

## Etiology and Treatment Options for Migraine Management

*Based on a presentation by James U. Adelman, MD*

### **Presentation Summary**

The physician's first responsibility when a patient presents with headache is to distinguish between primary and secondary headache. This can be done mostly on the basis of historical information, physical examination, and neurologic examination; laboratory tests usually are not required. For physicians to diagnose headache correctly, patients need to provide a lot of information about the characteristics of their headaches and about their headache triggers (eg, food, fasting, alcohol, hormonal

changes, or increased sensory input). In addition, patients need to provide information about symptoms associated with their headaches and about treatment they have received in the past. Family history, sleep patterns, and emotional profiles are important as well. The triptans give rapid relief of headache, are generally well tolerated, and help the nausea and vomiting. However, sumatriptan is associated with a recurrence rate of 35% to 40%. Zolmitriptan gives physicians another treatment option.

**T**he treatment of headaches is absolutely wonderful right now," James U. Adelman, MD, President of the Adelman Headache Center, Greensboro, North Carolina, commented, "and it's getting better and better."

The key is education of both primary care physicians and neurologists about basic principles for good headache care, according to Dr. Adelman. He said primary care physicians usually have greater success in treating headache than specialists who practice at tertiary centers for headache treatment because the specialists get the most difficult cases. In addition, he estimated that primary care physicians should be able to

diagnose and treat the majority of headache patients.

### **Primary vs Secondary Headache**

The first responsibility a physician has to a new headache patient is to determine whether the patient has primary or secondary headache. Patients tend to be afraid that they have secondary-type headache—for example, secondary to brain tumor, aneurysm, meningitis, or sinus problems. The distinction between secondary headache and primary headache is made mostly on the basis of historical information, physical examination, and neurologic examination. Laboratory tests usually are not required. Normal results of cranial com-

puted axial tomography (CAT) or MRIs give both physicians and their patients confidence in the diagnosis of primary headache. A sedimentation rate for older people should be determined to rule out the presence of giant cell arteritis.

quite as good as treatment for migraine headache right now.

Cluster headaches are intense, squeezing headaches that last at a peak level for 30 to 60 minutes. They may occur up to eight times a day for 2 to 4 months. They occur mostly in men, according to Dr. Adelman. The ratio of men to women with cluster headache is 6 to 1. Patients with cluster headache are restless and unwilling to sit still, noted Dr. Adelman. The intense pain causes men who have cluster headaches to seek medical treatment.

**Table 1.** Cost of Migraine

<ul style="list-style-type: none"><li>■ 56% of migraineurs miss more than 2 days of work per month</li><li>■ 89% of migraineurs work at half production for 6 days per month</li><li>■ Estimated lost-labor costs of migraineurs per year: \$572 for men and \$300 for women</li></ul>
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Source: See reference 3

Migraine headache is more common in women than men; the ratio of female to male migraineurs is 3 to 1. Eleven million Americans have fairly severe migraine headaches.<sup>1</sup> However, most patients who have migraine are neither diagnosed nor treated; only 41% of women and 29% of men with migraine understand that they do in fact have migraine.<sup>2</sup> "So we have the opportunity to make significant impacts on the lives of 59% of the women and 71% of the men with migraine," noted Dr. Adelman, "and these impacts can be very cost effective and cost efficient."

His conclusion is clearly that, as Table 1 shows, the impact of migraine in the United States is great (Table 1).<sup>3</sup>

### Types of Primary Headache

There are three types of primary headaches:

- Tension-type headache
- Cluster headache
- Migraine headache

Tension-type headaches are the most common source of head pain. However, "we know a lot less about tension headaches than we know about migraine headaches," Dr. Adelman said. The first type of tension headache involves tightness of the muscles in the neck and shoulders, such as would result from driving a long distance or spending hours working at a computer. The second type does not involve an increase in muscle tension. It probably relates to "neurochemical changes within the brain and is probably part of the spectrum of migraine headache," Dr. Adelman added. Possibilities include changes in dopamine and serotonin levels and other chemical changes that decrease patients' pain threshold. He further noted that treatment of tension headache is not

### Diagnosis of Migraine

The diagnosis of migraine is basically historical and "not very difficult," according to Dr. Adelman. Patients provide information about the characteristics of their headaches and about their headache triggers. Information about triggers is very important, noted Dr. Adelman, because patients often "follow their triggers to identify the headaches." In other words, a patient with migraine triggered by pollution or allergies might follow those triggers to an ear-nose-throat specialist or allergist. A patient with hormonally triggered migraine (ie, headache occurring just before or during her menses) might follow the trigger to her gynecologist. A patient with visual disturbances associated with the headache might see

an ophthalmologist. The results may be ineffective treatment and "doctor shopping," both of which increase costs.

