current treatment to headache specialists.
- Ensure that case managers probe long-term and increased use of prescription opioids, overuse of over-the-counter medications, and incidence of medication overuse headache.

SUMMARY

The misdiagnosis, undertreatment, and inappropriate management of migraine can lead to medication overuse, increased attack frequency, and progression to chronic migraine. Treatment should be initiated early with rapid-acting therapy that has the potential to address the central and peripheral mechanisms of migraine, reduce the risk of cutaneous allodynia and medication overuse headache, and minimize recurrence. The pharmacy and therapeutics committee class review of migraine therapies should include economic, pathophysiologic, and clinical considerations. The availability of multiple therapeutic options for acute migraine treatment may improve patient outcomes and reduce costs.

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Funding Source: None.

Author Disclosures: Dr Dunn reports receiving consultancies from Nautilus. Dr Calhoun reports board membership and consultancies from GlaxoSmithKline, Map Pharmaceuticals, Nautilus, and Zogenix advisory boards, and also reports receiving grants from GlaxoSmithKline and lecture fees from GlaxoSmithKline, Nautilus, and Zogenix. Dr Rapoport reports receiving consultancies from Allergan, Map Pharmaceuticals, Impax, Bristol-Myers Squibb, and lecture fees from Allergan and Nautilus. Dr Lopes reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (ML, JDD, AHC, AMR); acquisition of data (AMR); analysis and interpretation of data (ML, JDD, AMR); drafting of the manuscript (ML, JDD, AHC, AMR); and critical revision of the manuscript for important intellectual content (ML, JDD, AHC, AMR).

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