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MIGRAINE MANAGEMENT FAQs

**Practical advice from
physicians and allied
health professionals on
common issues arising
in the day-to-day
management of
migraine**

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When should your patients take their acute migraine medication? Is early treatment better?

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Acute migraine medications work best when given as soon as possible after the onset of headache. For methodologic reasons, researchers who conducted early clinical trials investigating acute migraine agents asked patients to wait until their pain was of moderate or severe intensity before taking the medication. When some patients deviated from the protocol and took the medication while their pain was still mild, they achieved much better results.¹

Many retrospective analyses and prospective trials have subsequently reported improved outcomes when triptans were used early to treat mild pain. For example, a post hoc analysis of an open-label trial identified a subgroup of 118 migraineurs who had each treated at least three mild and three moderate to severe attacks with almotriptan 12.5 mg during a 12-month study period; two-hour pain-free rates were 84% for the mild headaches and 53% for the moderate to severe

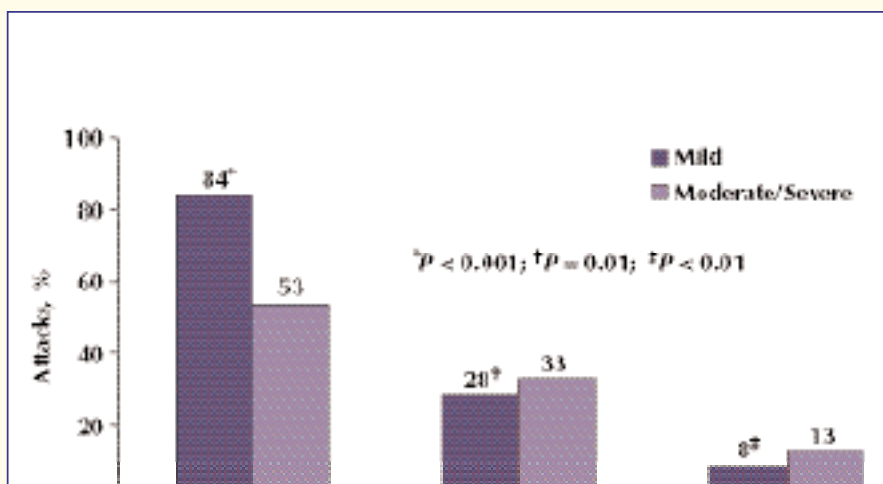
headaches, a significant difference ($P < 0.001$, Figure).²

The value of early treatment can be explained by some elegant research into the pathophysiology of migraine. Studies have shown that migraine initially develops as peripheral sensitization of the trigemino-vascular neurons, which manifests clinically as throbbing headache exacerbated by movement. This develops into central sensitization of the trigemino-vascular neurons, which manifests clinically as cutaneous allodynia (ie, exaggerated skin sensitivity).³ Allodynia develops in approximately 70% of migraine patients within 20 to 120 minutes of headache onset. Once allodynia has become established, migraines become more refractory to treatment.⁴ Therefore, by treating early, before the development of central sensitization, the effectiveness of acute migraine agents can be maximized.

There are some concerns, however, regarding early treatment. Clinicians must carefully monitor patients to guard against medication overuse, which can lead to medication overuse headache, and advise patients particularly to avoid using a triptan during prodrome or pre-aura/headache symptom that may suggest an impending migraine. Patients may be cautious about using up a limited supply of triptans, delaying treatment until they are sure

that they are experiencing a migraine and that the pain will be severe.⁵ However, most migraineurs are able to correctly predict their migraines based on premonitory symptoms,⁶ and it has been reported that the majority of migraines will progress to severe pain intensity.⁷ Another barrier to patients' treating early is concern about adverse events.^{5,8} However, the choice of a triptan with a low incidence of adverse events should alleviate this concern.

Figure



Two-hour pain-free rates, recurrence, and use of rescue medication for 118 migraineurs after treatment of at least three mild and three moderate to severe migraine attacks with almotriptan 12.5 mg in a 12-month open-label trial.

Data extracted from Pascual and Cabarrocas. *Headache*. 2002.²

After reviewing all of the evidence published to date, we recommend that patients treat their migraines early to achieve the best possible response, ideally while their pain is still mild.

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With seven triptans available, how do you select the appropriate agent for your migraine patients?

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Acute intervention strategies vary depending on the severity of the patient's headaches.¹ While mild, intermittent headaches may respond well to OTC medications and NSAIDs, triptans are recommended as first-line therapy for patients with moderate or severe headaches and for those whose headaches did not respond to nonspecific agents in the past.²

Once it has been determined that a patient is an appropriate candidate for a triptan, it is necessary to collect information on the patient and his or her particular migraine attack profile. It is a general rule of thumb that for the small percentage of patients whose migraine attacks reach peak intensity very quickly or are associated with severe gastrointestinal symptoms (nausea and vomiting), non-oral formulations may be necessary (ie, subcutaneous injection, nasal spray). For the more prevalent daytime attacks of moderate to severe pain intensity, it has been shown that approximately 70% will be relieved after oral administration of one of the triptans³—

the method of administration preferred by most patients.⁴ Migraines that develop gradually (over two to four hours) may be treated with one of the slower-acting triptans such as frovatriptan or naratriptan, which have also been successful as prophylaxis for menstrual migraine.