"At least in the practice we have, physical triggers are more important than the emotional stressors," Dr. Adelman said. He categorized the physical triggers into the following types:

- Increased sensory input (walking through the perfume area of a department store, light glaring off water and sand, a cold wind blowing on the face, or loud, disharmonious noises)
- Changes in circadian rhythms (going from one time zone to another, working split shifts, or working irregular hours)
- Environmental changes or changes in the weather
- Hormonal changes
- Any type of irritation around the head or neck (eg, ear infection, flare-up of temporomandibular joint syndrome, dental disease)
- Infection or irritation elsewhere in the body (eg, urinary tract infection)
- Dietary factors (eg, chocolate, cheese, nuts, pork, onions, alcohol)

"Migraine patients do best when their lives are regulated," Dr. Adelman said. When their rhythms of sleeping, eating, and working are disrupted, their headaches tend to occur, he noted.

In addition, patients need to provide information about symptoms associated with their headaches such as nausea, vomiting, photophobia, and phonophobia and about treatment they have received in the past. Family history, sleep patterns, and emotional profiles are important as well.

The age of patients is important as well. Although migraine headache can begin after the age of 40, "we're concerned about other causes and are less comfortable with headaches beginning at that age," Dr. Adelman said.

Some of the criteria created by the International Headache Society for migraine headache are summarized in Ta-

ble 2.<sup>4</sup> All pharmaceutical companies use these criteria in their studies of migraine medications. However, some patients with migraine may not fit these criteria exactly.

### Treatment of Migraine

"Communication between the doctor and the patient is absolutely essential," Dr. Adelman noted. The patient learns what headache triggers are and why lifestyle modifications (eg, sleep patterns, exercise) may be important.

Patient education is "without question cost effective," said Dr. Adelman. On the other hand, he believed that biofeedback and other behavioral therapies could be effective, he did not believe that they are usually cost effective as well.

"The goals of medicinal treatment are relatively simple," said Dr. Adelman. "One is to reduce the headache frequency and the second is to reduce the duration and severity of breakthrough headaches." The physician has to decide which to do first. For example, the physician treating a patient having four headaches a week should work on reducing the frequency of the headaches with preventive medication.

### Costly Mistakes

Costly mistakes that Dr. Adelman has seen in treatment of migraine are (1) failure to use preventive medications when the patient is having three or four

**Table 2.** International Headache Society Classification: Migraine Without Aura

Five or more attacks lasting 4 to 72 hours in conjunction with:	
Two of the Following	One of the Following
■ Unilateral	■ Nausea or vomiting
■ Pulsating	■ Photophobia and phonophobia
■ Moderate or severe intensity	
■ Aggravated by physical activity	

Source: See reference 4.

headaches a week, (2) failure to use preventive medications long enough, and (3) failure to identify and eliminate the things that are increasing patients' headaches. The last item is very important, according to Dr. Adelman.

#### Stepped vs Stratified Care

The stepped approach to care (ie, first-line treatment, second-line treatment, etc) will result in most patients not being satisfied, according to Dr. Adelman. Either the patients are going to lapse out of treatment, he noted, or they are going to increase the use of medication that isn't really effective. They may begin chasing their triggers and doctor shopping. They may develop "transformed" migraines—that is, migraines that progress from occurring a few times a month to occurring almost every day.

The stratified-care approach "plugs patients into the system depending on the degree and the intensity of their headache and other related symptoms," Dr. Adelman said. Patient education is part of that approach, as is selection of medication based on the patient's level of disability. Some severely impaired patients need treatment with a triptan; others with milder headaches may be able to use two ibuprofen tablets.

#### Preventive vs Acute Care Medication

Dr. Adelman noted that five criteria are used for selection of a preventive medicine: (1) efficacy, (2) side effects, (3) co-occurrence of disease or morbidity, (4) ease of administration, and (5) cost considerations, if all else is equal. Comorbidity has a great deal to do with how medications are selected at Dr. Adelman's clinic. For example, a patient with migraine, some depression anxiety, and problems sleeping will probably be started on amitriptyline. Dr. Adelman noted that good preventive medication can reduce the need for acute care medication, and vice versa.

