

## Clinical Considerations in the Use of New Migraine Medications

Based on a presentation by Constance Johnson, MD

### **Presentation Summary**

The opportunities for improving the lives of those with severe migraine have never been greater. Yet, even as physicians become more aware of today's more effective pharmacologic options, the tendency of this disease to manifest differently in individual patients means that even the clearest treatment guidelines will require monitoring and customization. The main choices for pharmacologic treatment of acute

migraine include over-the-counter combinations (for example, acetaminophen-aspirin-caffeine and nonsteroidal anti-inflammatory drugs), dihydroergotamine, and 5-hydroxytryptamine agonists. The efficacy of these agents is approximately 60% to 80%, and the choice of an agent for an individual patient often depends on dosing convenience, administration options, side-effect profiles, and individual response.

In the last decade, a variety of new antimigraine compounds have been synthesized. At the same time, existing agents have been reformulated to enhance their delivery, convenience, and effectiveness for the migraine patient. As a result, clinicians today have the benefit of several new effective agents that are backed by extensive clinical testing but were unavailable just 5 or 10 years ago.

The result is that patients who were chronic users of the tertiary headache center or the emergency room are now being treated much more effectively. For many patients, these new agents are miracle drugs.

Even with an overall failure rate of about 20%, the new self-administered parenteral therapies and nasal sprays have truly revolutionized migraine treatment.

The opportunity and the challenge is to educate physicians as to the best use of these revolutionary agents. Various national groups and societies are now seeking consensus on headache guidelines that explain the optimal use of these new agents in various patient scenarios. Managed care plans are eager to adopt and implement such guidelines.

Undoubtedly, this is the correct process, but managed care groups

must realize that the final guidelines will in all likelihood offer only general instruction in choosing the appropriate therapy. With limited head-to-head studies and a wide variation in

patients' therapeutic response, guideline modification is appropriate, because it will shift much of the management burden back to the primary care physician. So those who are developing and implementing migraine guidelines should take into account the perspective of the busy physician who manages headaches on a daily basis. Several common physician concerns involving migraine diagnosis and treatment are presented to highlight this practical perspective.

**Table 1.** International Headache Society (IHS) Criteria for Migraine

<p><b>Migraine Without Aura</b></p> <ul style="list-style-type: none"> <li>A. At least 5 attacks fulfilling criteria B through D</li> <li>B. Attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)</li> <li>C. At least 2 of the following characteristics:             <ul style="list-style-type: none"> <li>1. Unilateral locations</li> <li>2. Pulsating quality</li> <li>3. Moderate or severe intensity (inhibits or prohibits daily activities)</li> <li>4. Aggravated by climbing stairs or similar routine activity</li> </ul> </li> <li>D. At least 1 of the following:             <ul style="list-style-type: none"> <li>1. Nausea and/or vomiting</li> <li>2. Photophobia and phonophobia</li> </ul> </li> <li>E. At least 1 of the following:             <ul style="list-style-type: none"> <li>1. History, physical, and neurologic examinations do not suggest disorders in groups 5 through 11 of the IHS classification [<b>NOTE:</b> These include headache associated with: 1) head trauma; 2) vascular disorders; 3) nonvascular intracranial disorder; 4) substances or their withdrawal; 5) noncephalic infection; 6) metabolic disorder; and 7) facial pain associated with disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures.]</li> <li>2. History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations</li> <li>3. Such a disorder is present, but attacks do not occur for the first time in close temporal relation to the disorder</li> </ul> </li> </ul> <p><b>Migraine With Aura</b></p> <ul style="list-style-type: none"> <li>A. At least 2 attacks fulfilling criterion B</li> <li>B. At least 3 of the following characteristics:             <ul style="list-style-type: none"> <li>1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction</li> <li>2. At least 1 aura symptom develops gradually over more than 4 minutes or 2 or more symptoms occur in succession</li> <li>3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, the accepted duration is proportionally increased</li> <li>4. Attack follows an aura with a free interval of less than 60 minutes (can also begin before or simultaneous with the aura)</li> </ul> </li> <li>C. At least 1 of the following:             <ul style="list-style-type: none"> <li>1. History, physical, and neurologic examinations do not suggest disorders in groups 5 to 11 of the IHS classification (see note above)</li> <li>2. History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations</li> <li>3. Such a disorder is present, but attacks do not occur for the first time in close temporal relation to the disorder</li> </ul> </li> </ul>
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Source: See reference 1.