As all of the triptans have been shown to be safe and effective for the acute treatment of migraine, successful management should focus on the following desired outcomes of treatment: 1) patient should become pain free within two hours of using a triptan; 2) once a triptan is used, the headache should

Table. Comparison of Other Oral Triptans With Sumatriptan 100 mg

	2-Hour pain relief	Sustained pain free	Consistency of effect	Tolerability
Almotriptan 12.5 mg	=	+	+	++
Rizatriptan 10 mg	+	+	+(+)*	=
Eletriptan 40 mg	=/+	=/+	=	=
Eletriptan 80 mg [†]	+(+)	+	=	-
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Rizatriptan 5 mg	=	=	=	=
Sumatriptan 50 mg	=	=	=/-	=
Naratriptan 2.5 mg	-	-	-	++
Sumatriptan 25 mg	-	=/-	-	+
Eletriptan 20 mg	-	-	-	=

-, inferior; =/+, possibly inferior; =, no difference; +, better; +(+)*, possibly much better; ++, much better compared with sumatriptan 100 mg.

*The unusual design of the rizatriptan study makes it difficult to compare the consistency of effect with those of the other agents.

[†]Not an approved single dosage in the United States.

Reprinted from *The Lancet*, 358, Ferrari et al, Oral triptans (serotonin 5-HT_{1B/1D}) agonists in migraine management treatment, 1668-1675.³ Copyright © 2001, with permission from Elsevier.

not recur within 24 hours; 3) the triptan should be well tolerated and have minimal adverse effects; 4) while becoming pain free within two hours of triptan use is important, returning to full function is also desirable.

Because migraineurs differ in their needs, preferences, characteristics, and response to treatment, clinicians should be familiar with more than one triptan so that if one agent does not provide satisfactory results the patient can be switched to another. Results of a recent meta-analysis (24,089 patients enrolled in 53 clinical trials of oral triptans) have shown that while oral sumatriptan is currently the most commonly prescribed triptan, having been available for

the longest period of time, newer, second-generation triptans also should be considered, as there are subtle differences in efficacy, consistency, and tolerability among triptans that may be clinically relevant for individual patients (Table).⁵

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What do you recommend to a patient taking analgesics for headache on a daily basis?

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Daily use of analgesics is a serious issue which must be addressed. Individuals with headache often don't realize that overuse of analgesics can lead to rebound headache, also known as medication overuse headache (MOH), a growing worldwide problem. Epidemiologic data suggest that up to 4% of the general population overuse analgesics and other agents for the treatment of pain conditions such as migraine. Approximately 1% of the population in North America, Europe, and Asia have MOH, making it the third most frequent form of headache after tension-type and migraine.^{1,2}

The new International Headache Society classification system defines MOH as headache present on more than 15 days per month, markedly increasing in frequency during the use of pain medicine and resolving or reverting to its original pattern within two months after discontinuation of the pain medication (Table).³ The diagnostic criteria are broken down by the type of pain medication being overused, requiring intake on

10 days per month for more than three months for ergots, triptans, opioids, and combination medications and on 15 days per month for more than three months for simple analgesics.³

As some patients do not consult with a health care provider until their pain becomes unbearable and they are already overusing analgesics, they may already have MOH. The treatment of choice for MOH is abrupt and complete withdrawal from the pain medication being overused.^{4,5} Withdrawal can be achieved on an outpatient basis for patients who are highly motivated and self disciplined and who are not experiencing depression or anxiety; who are overusing single-agent therapies but not barbiturates, opioids, or tranquilizers; and who show no other signs or side effects of medication overuse.¹ Withdrawal symptoms, including withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness, can last from two to 10 days. Patients with tension-type headache and those overusing analgesics experience stronger withdrawal symptoms and a higher relapse rate.

Relapse rates one year after withdrawal were 73% in patients with tension-type headache and 22% in patients with migraine.⁶ One-year relapse rate after withdrawal from analgesics was 58%, compared with 20% with ergots and 19% with triptans. A similar trend

Table. Diagnostic Criteria of Medication Overuse Headache

Ergotamine 8.2.1	Triptan 8.2.2	Analgesic 8.2.3	Opioid 8.2.4	Combination 8.2.5
Headache present on > 15 days/month fulfilling criteria C and D and ≥ 1 of the characteristics in A				
A. Bilateral Pressing/tightening Mild/mod intensity	Mainly unilateral Pulsating Mod/severe intensity Aggravated by routine activity Nausea and/or vomiting or photo-/phonophobia	Bilateral Pressing/tightening Mild/mod intensity		Bilateral Pressing/tightening Mild/mod intensity
B. ≥ 10 d/mo on regular basis for ≥ 3 mos	≥ 10 d/mo on regular basis for ≥ 3 mos	≥ 15 d/mo for > 3 mos	≥ 10 d/mo for > 3 mos	≥ 10 d/mo for > 3 mos
C. Headache developed/ markedly worsened during overuse	Headache frequency markedly increased during overuse	Headache developed/ markedly worsened during overuse		
D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation				
Data extracted from Olesen et al. <i>Cephalalgia</i> . 2004. ³				

is to prevent its development in the first place. Headache patients must be informed of the risks of medication overuse and be provided with the most effective and specific pain medications available. Patients should also be instructed on the appropriate use of their acute medications and be followed closely to ensure that these agents are working, as efficacy failures may lead to chronic overuse. Open communication between patient and caregiver and careful patient monitoring should decrease the risk of medication overuse.

