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Views and Perspectives

Removing Barriers to Appropriate Migraine Treatment: Formulary Limitations and Triptan Package Size

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The main goals in the pharmacologic management of migraine headache are to avert or relieve debilitating pain, prevent escalating acute medication use, and improve day-to-day functioning. This review will examine the evidence supporting the early use of acute medication, usually when pain is mild, to enhance patient outcomes. We will also discuss imposed quantity limits as a practical impediment to the implementation of this strategy in the managed care setting, and will identify strategies for overcoming this barrier to effective care. Quantity limits imposed on triptan therapy by health plans can hinder the optimal acute treatment of migraine. A standard triptan quantity limit sufficient to permit early migraine treatment and a movement by manufacturers to provide blister packs consistent with a standard quantity limit should reduce patients costs, permit brand mobility when appropriate, and bolster long-term cost effectiveness by removing an important impediment to the use of triptans when they are most effective, early in the migraine attack when pain is often still mild.

Key words: migraine, triptans, pharmacoeconomics, managed care, formulary

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A common disorder in the primary care setting, migraine headache affects at least 6% of men and 18% of women in the United States.[1] Because of its prevalence and debilitating symptomatology, migraine headache is associated with substantial morbidity and economic burden. The utilization of prescription drugs and diagnostic services are increased 250% and 600% for migraineurs compared with nonmigraineurs.[2] The total direct costs linked to migraine approaches $10 billion annually, stemming chiefly from the costs associated with clinic visits ($5.1 billion) and prescription drugs ($2.7 billion). Since the prevalence peaks between the ages of 25 and 55 years, migraine also results in substantial indirect costs, chiefly lost productivity. Migraine has been linked to the loss of almost 20 workday equivalents (absenteeism plus reduced workdays) yearly.[3] In fact, the majority (53%) of individuals who experience a severe migraine headache require bed rest or are substantially impaired.[4,5] The economic losses secondary to increases in "bed days" and restricted activity days for migraineurs have been estimated to range from $5.6 billion to $17.2 billion annually, losses that exceed those associated with type 2 diabetes.[2] The recent American Productivity Audit demonstrates that headache is the most common pain condition leading to lost productivity time followed by back pain and arthritis.[6]

The main goals in the pharmacologic management of migraine headache are to avert or relieve debilitating pain, prevent the escalation of acute medication, and improve day-to-day functioning.[7] These patient-centered therapy goals will undoubtedly

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achieve a reduction in the economic burden of migraine. Recent clinical guidelines for the management and prevention of acute migraine attacks advocate the rapid treatment of migraine as an important step in averting the progression of pain within a migraine attack and reducing attack-related disability.[1,7] This review will examine the evidence supporting the early use of acute medication, usually when pain is mild, to enhance patient outcomes. We will also discuss imposed quantity limits as a practical impediment to the implementation of this strategy in the managed care setting, and will identify strategies for overcoming this barrier to effective care.

EARLY TREATMENT FOR MILD MIGRAINE: COMPELLING EVIDENCE

The triptan class of medications represents the single most important therapeutic advance in the acute treatment of migraine. However, over the past 15 years, clinical triptan trials have required patients to wait until pain is moderate or severe before administering treatment. The main reason for this requirement was to increase the percentage of "responders" on a 4-point ordinal pain scale and increase the likelihood of demonstrating a statistically significant difference compared with placebo. Deferring treatment until pain becomes moderate or severe became a clinical recommendation from physicians, and part of a larger misguided marketing campaign by pharmaceutical companies, implying that these drugs are effective any time during the course of an attack. Because of the limited monthly number of tablets enforced by pharmacy plans, patients were inclined to follow these instructions, however counterintuitive this recommendation may have appeared.[8] Over the past several years, considerable advances have been made in our understanding of migraine pathogenesis. This understanding, combined with data from clinical trials that have compared acute treatment during mild pain versus moderate or severe pain, has provided very compelling evidence that should be guiding clinical practice.