### Defining Headache

The diagnosis of headache has not changed in recent years. No test for migraine exists, only tests to exclude organic headache disorders. The definition of headache remains clinical. The International Headache Society (IHS) classification that defines migraine as head pain with migrainous features remains the best guide (Table 1).<sup>1</sup> However, even though the diagnosis of headache has not advanced significantly, clinicians must pay more attention to their own tendency to classify the headache and the patient.

Neurologists still do not agree on whether all headaches are variations of the same disorder or discrete manifestations of separate disorders. As a result, the old "lumper vs splitter" debate goes on.

Although the debate at the pathophysiologic level may be academic, the very practical implications of physician and patient beliefs regarding headache origins should be recognized. For example, if a certain physician believes that diet is a major trigger of headache, he or she may end up with patients for whom this is true. Similarly, a gynecologist who treats menstrual migraine may have a practice that attracts women for whom a timed prophylactic treatment works best. There is referral bias at work, and the physician's definition shapes the treatment choice.

Even the classification of headaches in terms as basic as frequency and severity may not always be clear cut. For example, there are always patients who have headaches that fit the IHS classification of migraine only once a year or every other year. But perhaps these patients have tension headaches that require treatment every month. Many patients actually present with this type of mixed disorder. Should they be treated for migraine? The answer hinges on the physician's interpretation of the often vague patient-reported frequency. Severity alone cannot be the guide to defining migraine, because many patients with mixed headaches have very severe tension headaches.

In defining a patient's migraine frequency over the longer term, the clinician often will identify periods of remission and exacerbation. Over the course of a 15- to 20-year physician-patient relationship, there will undoubtedly be good migraine times and bad migraine times. This has

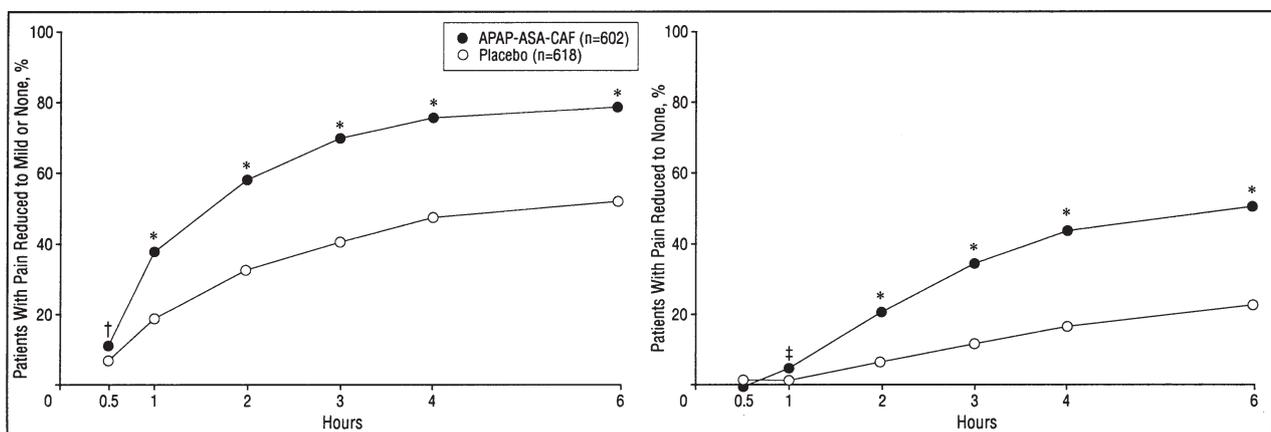
implications for evaluating outcomes of both prophylactic and alternative therapies. Is the patient getting better because of therapy, or is it a spontaneous remission? Such waxing and waning of disease also has implications for possibly tapering treatment.

Such practical diagnostic issues such as special patient populations, infrequent migraines, and long-term remissions have not been addressed in treatment trials and are difficult to incorporate in guidelines.

### Pharmacologic Treatment

Choices of pharmacologic migraine therapy can be divided into 3 types: acute symptomatic treatment, acute abortive treatment, and prophylactic treatment. Because migraine is generally a paroxysmal disorder, acute treatments receive the most attention. Recommendations regarding the mainstays of acute therapy from several publications are highlighted, not so much to guide drug choice as to illustrate the similarity of results seen

**Figure 1.** Investigators' Global Evaluations of Headache Pain Relief



\* $P \leq 0.001$  vs placebo,  $^{\dagger}P \leq 0.05$  vs placebo,  $^{\ddagger}0.01$  vs placebo

Source: Reprinted from Lipton RB, Stewart WF, Ryan RE, et al. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain. *Arch Neurol* 1998;55:210-217. Copyright 1998. American Medical Association.

with these classes of available agents.