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was seen in four-year relapse rates: 91% for tension-type headache versus 32% for migraine, and 71% for analgesics versus 21% for triptans.⁷

The best strategy for reducing the prevalence of MOH

studies, initial relief of mild pain and recurrence of moderate pain was sufficient. Some trials allowed the use of rescue medications with or without the requirement to report them. The recurrence window has been defined as from two to 24 hours postdose or from four to 24 hours or up to 48 or 72 hours. Finally, recurrence rates have been presented as a percentage of all patients (including nonresponders), rather than as a percentage of responders only.

Can you compare headache recurrence rates among agents that achieve different initial response rates?

Jeffrey R. Unger, MD, and Patricia Stanley, NP

Headache recurrence (or relapse) is a limitation of all acute migraine medications and is often given as a reason for stopping a drug. Definitions of recurrence have varied in the literature, making interpretation difficult.¹ In some studies, patients must have achieved pain-free status initially and subsequently experienced recurrence of at least mild pain; in other

Recurrence appears to be consistent for individual patients using a particular drug; patients who have recurrence of the first attack treated with a drug are likely to experience recurrence of all attacks treated with the

same drug.¹ However, headache recurrence is not necessarily consistent across drugs.

Headache recurrence rates cannot be compared easily across drugs, even within the same trial, because of differences in initial response rates and use of rescue medication. Even in a crossover trial, the attacks that respond to treatment by the different drugs will have different profiles, making them unable to be compared. When evaluating two drugs, the more effective agent will result in a higher initial response rate by relieving attacks (more severe, longer duration) that would not have responded to the less effective drug. Such headaches are more difficult to treat and may be more susceptible to headache recurrence. Indeed, a study exploring the risk factors for headache recurrence after

sumatriptan use reported that recurrence was more frequent in patients who had migraine attacks associated with severe symptoms and a longer untreated attack duration.²

Using published rates of two-hour pain relief and recurrence at two to 24 hours, a simple calculation shows that triptans with lower recurrence rates result in the fewest patients with pain relief at 24 hours by virtue of their lower initial (two-hour) pain-relief rates (Table).

Therefore, it is now being recommended that sustained pain free be used as the endpoint to evaluate acute migraine therapy. Sustained pain free is a composite measure defined as the proportion of patients who are pain free by two hours postdose who do not experience a recurrence of moderate or severe headache and who

do not use any rescue medication two to 24 hours postdose.^{3,4} Although this endpoint is difficult to achieve (rates range from 10.6% for eletriptan 20 mg to 25.9% for almotriptan 12.5 mg),³ it captures the features patients say they want from an acute migraine therapy.

Table. Calculation of 24-Hour Pain Relief From Two-Hour Pain Relief and Recurrence

	2-Hour pain relief, %*	Recurrence 2-24 hour, %*	24-Hour pain relief, %†
Frovatriptan 2.5 mg	42	17 [‡]	35
Naratriptan 2.5 mg	49	21	39
Sumatriptan 100 mg	59	30	41
Zolmitriptan 5.0 mg	66	34	44
Rizatriptan 10 mg	69	37	44
Almotriptan 12.5 mg	61	26	45
Eletriptan 40 mg	60	21	47

*Data extracted from Silberstein SD. Migraine. *Lancet*. 2004;363:381-391.

†Calculated as follows: [(100–recurrence rate)/100] x 2-hour pain relief rate.

‡Data extracted from Goldstein J. Frovatriptan: a review. *Expert Opin Pharmacother*. 2003;4:83-93.

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Do all acute migraine agents have similar tolerability profiles?

Timothy R. Smith, MD, RPh, FACP, and Jill Stoneman, FNP

While ergot alkaloids had been commonly used for the acute treatment of migraine, these agents were associated with consistently higher rates of adverse events, especially nausea and vomiting, compared with placebo, sumatriptan, and other acute agents.¹ Triptans are now recommended as first-line agents for the acute treatment of migraine in patients with moderate or severe headache and in individuals with

headache of any severity for whom nonspecific medications are found to be ineffective.²

It is important to distinguish between safety and tolerability. All triptans are safe medications provided they are not used in patients with contraindications or major risk factors, and no one triptan is demonstrably safer than the others.³

Despite being contraindicated for patients with cardiovascular disease, recent reports have concluded that the incidence of triptan-associated serious cardiovascular adverse events is extremely low⁴⁻⁷ and the cardiovascular risk–benefit profile of triptans favors their use