Data from post hoc analyses from placebo-controlled trials, prospective open-label trials, and randomized placebo-controlled trials support the conclusion that the response to triptans is significantly enhanced when treatment is administered when pain is mild (which often means early) versus moderate or severe. Pain-free and sustained pain-free response rates are as high as 85% and 66%, respectively, when triptans are administered when pain is mild.[8-11] By contrast, a meta-analysis that evaluated the results from 53 randomized controlled triptan trials found median pain-free and sustained pain-free response rates of 29% and 20%, respectively, when triptans are administered when pain is moderate or severe.[12] In addition, headache recurrence rates and the use of rescue medication is more than halved when a triptan is taken when pain is mild compared with moderate or severe.[10]

These trials, together, demonstrate that treating migraine headache with triptans when pain is mild, which for most patients often means early in the course of an attack, results in improved acute treatment outcomes. Reducing headache recurrence, eliminating pain completely, and thereby reducing the need for redosing, rescue medication, office calls or visits, and emergency department use are important aspects of cost-effective treatment that may be more readily achieved with early treatment, when pain is usually mild.

Although clinical treatment guidelines now advocate a more aggressive approach to the management of early migraine,[7] most formularies place limits on the availability of tablets. This restriction may cause patients to ration therapy, resulting in a delay in treatment. As a cost control measure, quantity limits may impede the optimal therapy of acute migraine and unintentionally increase long-term costs.

AFFORDABILITY ISSUES AND OPTIMAL ACUTE MIGRAINE MANAGEMENT

Affordability issues related to triptan quantity limits can impede the use of triptans in the early treatment of mild migraine attacks—a time when acute therapy is most effective.

Package Size and Health Plan Quantity Limits.— As triptans prepared for market entry, market research suggested that the initial stocking of product in retail pharmacies was going to be a challenge.

Table.—Cost of Migraine-Specific Triptan Medications

Brand (Generic)	Mg per Dose	Cost per Unit ($)	Tablets or Doses/pkg
Axert (almotriptan)	12.5 mg	16.66	6
	6.25 mg	17.34	6
Relpax (eletriptan)	20 mg	15.36	6
	40 mg	15.36	6
Frova (frovatriptan)	2.5 mg	15.26	9
Amerge (naratriptan)	1 mg	19.60	9
	2.5 mg	19.60	9
Maxalt (rizatriptan)	5 mg	16.42	6
	10 mg	16.42	6
Maxalt-MLT (rizatriptan)	5 mg	32.83	3
	10 mg	32.83	3
Imitrex (sumatriptan)	100 mg tab	15.78	9
	50 mg tab	15.55	9
	25 mg tab	17.00	9
	5 mg nasal	25.19	1
	20 mg nasal	23.80	6
	6 mg inj vial	54.60	5
	STAT dose	56.17	2
	STAT dose Pen	117.58	1
Zomig (zolmitriptan)	5 mg	17.00	3
	2.5 mg	14.95	6
Zomig-ZMT (zolmitriptan)	5 mg	17.77	3
	2.5 mg	14.81	6
Zomig nasal spray (zolmitriptan)	5 mg	21.59	6

Source: http://www.drugstore.com, 29 September, 2004.

Because of high up-front costs, triptans are not automatically shipped to pharmacies by wholesalers in large-quantity containers, such as 100-tablet bottles. For example, a bottle of 100 triptan tablets might represent an inventory cost of $1,600, a daunting expense for many pharmacies. To ensure availability, manufacturers chose an alternative method less costly to pharmacies: blister packs containing a small number of tablets (Table).

In an effort to manage their burgeoning monthly utilization of expensive triptan medications, a decision was made by many health plans to limit the number of doses a patient can access in a given month. This decision was driven largely by the economics of distribution rather than by clinical considerations. This approach has resulted in a wide variation in quantity limits among the different health care plans and the establishment of limits that are often too low to permit the patient to comfortably treat early, when migraine pain is still mild.

QUANTITY LIMITS VARIATION AMONG SELECTED HEALTH PLANS

Arbitrary quantity limits may impede optimal acute treatment of migraine. Migraineurs in practice often delay treatment of acute migraine attacks, at least in part to conserve the limited number of tablets allotted per month. As discussed, this strategy of conservation may lead to rapid depletion of the monthly supply because of persistent or recurrent pain and the need to redose with a 2nd and sometimes a 3rd tablet. This scenario, in turn, may increase long-term costs associated with clinic visits, the principal driver of the direct costs associated with migraine treatment.

Quantity limits on triptans have been shown to decrease inappropriate utilization and per-migraineur per-month drug costs, especially in conjunction with drug utilization reviews that identify individuals suboptimally treated.[13] Yet, to be truly cost-effective, the quantity limit imposed by a health plan should not hinder the early treatment of migraine attacks and

should address the all-too-common need to treat multiple migraine attacks each month. In fact, almost half of migraineurs experience more than 1 day of severe headache monthly, and 20% of those individuals experience 10 or more days of severe headache over a 3-month period.[4] Therefore, monthly requirements will vary considerably among migraineurs.