The over-the-counter (OTC) medications are still the mainstays of acute symptomatic treatment. Most headache patients have some personal history of using aspirin and aspirin-caffeine combination products by the time they visit a physician. Potential overuse of these products should be discussed with patients who consult their physicians.

In a recent double-blind, placebo-controlled trial, the nonprescription combination of acetaminophen, aspirin, and caffeine was highly effective in reducing migraine headache pain as well as alleviating nausea, photophobia, and phonophobia (Figure 1).<sup>2</sup> In this study of more than 100,000 migraineurs who suffered moderate to severe pain, the pain was reduced to mild or moderate after 2 hours in 59.3% of the 602 drug-treated patients vs

32.8% of the 618 placebo-treated patients ( $P < 0.001$ ). The drug combination was well tolerated in this population.

The nonsteroidal anti-inflammatory drugs (NSAIDs), which were introduced 10 to 20 years ago, led to the first revolution in acute migraine therapy.<sup>3</sup> Nonsteroidals such as ibuprofen, naproxen sodium, and ketorolac have now become staples of migraine management.

With the transition of several NSAIDs to OTC status, many patients now present to the headache clinic who are already self-medicating at prescription-level doses. With so many potent and potentially toxic OTC options for headache pain, patients should always be questioned about any history or continuing pattern of self-medication.

For treatment of more severe headaches, combination products that contain aspirin or acetaminophen plus a sedative (for example, butalbital) or a mild vasoconstrictor (for example, isometheptene) are often used.<sup>4</sup> A mild sedative such as dichloralphenazone is also sometimes part of the combination. Because these combination products have been available for years, most physicians are familiar with their limitations, such as the addictive potential of products containing barbiturates and the contraindications of preparations containing isometheptene in patients with glaucoma, hypertension, or liver disease, as well as those taking monoamine oxidase inhibitors (MAOIs).

In terms of abortive therapies for severe headaches, the main choices are medications containing ergotamine and the selective serotonin agonist medications. Algorithms have been created by many practitioners to aid in selecting particular agents at particular times; one such algorithm is shown in Table 2. For the very busy provider, such charts can be valuable

**Table 2.** Algorithm for Migraine Management

STAGE	Mild	Moderate	Severe
<b>CHARACTERISTICS</b>	Occasional mild headache, no nausea or vomiting	Moderate or severe headache with or without nausea or vomiting	Severe headache or frequent moderate-severe headache, nausea +/- vomiting, functional impairment
<b>TREATMENT</b>	OTC analgesic NSAID	Combination analgesic NSAID Triptan Ergot alkaloid Antiemetic	NSAID Triptan Ergot alkaloid Antiemetic Prophylactic medication

in treating the majority of patients; however, they have major limitations.

Many migraine patients have mild, moderate, and severe headache episodes rather than stages characterized by increasing headache severity. The patient may require medication from each category to manage individual migraines. "Staged" is a term used in managed care to indicate the types of treatment to be covered at a given stage of a disease. It is not well suited to migraine, where the number of exceptions approaches the rule. The primary care practitioner must appreciate the potential need to prescribe numerous migraine medications for an individual patient. Because of the explosion of new triptan medications, another layer of complexity arises. The following two sections review the new medications and summarize their similarities and differences.

### Ergotamines

Ergot alkaloids have been used as antimigraine therapy for more than half a century. Patients can now take drugs containing ergotamines orally, sublingually, rectally, intramuscularly, intravenously, or intranasally. Some products are combined with caffeine or a barbiturate. Because of their long history of use, most physicians know that the ergotamines are relatively nonselective pharmacologic agents that affect adrenergic and dopaminergic receptors as well as serotonergic sites. Nausea and vomiting, symptoms that are already present in many patients with severe migraine, occur in one or two of every 10 patients who take ergotamine and remain a major drawback.<sup>4</sup>

Because of the erratic gastrointestinal absorption of oral ergotamine products, injectable or nasal forms of dihydroergotamine (DHE) are often preferred in severe migraine. DHE nasal spray is a unique way to deliver DHE intranasally and has long been

available for parenteral administration. Although DHE is effective when it is given to the patient intramuscularly, the injection site is usually painful, making this method unacceptable for many patients.