Table. Placebo-Subtracted Adverse Events

	Number of patients	Any, % (95% CI)	CNS, % (95% CI)	Chest, % (95% CI)
Zolmitriptan 5 mg	2005	24.5 (15.5; 33.5)	11.5 (6.1; 16.8)	2.9 (1.2; 4.6)
Eletriptan 80 mg	1393	18.9 (11.2; 26.6)	14.6 (10.2; 19.0)	2.6 (0.6; 4.5)
Zolmitriptan 2.5 mg	2392	15.9 (9.6; 22.1)	9.9 (4.3; 15.5)	2.0 (0.7; 3.3)
Rizatriptan 10 mg	2783	13.5 (10.6; 16.3)	9.4 (7.2; 11.6)	1.5 (0.8; 2.3)
Sumatriptan 100 mg	3407	13.2 (8.6; 17.8)	6.3 (3.2; 9.5)	1.7 (0.8; 2.5)
Rizatriptan 5 mg	1963	7.9 (4.7; 11.1)	6.1 (3.2; 9.0)	0.9 (−0.04; 1.8)
Sumatriptan 50 mg	2528	7.8 (2.6; 13.1)	3.7 (1.0; 6.4)	1.9 (0.4; 3.3)
Eletriptan 40 mg	1870	7.3 (2.7; 11.8)	7.5 (4.5; 10.6)	0.9 (−0.2; 2.0)
Sumatriptan 25 mg	1462	4.4 (0.1; 8.8)	1.7 (−1.2; 4.7)	0.8 (−1.0; 2.6)
Naratriptan 2.5 mg	1211	2.4 (−2.2; 7.0)	1.9 (−1.2; 5.0)	0.4 (−0.8; 1.6)
Eletriptan 20 mg	499	1.9 (−15.5; 19.3)	2.6 (−6.6; 11.7)	−0.3 (−3.3; 2.6)
Almotriptan 12.5 mg	719	1.8 (−2.7; 6.2)	−1.5 (−3.9; 1.0)	−0.4 (−1.6; 0.8)

CI, confidence interval; CNS, central nervous system.

Data extracted from Ferrari et al. *Cephalgia*. 2002.³

in the absence of contraindications.^{4,8}

Perhaps because of their different pharmacokinetics, the triptans are associated with varying degrees of tolerability. This is an important factor considering that 71% of migraineurs reported in a recent survey that they delayed or avoided taking their medication due to concerns about side effects.⁹ A recent review of triptan formulations concluded that almotriptan, frovatriptan, and naratriptan may be good choices for patients with a history of susceptibility to adverse events.¹⁰ A meta-analysis of oral triptans reported a mean placebo-subtracted rate of any adverse events of 13.2% (95% confidence intervals: 8.6, 17.8) for sumatriptan 100 mg (Table) and ascribed superiority and inferiority to other agents when their 95% confidence intervals did not overlap those of sumatriptan 100 mg.³ Sumatriptan was chosen as the comparator because it has been available for the longest period of time and therefore has the largest database of all the triptans. Only almotriptan 12.5 mg and naratriptan 2.5 mg had significantly lower adverse event rates, which were also not different from placebo.

Chest symptoms, characterized by pressure or discomfort in the chest, shortness of breath, or palpitations, are generally not serious and not explained by ischemia⁴ but are of particular concern to patients and

clinicians because they mimic acute angina pectoris or myocardial infarction. Chest symptoms were reported by around 20% of patients with migraine treated with triptans;¹¹ almotriptan, however, was associated with an incidence of chest symptoms in less than 1%.¹² In the meta-analysis, only almotriptan 12.5 mg

had a significantly lower rate of chest adverse events than did sumatriptan 100 mg (Table).³ It has been suggested that the low incidence of chest adverse events associated with almotriptan is due to its lower intrinsic activity on pulmonary arteries and veins, compared with other triptans.¹³

With regard to central nervous system (CNS) adverse events, the meta-analysis showed most triptans to have rates similar to that of sumatriptan 100 mg, except for eletriptan 80 mg, which had significantly higher rates and almotriptan 12.5 mg, which had significantly lower rates (Table).³ Almotriptan's low rate of CNS adverse events may result from the absence of an active metabolite and its low lipophilicity (used to predict a compound's ability to penetrate the blood-brain barrier).^{14,15}

Since the acute treatment paradigm is moving towards treating early and patients tend to delay treatment because of concern about side effects, effective acute agents with excellent tolerability profiles should be our treatments of choice.

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How do you manage a patient complaining of sinus headache?

Arthur H. Elkind, MD, and Barbara Parrilli, RN, MS

Sinus headache is a common but nonspecific diagnosis given to headaches associated with facial pain and pressure. While it is often incorrectly self-diagnosed by patients,¹ headache specialists consider sinus headache to be relatively rare, even in the presence of noninfectious sinus inflammation.²

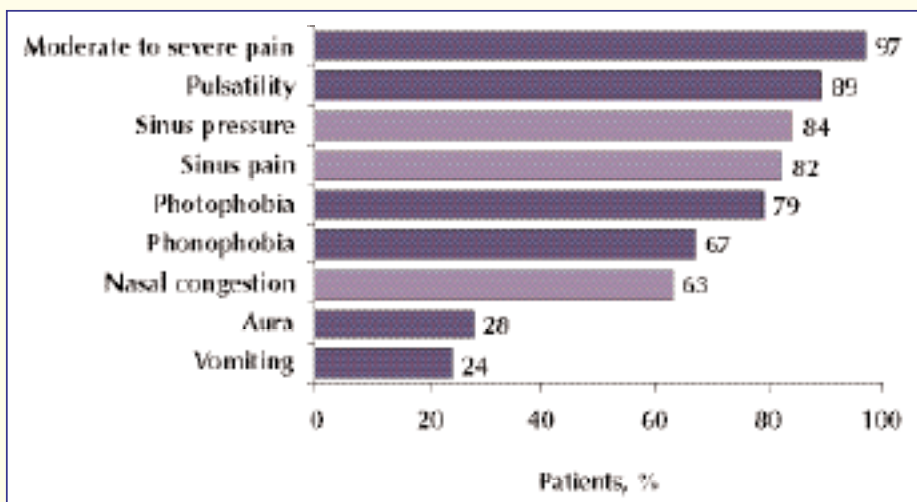
When 47 subjects with self-diagnosed sinus headache underwent a complete medical and neurologic evaluation, 90% were found to have headaches that fulfilled the International Headache Society (IHS)