The newer, acute care medications should decrease the need for migraine

preventive medications, said Dr. Adelman. He noted that 90% of migraine patients have migraine once a week or less, so that group should be treated only with acute care medicines, assuming that these medicines are effective. The remaining 10% should be treated with preventive medications.

"The triptans have been a huge breakthrough," Dr. Adelman said. They give rapid relief of headache, are generally well tolerated, and help the nausea and vomiting. However, sumatriptan (Imitrex) is associated with a recurrence rate of 35% to 40%.<sup>5</sup> Zolmitriptan (Zomig) gives physicians another treatment option.

#### Summary

"In headache treatment today," Dr. Adelman said, "we have a wonderful product, but frequently we don't sell it well, and that escalates the cost. If we sell it well, the patients are going to buy into it, and they're going to do what they need to do to make the lifestyle changes necessary to reduce their headache." These changes along with new pharmacologic agents can reduce headache frequency and stop migraine headaches quickly, Dr. Adelman said.

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#### ... DISCUSSION HIGHLIGHTS ...

*After Dr. Adelman had given his presentation, he answered questions from the symposium participants. Dr. Adelman presented a case study to demonstrate specifics relating to some of the principles that had been discussed during the day.*

**Dr. Adelman:** I thought we'd start this way because typically there is confusion about what we're talking about in stepped and staged care. So this is a patient who I saw recently—a typical patient that we see in our office. He's a 52-year-old male (a little atypical there), and he has asthma and five migraines per month. The headaches are left-sided and really fit the characteristics of

migraine. He calls the healthcare provider three times a year. He's never gone to the emergency room. He misses 1 day of work every 2 months. Let's take this in the traditional stepwise fashion.

What are we going to start with? We start with aspirin. Then we go to acetaminophen-aspirin-caffeine (Excedrin Migraine), naproxen sodium (Aleve), and isometheptene-dichloralphenazone-acetaminophen (Midrin); he might get butalbital-aspirin-caffeine (Fiorinal), and then he might get a triptan. This is a typical stepped-care approach.

Now let's talk about the staged care. If we're going to give this patient staged care, what are we going to start him with?

There are good data that nonsteroidal anti-inflammatory agents (NSAIDs) and metoclopramide or aspirin and metoclopramide or acetaminophen-aspirin-caffeine might reduce the intensity of these headaches by 50% or 60% or 70%. So let's say in staged care when he feels his headache coming on, he's taking one metoclopramide tablet at 9 cents and three naproxen sodium tablets for 27 cents. So for 40 cents, he has his four headaches a month still. He's then preventing half of the headaches from getting to the stage where a triptan is going to be needed. So when the other ones get bad enough, he uses the sumatriptan or the zolmitriptan. That's the second stage, so to speak. He starts out with the metoclopramide and the NSAID. The second stage is the triptan. In a stratified-care approach, his migraines were determined to be intense, and a triptan was used at this point.

We had a question before about whether we ever use butorphanol (Stadol). He uses butorphanol nasal spray if the sumatriptan doesn't work (in rare cases, this and other medications fail to provide headache relief) and to keep from going to the hospital.

**Question:** *Wouldn't you repeat sumatriptan at least one more time?*

**Dr. Adelman:** The data is that with sumatriptan, at least with the injection, if the first dose is not effective, the second dose probably will not be effective. So if we're talking about the 6-mg subcutaneous, I would not do that.

Now, let's talk about stratified care. With stratified care, what do we do?

**Reply:** Treat the headache.

**Dr. Adelman:** In this scenario we put in the sumatriptan 50 mg. We're not starting with 25 mg. We're starting with 50 or 100 mg. If he has nausea or vomiting with it, we use the subcutaneous preparation. In my mind, certainly, the stepwise approach should not be used.

*"There are good data that nonsteroidal anti-inflammatory agents (NSAIDs) and metoclopramide or aspirin and metoclopramide or acetaminophen-aspirin-caffeine might reduce the intensity of these headaches by 50% or 60% or 70%."*

— James U. Adelman, MD

**Comment:** At five headaches a month, I think there's a role for prophylaxis and I also think clearly there's a role for rescue therapy.