Future Direction: Rational Triptan Quantity Limits and Packaging.—Deciding on a specific triptan quantity limit across health care plans will be at once arbitrary, in addition to challenging since reasonable patients and physicians will disagree based on personal experience, there already may be an emerging trend to set a limit of at least 12 tablets per month for all triptans. A quantity limit of 12 triptan tablets per month has been shown to not only provide cost savings to the plan,[13] but may also be an important step toward allowing the patient the flexibility to treat migraine early without incurring additional out-of-pocket costs related to repeat copays or direct triptan purchases. At the same time, a quantity limit of 12 tablets would also be insufficient to lead to medication overuse headaches.[14] Medication overuse headache may occur when acute headache medications are used on 10 or more days, not 10 tablets per month. While the average number of triptan tablets needed per attack varies between 1.3 and 1.8 depending on the individual triptan, it is expected that the need for repeat dosing due to incomplete relief or headache recurrence will decrease if an early treatment strategy is adopted. While the average number of tablets per attack will not approach 1, especially if recurrent attacks occur during menstruation, the consistent need for more than 12 tablets per month should signify to the clinician the presence of at least two attacks per week, inadequate response to current triptan, or an inadequate treatment strategy (late during moderate or severe pain). This should facilitate a change in strategy which may require switching acute therapy or changing formulations, emphasizing the need for treating mild pain, or the need for initiating or changing prophylactic medication. In addition, the acceptance across health plans of a standard quantity limit for triptans would enhance brand mobility, permitting smooth brand switching when this becomes medically necessary or economically attractive. For individuals with prescription drug copayments, triptan package size, itself, has become another important cost consideration. For instance, unit copayment may be less with triptans that contain nine tablets per blister pack, when compared with packs that contain fewer tablets.[15] Discerning the most cost-effective packaging option can be a daunting task for the patient and clinician. Standardizing triptan package size would remove this variation and simplify treatment. This would also help ensure that the selection of triptan therapy is based on the patient's clinical profile and the most appropriate dosage formulation instead of the least restrictive quantity limit. Optimizing acute migraine treatment in the most cost-effective manner will require a coordinated effort between health plans and manufacturers so that medically sound, standardized quantity limits can be implemented in conjunction with triptan packaging that complements those limits.

It is important to bear in mind that individual exceptions to this quantity limit will occur. Like any chronic and recurrent illness, acute migraine therapy requires individualized treatment approach for each patient. For example, a quantity limit of 12 may not be sufficient for a young woman who may need to use daily triptans for 5 days for attacks that occur at the time of menstruation. Perimenstrual prophylaxis with a number of triptans has been shown in placebo-controlled trials to be safe and effective.[16,17] Therefore, quantity limits must be flexible, amenable to modification on an individual basis and at the expert discretion of the treating physician.

Finally, because the high cost of these medications in part accounted for the monthly restriction on quantity, manufacturers should be encouraged to decrease the cost to consumer of this class of medications. Migraine is a highly prevalent and disabling condition for which the gold standard is a class of drugs that may be out of the reach of a great number of patients. While there is a national dialogue about the uninsured and underinsured in the United States, until access to gold standard therapies is made available to those in need, the healthcare industry, including providers and industry, should do everything possible to fulfill our collective responsibility to our patients.

SUMMARY AND CONCLUSIONS

Migraine headache continues to result in significant morbidity and lost productivity. Over the past 5 years, clinical and scientific data have emerged in support of a more aggressive and early approach to the acute treatment of migraine. Treating migraine pain early, when pain is still mild, usually leads to improved patient outcomes, reduced headache recurrence, and decreased consumption of acute and rescue medications, as well as more rapid restoration of function. These positive clinical outcomes should result in a reduction in office and emergency department visits, which account for over half of the $10 billion in direct costs associated with migraine. Quantity limits imposed on triptan therapy by health plans can hinder the optimal acute treatment of migraine. A standard triptan quantity limit sufficient to permit early migraine treatment and a movement by manufacturers to provide blister packs consistent with a standard quantity limit should reduce patients costs, permit brand mobility when appropriate, and bolster long-term cost effectiveness by removing an important impediment to the use of triptans when they are most effective, early in the migraine attack when pain is often still mild.

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