criteria for migraine; subsequent treatment with a migraine-specific medication resulted in a significant response.² A larger trial enrolled patients (N = 2,991) with self-described or clinician-diagnosed sinus headache who reported an average of three headaches per month.³ Although a large proportion of the patients reported sinus symptoms such as sinus pressure (84%), sinus pain (82%), or nasal congestion (63%), large proportions also reported IHS migraine symptoms, such as moderate to severe pain (97%), pulsatility (89%), photophobia (79%), and phonophobia (67%); 28% reported aura and 24% reported vomiting (Figure). An IHS diagnosis of migraine with or without aura was applied to 80% of the patients, with an additional 8% meeting IHS

criteria for probable migraine. These studies revealed that most individuals who believe, either because of self- or clinician-diagnosis, that they have sinus headaches actually have headaches that fulfill IHS criteria for migraine or probable migraine.

The American Academy of Otolaryngology-Head and Neck Surgery⁴ and IHS⁵ diagnostic systems describe useful signs and symptoms to help differentiate rhinogenic headache from

Figure



Typical sinus symptoms (light bars) and International Headache Society migraine symptoms (dark bars) reported by patients with self-described or clinician-diagnosed sinus headache.

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migraine (Table): the characteristics of the patient's head or facial pain and pressure; its location, severity, frequency, and duration; any association with nausea, vomiting, or photophobia; the presence or absence of nasal symptoms (especially purulent dis-

Patients with noninfectious rhinogenic symptoms with headache as a minor complaint should be given nasal steroids, systemic decongestants, and/or selective antihistamines. Antibiotics are useful for patients with infectious sinusitis manifested by symptoms of discol-

ored nasal drainage, nasal obstruction, facial pressure, and opacification of sinuses or mucosal thickening on CT scans. Patients with headaches secondary to or triggered by structural rhinogenic causes should be referred for otolaryngologic or allergy evaluation as surgical approaches (eg, septoplasty, resection of the concha bullosa) may be needed.

It should be stressed that the vast majority of patients presenting with self-diagnosed sinus headache—or one that was misdiagnosed by a health care provider—probably have migraine. For decades, headache specialists have advised patients of migraine masquerading as sinus headache and the recent studies elegantly substantiate this fact.

While nonspecific medications may be helpful for some patients,

most patients who present with problematic recurrent headaches are likely to have already tried several OTC analgesics. We therefore recommend a trial of migraine-specific medication, a triptan, and an appointment for a follow-up evaluation.

Table. Diagnostic Criteria for Rhinosinusitis

American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) criteria ⁴		International Headache Society (IHS) diagnostic criteria for headache attributed to rhinosinusitis ⁵
A diagnosis of rhinosinusitis requires at least two major factors or at least one major and two minor factors:		<p>A. Frontal headache accompanied by pain in one or more regions of the face, ears, or teeth and fulfilling criteria C and D</p> <p>B. Clinical, nasal endoscopic, CT and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis (may include purulence in the nasal cavity, nasal obstruction, hyposmia, anosmia, and/or fever)</p> <p>C. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis</p> <p>D. Headache and/or facial pain resolve within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis</p>
Major factors	Minor factors	
Purulence in nasal cavity	Headache	
Facial pain/pressure/congestion/fullness	Fever (all non-acute)	
Nasal obstruction/blockage/discharge/purulence	Halitosis	
Fever (acute rhinosinusitis only)	Fatigue	
Hyposmia/anosmia	Dental pain	
	Cough	
	Ear pain/fullness	

Sources: Lanza and Kennedy. *Otolaryngol Head Neck Surg.* 1997⁴ and Headache Classification Subcommittee of the International Headache Society. *Cephalalgia.* 2004.⁵

charge); and the temporal relationship between the headache and nasal symptoms. Diagnostic nasal endoscopy and CT imaging may be required in certain patients to confirm rhinosinusitis or reveal anatomic abnormalities.

Some tips for differential diagnosis are: 1) a stable pattern of recurrent headaches, with headache as the presenting complaint, which alter daily function is most likely migraine; 2) recurrent, self-limited headaches that are associated with rhinogenic symptoms are most likely migraines; 3) patients with evidence of infection or prominent rhinogenic symptoms with headache as one of several complaints should be evaluated carefully for ENT pathology; and 4) headache with associated fever and purulent nasal discharge is likely rhinogenic in origin.⁶

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What do you do if the oral triptan you prescribed for your migraine patient is not effective?