**Dr. Adelman:** At five a month, why is there a role for preventive medicines?

**Reply:** It's five a month times 24 hours; that's quite a few days out of my month that you're gone.

**Dr. Adelman:** We're assuming with the model that you have a good acute care medicine.

**Reply:** In this model, that's 60% effectiveness on the acute care.

**Dr. Adelman:** You're 60% effective in 2 hours.

**Reply:** Right, but only 60% effective.

**Comment:** I don't agree. I think they're going to have to treat the headache. Historically, we've treated trigger factors. We've done a number of things. But patients want relief. We treat the headache, and we have the abortive medications to do that. With a 60% response rate on five headaches a month, I have two headaches that are not responding. Now, if I could use something for prophylaxis against those two, then I've got the best of both worlds.

**Dr. Adelman:** The first thing I'm going to do in that patient with five headaches a month (and this is my opinion) is find out if there is a good acute care medicine. If there is, that's what I'm going to stick with. If there's not, you're 100% right. If I can't find an acute care medicine that stops that headache well within a couple of hours consistently, then I'm going to go to a preventive medicine.

**Comment:** For clarification of your discussion, when you talk about the 30% to 40% failure rate as far as aborting headaches, are those individuals who failed to respond ever or are those headaches that failed to respond to the medication? There's a very clear difference there. Long-term clinical trials demonstrate that if a triptan is found to be effective, the consistency of response will be greater than 80% in migraineurs.

**Question:** *Dr. Adelman, when do you use the sumatriptan nasal spray? How do your patients feel about it? Are they satisfied with it?*

**Dr. Adelman:** Yes. The nasal spray has a definite role in migraine treatment. Data show that it's intermediate in quickness of response—between the oral and the injection and intermediate as far as efficacy. My experience is that

many patients don't stay on it because of the taste. Many patients ask for it. I would say that of those who try it, less than a third of them remain on the medicine, preferring to return to an oral or subcutaneous medication for effectiveness and speed.

**Question:** *In the general population, what percentage of headaches are new migraines versus tension headaches?*

**Dr. Adelman:** Again, in my opinion, the majority are clearly tension-type headaches. We're talking about probably 20% to 30% being in the migraine category. We know a lot about migraine. We know a lot less about tension-type headaches, but they're probably within a spectrum where at one end you have the migraine with aura, then you have migraine without aura, and then you have mixed migraine-tension headaches. Many patients have both tension and migraine headaches as part of the spectrum.

**Comment:** Bad tension headaches are quite often categorized as a migraine, but everybody has this mental picture that if it's a mild headache, it's a tension headache, and if it's a severe headache, it's a migraine headache irrespective of symptoms.

**Comment:** Also, if there's an aura, it is considered a migraine, and if there's no aura, then you've got a little decision to make.

**Dr. Adelman:** Aura is in only 10% of the migraine patients. So you're already missing 90%. Other migraines are misdiagnosed because they are bilateral. Although 40% of migraines are bilateral, they are still undiagnosed.

**Question:** *Relative to all of the publicity that dihydroergotamine nasal spray got at the Super Bowl, were you bombarded with requests for it from your mi-*

*graineurs? I don't see much use of it in my health plan.*

**Dr. Adelman:** You don't see much use for it or you don't see it used much?

**Reply:** I don't see much of it being used.

**Dr. Adelman:** I believe that dihydroergotamine nasal spray does have an important role. Dihydroergotamine, remember, is a medicine we've used since the 1950s. I think it has a lot of advantages that the triptans may not have. One, we know that it can break the cycle of a chronic headache. Dihydroergotamine nasal spray may have a very important role in stopping the daily headaches and bringing patients back to an episodic headache. Two, because it's a less clean drug (in other words, it acts on more receptors), it may have more advantages in treating the generator of the headaches, perhaps by acting in different ways. It's a different drug.

The nasal spray may have a role with use a few times a day in certain patients to break cycles and to break prolonged headaches. The 24-hour data are far better than the sumatriptan data because the incidence of recurrence is much lower. So if you have a patient who has a menstrual migraine lasting for 3 or 4 days, dihydroergotamine nasal spray may be far preferable than short-acting triptans.

**Question:** *In a primary care setting a patient more often comes to you with a long-standing headache than with a new diagnosis. You almost never see a patient who has a headache for the first time. It's people who have had headaches for prolonged periods of time. Is there a place to use the triptans in the diagnosis of headache when you've got one of these gray zones—to do a therapeutic trial to see if that gets a response?*

**Dr. Adelman:** I don't think so. I think that the diagnosis is not very difficult. But I don't think that the medicines at

this stage can be used to diagnose disease. In fact, I've been involved in some litigation cases where sumatriptan has been used. The headache didn't quite fit, and they used sumatriptan. Those were cases where the patients had major complications because the drug was used diagnostically instead of in clear therapeutic ways.