DHE nasal spray was evaluated in a double-blind, placebo-controlled study in which 70% of the patients reported that their headache had resolved at 4 hours. Only 14% of the patients in whom the headache had completely resolved reported a recurrence within 24 hours. The rates of nausea with the 2-mg dose of DHE were not markedly higher than those seen in the placebo group.<sup>5</sup>

DHE spray offers migraine patients an important option for aborting or greatly ameliorating migraine pain by providing once-a-day dosing with a low recurrence rate. Use of the present DHE delivery system is awkward compared with sumatriptan nasal spray. An improved nasal delivery device could further improve the ease of self-administration.

### Triptans

The selective 5-HT<sub>1</sub> agonists have been designed to target the subset of neurotransmitter receptors implicated in migraine pathophysiology without disturbing noninvolved receptors. Although the vascular and neurogenic actions of these drugs are still being debated, these new agents have demonstrated efficacy in relieving acute migraine pain and decreasing nausea and vomiting.

There are now 4 triptans on the market (Table 3). The first triptan to be approved by the Food and Drug Administration (FDA) was sumatriptan, which was released in 1993. It was evaluated in a double-blind, placebo-controlled clinical trial as a 6- or 8-mg subcutaneous injection. Pain severity was assessed at 30, 60, and 120 minutes after treatment, which produced statistically significant response rates of about 50%,

70%, and 90%, respectively. The difference between the 6- and 8-mg dose was not significant,<sup>6</sup> and the drug was approved by the FDA at the lower dose.

Trials with the oral tablets demonstrated similar efficacy with a slower onset of action.<sup>7,8</sup> The optimum dose of oral sumatriptan was recently evaluated in a controlled study involving 1003 patients that compared 25-, 50-, and 100-mg doses. Both the 50- and 100-mg doses were more effective than the 25-mg dose, and the 50-mg dose was associated with fewer side effects than the 100-mg dose.<sup>9</sup> As might be expected, the nasal spray had a more rapid onset than the tablets, but it was less than the injectable. The 5-mg dose is less effective than the 20-mg dose, 45% to 49% vs 60% to 64% (PI Imitrex Nasal Spray), making the higher dose comparable to the injectable or the 50-mg oral dose. The newer triptans are all oral preparations, of which naratriptan has the longest half-life. The efficacy was 68%, compared with placebo

4 hours after a dose in a double-blind trial.<sup>10</sup> Zolmitriptan and rizatriptan have also been evaluated in double-blind, placebo-controlled trials and demonstrated efficacy similar to that of sumatriptan and naratriptan.<sup>11,12</sup> Rizatriptan is available as a tablet and a melt, the MLT. The melt disintegrates quickly when placed on the tongue, which does not result in more rapid absorption but increases the ease of administration.

These triptan studies exemplify the best and worst that published evidence can offer the busy practitioner. On the one hand, they clearly demonstrate that the new agents are effective in about 60% to 80% of patients, which is about double the efficacy of placebo, and that the migraineur's quality of life can be immensely improved; on the other hand, they offer little guidance in terms of which agent to choose and what to do when it fails.

Despite differences in receptor-binding affinities and pharmacokinetic

**Table 3.** Triptans 5 HT, Agonists

	t 1/2 (hours)	Cost	Maximal Initial Dose	Maximal in 24 Hours
Sumatriptan (Imitrex)				
injection s.c. 6 mg	2	\$\$\$	6 mg	12 mg
tablets 25, 50 mg	2 1/2	\$	100 mg	200 mg
nasal spray 5, 20 mg	2	\$	20 mg	40 mg
Zolmitriptan (Zomig)				
tablets 2.5, 5.0 mg	3	\$	5 mg	10 mg
Naratriptan (Amerge)				
tablets 1, 2.5 mg	6	\$	2.5 mg	5 mg
Rizatriptan (MAXALT)				
tablets, MLT (5, 10mg)	2-3	\$	10 mg	*30 mg

\*The maximum in 24 hours is twice the maximal initial dose with the exception of rizatriptan.

ic distribution, the selective serotonin agonists appear to be very similar in terms of clinical effectiveness and tolerance. They are similar with regard to side effects, contraindications, and prescribing limitations when used in pregnant women, the elderly, and those with renal failure or liver disease. The use of selective serotonin agonists is contraindicated in the presence of coronary artery disease or in patients who are at risk for coronary artery disease. Similarly, efficacy distinctions between members of this class are difficult to make at this time.