Timothy R. Smith, MD, RPH, FACP, and Jill Stoneman, FNP

Failure to respond to one triptan is not predictive of failure with other triptans. Just as migraine headaches have different qualities, individuals who experience migraines have different characteristics and respond differently to treatment. Also, a patient might experience adverse events with one triptan, but not with a different one. In addition, although surveys show that migraineurs consider complete and consistent pain relief, absence of recurrence, rapid onset of action, and absence of side effects to be the most important attributes of acute migraine agents,¹ individual needs and preferences vary. Matching the individual migraineur with the right triptan might involve a degree of trial and error. While it is impractical to expect clinicians to be aware of the subtle differences among seven triptans,

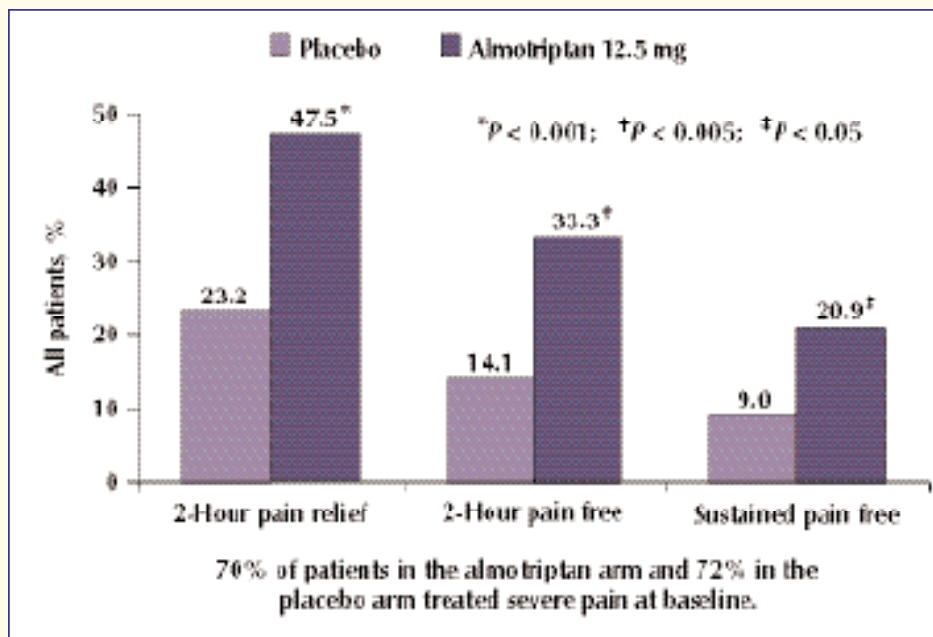
it is worthwhile to be familiar with two or three of them. A large meta-analysis of oral triptans reported that there are differences in the efficacy, consistency, and tolerability of the triptans that can be clinically important for individual patients;² these differences may be a result of the diverse pharmacokinetics exhibited by the various agents. The authors of the meta-analysis conclude that at approved dosages, almotriptan 12.5 mg and rizatriptan 10 mg offer the highest likelihood of consistent success.

Individual response to a particular triptan is likely to be consistent across attacks; if two attacks respond to a particular triptan, the third is also likely to respond.³ Conversely, if two attacks do not respond, it is unlikely that the third attack will respond and a different triptan should be tried. For example, a recent clinical trial enrolled patients with a history of two previous poor responses to sumatriptan.⁴ As expected, after treatment of a subsequent attack with sumatriptan, 73% did not achieve pain relief at two hours. These nonresponders

were then randomized to treat their next attack with almotriptan 12.5 mg and 48% achieved pain relief at two hours—significantly better than placebo. Pain-free and sustained pain-free rates with almotriptan 12.5 mg were also significantly better than placebo (Figure).

Since lack of response to one triptan does not predict likelihood of response to another, we recommend that patients who do not respond to or are dissatisfied with a particular triptan be switched to another agent in this class. To minimize the chances of a second triptan failure

Figure



Efficacy of almotriptan versus placebo in nonresponders to sumatriptan. Sustained pain free is defined as pain free at two hours after taking medication with no recurrence of moderate or severe headache and no rescue headache medication two to 24 hours postdose.

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that might cause such patients to discontinue treatment, clinicians should select the agent most likely to achieve an effective and well-tolerated response.

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How can we increase migraine patients' satisfaction with their acute therapy?

Arthur H. Elkind, MD, and Barbara Parrilli, RN, MS

Studies have shown that migraine is both underdiagnosed and undertreated. One survey revealed that only 69% of migraineurs had ever consulted with a clinician regarding their migraine (48% were still consulting and 21% had lapsed from care) while 31% had never consulted.¹ Fifty-two percent of migraineurs were using only OTC medications to treat their migraines while 21% used both OTC and prescription medications. The underuse of migraine-specific agents like triptans persists despite the recommendation of the American