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**Question:** *What's your experience from your practice or anecdotally of patients coming to you with a misdiagnosis—either migraineurs who have not been diagnosed or people without migraine who have been diagnosed as migraineurs?*

**Dr. Adelman:** The great majority of patients come to us and they say, doctor, I have hormonal headaches, I have sinus headaches, I have headaches from this or that. What we try to do is unify it for them and tell them, yes, we know that your allergies are triggering your headache. Yes, we know that the headaches come before your periods. The majority of the patients who come to us don't believe that they have migraine headaches, or they don't believe that all of their headaches are migraine. They don't understand the unifying principle.

They say I know I don't have migraines because my grandmother had migraine, and I remember she was in her bed with a cold rag on her head; and every time we spoke, she got upset with us and we had to stay out of the room.

That's what our population thinks a migraine headache has to be. What we're saying it does not have to be is unilateral, it does not have to be pulsating, it does not have to have an aura, it does not have to have vomiting; but it's still a migraine headache. That's the educational process that we're trying to promote so that people understand that there is treatment for these "other types" of headaches, which are migraine, no matter what the trigger.

**Question:** *In which patients in your practice does zolmitriptan offer a breakthrough?*

**Dr. Adelman:** One, the group of patients who haven't responded to the other medicines. In other words, you know that 30% of the people aren't going to respond to sumatriptan. So we have another option in those patients, which is very important. Two, the group of patients who don't tolerate the sumatriptan because of the side effects. Three, the group of patients in whom the headaches recur on sumatriptan or other medications.

**Question:** *Are you saying that you're using it as first-line therapy?*

**Dr. Adelman:** I'm saying in patients with severe migraine who are able to take an oral preparation who are having headaches once a week or less, zolmitriptan is a first-line drug, I'm not saying that I don't use other things. I certainly do use other medications. But in the scenario I just presented, zolmitriptan now is my first-line drug... by stratified care.

**Question:** *In patients who present with very severe headaches, once a week or less, you go right to zolmitriptan?*

**Dr. Adelman:** Yes, because their headache frequency is in the range where I'm

going to use acute care medicines. If the acute care medicines are effective, I'm not going to need to use preventive medicines. I am likely to get a good response initially without going through a bunch of other medicines before I get to this point.

**Question:** *If a patient comes in and says he or she is having a headache two or three times a week...*

**Dr. Adelman:** Two or three times a week is different from the scenario I used. I agree that preventive medicine should be used then. But if a patient is having four headaches a month, it depends on what I'm using for a preventive. Let's say I have a patient who has insomnia as well as migraine. I'm going to use amitriptyline early. Or if the patient has hypertension, it may be very appropriate to use one of the antihypertensive medicines.

**Comment:** The majority of patients are not coming in with headaches four times a month.

**Dr. Adelman:** But the data that I showed you is that 90% of the migraine population have one headache a week or less. So 90% of that group falls into the pattern where you should be using acute care medicines and not preventive medicines. In 10%, you could make the case for preventive medicines.

**Comment:** I'm getting a message here that you don't need to prevent [the migraine headache] if you're aborting with a triptan, and that's not what we see in practice. We're seeing both.

**Dr. Adelman:** I'm trying to individualize the use of the preventive medications depending on certain characteristics of the patient.

I think the problem is that most doctors don't use medications very well for migraine. Many patients we see are on a hodgepodge of medicines and the trip-

tans have not reduced use of other medications. One of the things that we try and do is to reduce the number of medicines, which are probably increasing the headaches rather than decreasing the headaches.

Many patients will have a feeling that they're going to have a headache. What I tell patients is that when you have this feeling, take 10 mg of metoclopramide (Reglan), which costs about nine cents a pill. It's a very inexpensive medication. Metoclopramide keeps the gut moving. During a migraine, there may be gastric stasis so the oral medicines aren't effective. If the patients take, let's say two or three naproxen sodium (Aleve) or ibuprofen (Advil) tablets with the metoclopramide, there's good evidence that that will adequately treat 60% or 70% of the migraines. Most of the time you're not going to get into an overuse situation when patients do that and then use, for example, zolmitriptan or sumatriptan when the more severe migraine develops. In addition, they're reducing the use of the triptans.

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