Recent publications that provide direct comparative data suggest that the oral agents are quite similar in terms of efficacy and side effects.<sup>13,14</sup> In terms of cost, injectable sumatriptan is the most expensive.

Because of a lack of consensus regarding the differences between products, most physicians now rely on their own experiences with patients to guide drug selection. In most cases, the choice among triptan agents is less important than that of the route of administration. The tradeoffs involve the fast action of the injectables and the nasal sprays compared with their slightly higher levels of side effects. Many patients report more intense paresthesia, tingling, and tightness in the chest, as well as intensification of the headache when the injectable and spray routes are used. On the other hand, the tablets produce fewer side effects, but they take longer to provide relief.

At present, primary care physicians are trying to keep up with an explosion of knowledge in all areas of medicine, of which headache is just one small niche. Whereas most physicians are very comfortable advising patients on the use of OTC analgesics and NSAIDs, they increasingly ask for help in the selection and use of the new DHE spray and the 5-HT<sub>1</sub> ago-

nists. Physicians who do not see large numbers of patients with severe headaches often are especially hesitant to prescribe these new products. A consensus on treatment guidelines will be especially useful in encouraging such physicians to treat moderate to severe headaches more responsively at the primary care level.

*“Dosing is another problem that must be addressed by clear guidelines. Primary care physicians often dose the new agents inadequately and then seek a referral through their managed care group when drug therapy fails.”*

—Constance Johnson, MD

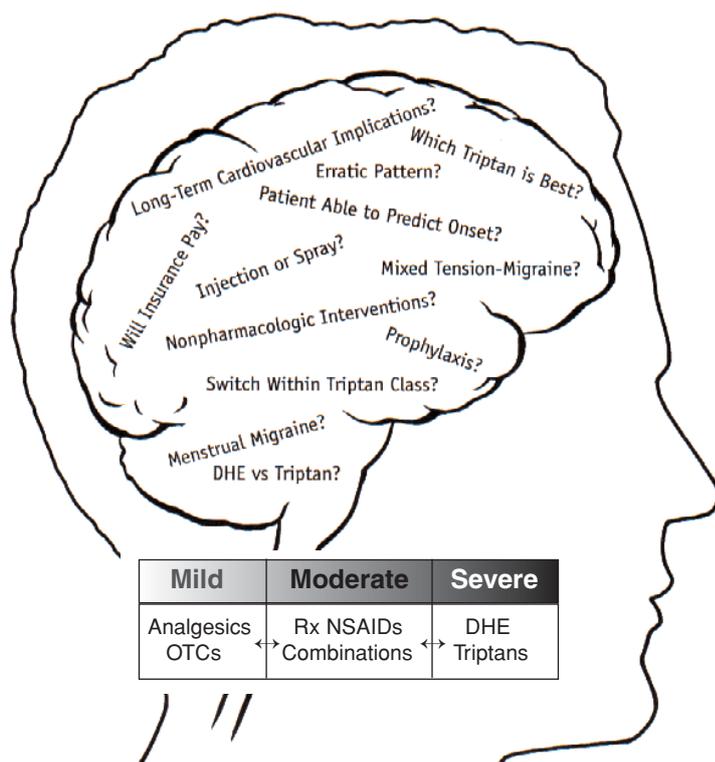
Dosing is another problem that must be addressed by clear guidelines. Primary care physicians often dose the new agents inadequately and then seek a referral through their managed care group when drug therapy fails. The typical patient complaint related to underdosing is that the headache went from a level 8 to a level 4, but then it returned to level 8 at 4 hours. Because migraines are known to last from 4 to 72 hours and the half-lives of these drugs are only 1.5 hours to 6 hours for the triptans and about 10.5 hours for DHE, the need for multiple dosing in many patients should be no surprise. In such a common situation, the critical message for physicians involves not the particular agent selected but adequate dosing and redosing with that agent. Many patients require multiple dosing, while at the same time dosage

limits must be observed. For busy practitioners who are struggling to remember all this dosing information, an easy reminder is that the maximum triptan dose in 24 hours is 2 times the maximal initial dose, with the exception of rizatriptan, the newest product, for which the maximum dose is 3 times the maximum initial dose.