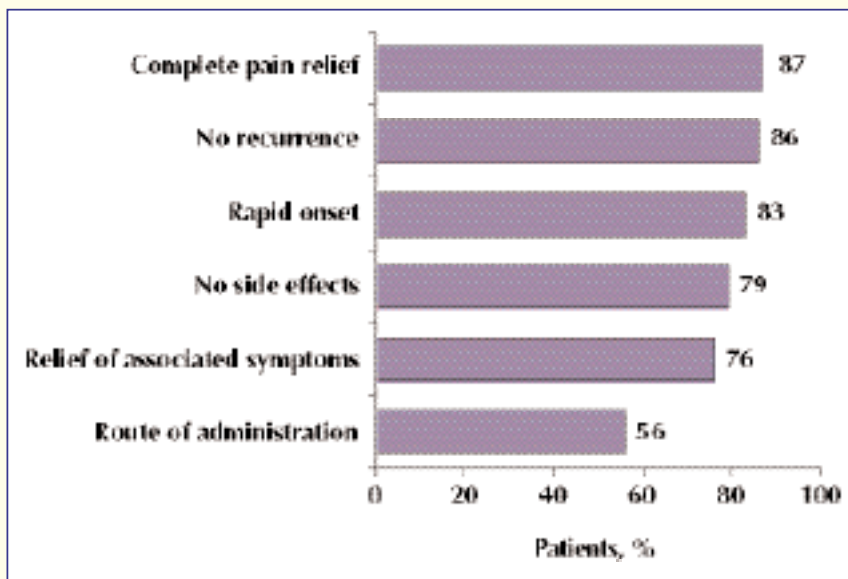
Academy of Neurology that they be used as first-line agents for moderate to severe migraine headaches or for headaches of any severity when nonspecific medications did not provide adequate relief in the past.²

Part of the reason for migraineurs' dissatisfaction with their acute therapy may be a result of their underuse of triptans. The stratified-care approach to treatment (using the patient's burden of disease to determine the initial treatment for an attack) provided significantly greater headache response at two hours and significantly less disability time compared with the stepped-care approach (same initial therapy for all patients).³ Furthermore, most patients seeking medical care for their migraine will have already tried one or more OTC agents for relief. We therefore recom-

mend the stratified-care approach and suggest that patients with more severe headaches and more disabling headaches be started on triptans rather than face a failed trial of a nonspecific pain medication.

To increase migraine patients' satisfaction with their therapy, it is important to give them what they want. The properties of acute migraine agents that migraineurs consider important or very important are complete pain relief, no recurrence, rapid onset, and no side effects (Figure).⁴ The endpoint typically used to compare acute agents, two-hour pain relief, and even two-

Figure



Percent of migraineurs reporting variable as important or very important.

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hour pain free, do not capture all of these desired features. Therefore, composite endpoints such as sustained pain free (pain free at two hours postdose with no recurrence of headache and no use of rescue medication from two to 24 hours postdose) and sustained pain free with no adverse events should be used to select an agent more likely to offer patient satisfaction.

For patients who are dissatisfied with their current acute therapy, switching to an alternate triptan has been shown to be a successful treatment strategy, as failure to respond to one triptan does not predict failure to respond to all agents in the class.⁵ An additional way to increase patient satisfaction is to treat migraines early, while the pain is still mild. Early intervention has been shown to result in higher pain-free rates, lower recurrence rates, and less need for rescue therapy.⁶

Overall, the best way to maximize patient satisfac-

tion is to improve patient–clinician communication. Caregivers need to develop a partnership with their patients to understand their needs and manage their expectations. By working together on a treatment plan, accuracy, efficiency, and supportiveness will be enhanced, health outcomes will be improved, and patient satisfaction will be maximized.

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What are the attributes of an ideal triptan?

Jeffrey R. Unger, MD, and Patricia Stanley, NP

The ideal triptan would be administered orally and would work quickly and completely with no headache recurrence and no side effects. The drug could be taken by all patients and have no contraindications or drug interactions. The ideal triptan would also relieve all migraine-associated symptoms and return the patient to full functioning quickly without risk for dependency or addiction. Although no such medication exists, highly effective acute migraine therapies are available for most patients.