### Other Current Issues

- The use of DHE and the triptans is contraindicated in patients who have coronary artery disease or coronary vasospasm. Chest symptoms and coronary vasoconstriction occur with the use of DHE and triptans.<sup>15</sup> Migraine can persist to age 50, 60, or 70, at which point coronary artery disease is already rampant. Given this potential for coronary vasoconstriction, how can a physician manage the patient who continues to suffer migraines during these higher-risk years?
- At the other end of the age scale, data are beginning to emerge regarding the use of triptans in children. A downward adjustment of doses, for example use of sumatriptan 25-mg tablets and 5-mg nasal spray, appears to provide the needed benefit.
- Although current package insert recommendations advise that triptans should not be mixed with each other or with ergotamine, many migraine clinics are using these agents in close proximity. For example, if a patient is given a sumatriptan injection for a rapidly accelerating headache and the headache recurs, some clinicians may give naratriptan tablets an hour or two after the injection.
- One of the widest gaps in our knowledge of dosing concerns the upper limit of triptans or DHE. We see no physical or psychological tolerance to these drugs, so how many doses can a patient take in a week or a month? Even in the absence of evidence, many health plans are arbitrarily allowing only two treatments per week or 6 to 8 per month. This can be a serious problem for many lower income migraine patients.
- Paradoxically, this same health plan may allow the patient to take propranolol for prophylaxis every day. Certainly, this beta-blocker has a lower cost per pill, but the evidence for its efficacy in prevention is slim, and there may be other considerations, such as a

**Figure 2.** The Physician's Dilemma: Moving From Core Concepts



Although most primary care physicians are aware of the core concepts in the diagnosis and treatment of migraine, effective treatment is often stymied by the lack of answers to complex questions involving individual patients. Practical treatment guidelines, while not answering all questions, should encourage improved headache therapy in primary care and prompt referral when appropriate.

reduction in the patient's exercise tolerance, which are completely overlooked.

- In women who suffer menstrual migraines and are able to predict their migraines, prophylactic use of triptans may be indicated. Sumatriptan 25 mg 3 times a day led to a marked reduction in frequency.<sup>16</sup>
- Finally, should triptans be used for moderate and severe tension headache? Many migraine patients report pain relief when they use triptans for their tension headaches.<sup>17</sup>

The foregoing are just a few of the issues that practicing physicians must address today. Although most care providers are aware of the core concepts in the diagnosis and treatment of migraine, truly effective treatment is often stymied by a lack of answers to these types of complex questions as they relate to individual patients (Figure 2). Consensus-based practice guidelines may address some of these issues, but a continued dialogue between specialists and primary care physicians will be necessary to fill in the remaining gaps as experience with the new agents grows.

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... DISCUSSION HIGHLIGHTS ...

At the conclusion of Dr. Johnson's presentation, symposium participants discussed the use of the new migraine medications.

**Dr. Brown:** If a patient is not responding to sumatriptan despite adequate dosages over a 2-month period, would you switch to another triptan? Or are the triptans all alike?

**Dr. Johnson:** If my patients are on 50 mg of sumatriptan and I take them to a 100-mg dose and they still do not respond, I would consider switching to another triptan. Some patients

respond to a different member of the same class.

**Dr. Gallagher:** We just completed a study of more than 1600 patients that compared sumatriptan and zolmitriptan and showed some differences between the agents. The average family doctor might not recognize these differences, but the neurologist or specialist would.

**Dr. Mondell:** What is the current status of the warning to reduce the dose of rizatriptan in patients who are also taking propranolol?

**Dr. Brown:** Apparently this warning was added because propranolol decreases the hepatic clearance of the triptan by about 70%. The recommendation is to use a 5-mg tablet instead of a 10-mg one. We may learn more about this interaction in the future, including whether other beta-blockers and triptans share this interaction, but for now that is the recommendation. The other precaution in coprescribing concerns the triptans and the selective serotonin reuptake inhibitors (SSRIs).

**Dr. Johnson:** But that is a very idiosyncratic reaction, as in the case of selegiline and the SSRIs. Certainly, if your patient is on an SSRI and you add a triptan and they get flushing and weakness and so forth, the interaction is there. However, practically speaking, this is not a big issue.

**Dr. Brown:** We caution physicians about using MAOIs with the triptans, but we do not say they cannot give them together. However, concomitant use of MAOIs is contraindicated with all the triptans except naratriptan (Amerge), because MAOIs can reduce the clearance of triptans, resulting in increased plasma concentrations and prolonged elimination from the body. Concurrent administration of MAOIs or their use

within 2 weeks of their discontinuation is contraindicated. MAOIs do not significantly affect the elimination of naratriptan; however, their use is not contraindicated with this specific triptan.

**Dr. Lake:** From our perspective in a comprehensive/tertiary care headache center, we are seeing an increasing number of patients using sumatriptan daily. As an extreme example, we had one cluster headache patient taking it every 3 to 4 hours for 2 years, as well as prednisone bursts every 2 weeks. His initial request for referral to our center at the beginning of this 2-year span had been denied by the insurance company, which continued to pay a large amount of money to medicate a patient who remained disabled. Our perspective is that these drugs may actually contribute to recurrent, rebound pain in some patients, and that this overreliance on acute care actually crosses over into prophylactic care in an intractable case. Inpatient treatment for triptan withdrawal and appropriate prophylactic medication led to a significant reduction in headaches, improved functioning, and reduced costs over the long term.

**Dr. Johnson:** There is no evidence that the acute treatment agents do or do not cause rebound. Clearly, we should not think about them in the same way as we think about narcotics. However, we all see that small percentage of patients who blur the line between acute and prophylactic care. Of course, 2 or 3 years from now we may have a triptan that possesses no cardiac effects and can be used safely every day, cost issues aside. In addition, if our guidelines set usage limits on triptan, we need to provide physicians with longer time frames. Some patients tend to have 5 attacks concentrated in 1 month and then no attacks for 2 months. Perhaps we need to specify an average number of doses

over several months rather than so many doses in 1 week or 1 month.

**Dr. Gallagher:** Keep in mind as well that the earlier the intervention, the less likelihood of the need for a repeat dose. If we can educate the patient to recognize and treat headaches at the moderate stage, he or she might need only one pill instead of two.

**Dr. Lake:** Beyond the pharmaceutical options, there may be some patients who require a multidisciplinary system of care. We are beginning to recognize this progression of cases in which the intractable patient contributes more than might be expected to the overall impact on productivity and healthcare costs. The multidisciplinary approach, including the psychological aspects, may very well fit within a new cost-justified disease management approach.

**Dr. Gallagher:** Many of us have mentioned the need for head-to-head studies. These studies are very costly and not above criticism in terms of design. An alternative to large, expensive, head-to-head trials is to use the "numbers needed to treat" approach, which essentially permits comparison of the package insert study data and other studies with data on the placebo controls.

**Dr. Mondell:** I believe it is dangerous to compare package inserts; it is like comparing apples and oranges, with different populations being treated.

**Dr. Gallagher:** Admittedly, it is not ideal. However, for managed care companies or physicians who need to compare drugs and lack the head-to-head data, it is valuable as a practical comparison.

**Dr. Schweitzer:** Even if we assume that we see differences in efficacy or safety between two treatment options,

will the ideal managed care protocol then mandate use of the most effective agent?

**Ms. Bowman:** New drugs come along every day. Isn't there a place for step therapy here?

**Dr. Ward:** Tailored therapy, rather than step therapy, is probably more cost effective for these migraine patients. Not every migraine patient has the same kind of attack each time, so you must tailor treatment to whatever is going on. If the attack is mild and the patient is not sick, maybe acetaminophen-aspirin-caffeine (Excedrin Migraine) would work. However, if the patient wakes up with the headache from hell and he or she is in the bathroom vomiting, then maybe the patient wants a sumatriptan injection or a nasal spray that contains sumatriptan or DHE. If you start with a "one-size-fits-all" protocol, many patients will be dissatisfied.

**Dr. Mondell:** But simple guidelines can work well. I am not suggesting that you should always start with drug X for a headache of Y intensity. The ideal guideline would generally include suggested classes, the timing of dosage, and the routes of administration. For example, if a patient has significant nausea and emesis, you would want to use the parenteral forms, such as nasal sprays. We are not talking about a complex algorithm.

**Dr. Parham:** When we apply a set of recommendations to local practices, we need things that are consistent and nationally recognized as being valid. The recommendations also need to be flexible enough to allow for repeated application during a patient's natural history and to permit the introduction of new therapies as they become available.

**Dr. Mondell:** Obviously, the recommendations need to be fluid. The point is that we need to start somewhere. We do not have such a set of recommendations now. We need to initiate a habit of consistent therapy so we can validate it and move on.

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