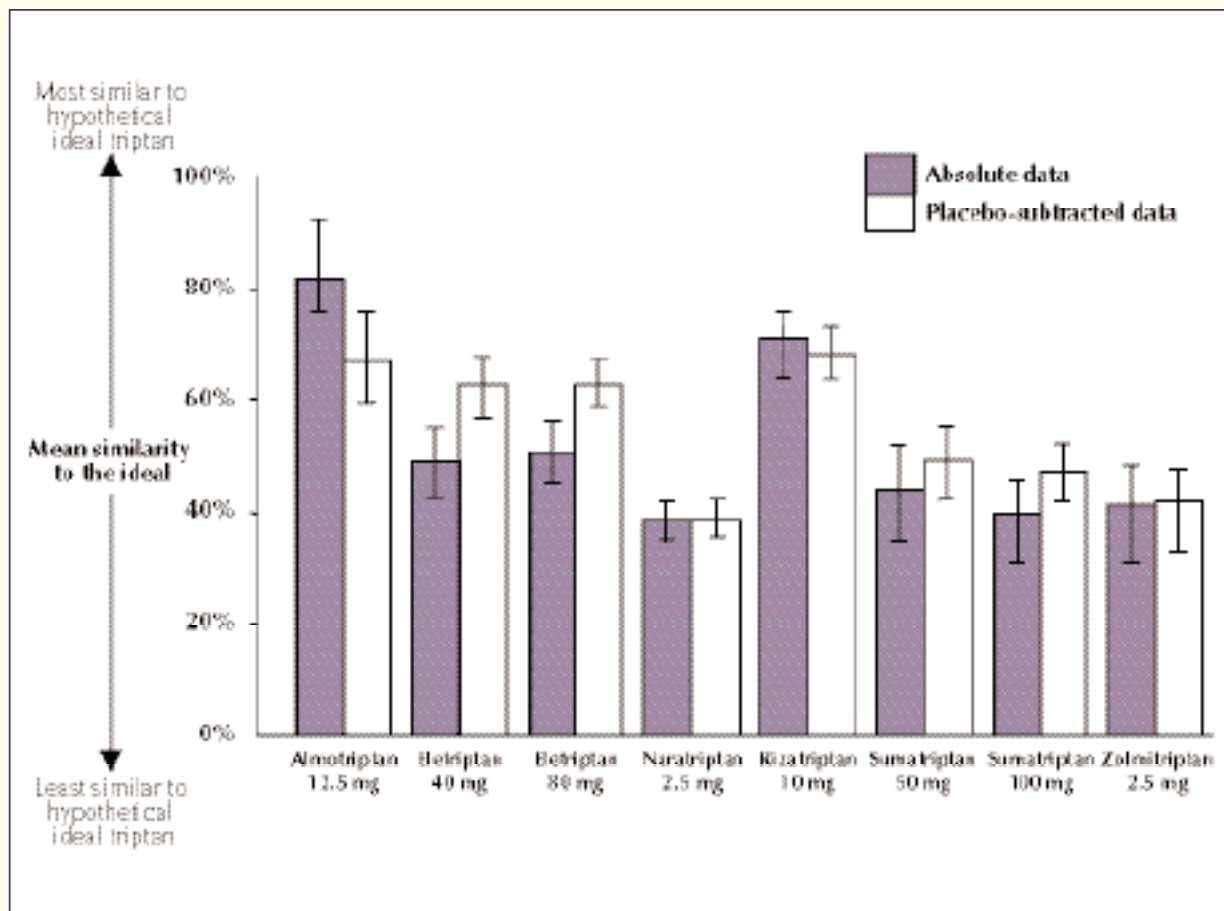
Despite the availability of effective antimigraine agents, however, a survey of migraineurs showed that only 29% were very satisfied with their usual acute treatment for migraine.¹ This survey and others indicated that migraineurs consider complete pain relief, no recurrence, rapid onset, and no side effects to be the most important attributes of acute treatment.¹⁻³ The most common reasons given for dissatisfaction with therapy were delayed pain relief, incomplete relief, inconsistent relief, headache recurrence, and too many

adverse effects. Retrospective analyses of clinical trial data corroborate these surveys, showing that fast and complete pain relief predicts patient satisfaction and health-related quality of life.⁴⁻⁶

The importance of tolerability was shown in a survey in which more than two thirds of migraine patients reported avoiding or delaying taking their migraine medication because of concern over adverse events.⁷ A recent preference study reported that close to 80% of patients preferred a slower drug with fewer adverse effects or a slower drug with a longer duration of action compared with a drug that works faster but has more adverse effects or shorter duration.⁸

When neurologists and primary care physicians were asked to weigh the relative importance of specific attributes of triptan treatment, they ranked efficacy as more important than tolerability or consistency. With regard to efficacy, they ranked sustained pain free as more important than one-hour or two-hour pain free.^{9,10} A multiattribute decision model was used to combine all possible combinations of the relative importance of these treatment attributes with the actual performance of the triptans in clinical trials. The model found that when all logically possible combina-

Figure



Similarity to the ideal triptan, averaged across all possible orderings of relative importance of outcome measures considered.

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tions of relative importance of the treatment attributes were considered, almotriptan and rizatriptan were more similar to a hypothetical ideal triptan; these were followed by eletriptan and sumatriptan, with zolmitriptan and naratriptan having the least similarity to the hypothetical ideal triptan (Figure).¹¹

Randomized, placebo-controlled clinical trial data can describe the likelihood of response and side effects for populations of patients and give clinicians a rough guide to treatment selection; in most patients, however, trial and error may be required to determine the safest and most efficacious way to acutely treat migraine.

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When do you recommend migraine prevention?

Frederick G. Freitag, DO, and Gayle Blake, PA-C

Frederick G. Freitag, DO, is Associate Director of the Diamond Headache Clinic in Chicago. Gayle Blake, PA-C, works at the Diamond Headache Clinic.

The goals of migraine prevention are to reduce the frequency, duration, and severity of migraine attacks, to improve responsiveness to acute medications, and to improve patients' ability to function.¹ Traditionally, preventive agents were used only for patients with migraine conditions in which certain acute agents are contraindicated (eg, hemiplegic migraine, basilar migraine, migraine with prolonged aura) or for patients with frequent migraines (more than two days per week). However, a clinician's decision to initiate prevention should not be based solely on headache frequency. Preventive therapy also should be recommended when patients are experiencing a pattern of increasing attacks over

time or recurring migraines that, despite the use of acute medications, are interfering with their daily lives. This might be just two or more attacks per month with disability lasting three or more days or less frequent headaches that are associated with severe disability. Prevention should also be used for patients who are not satisfied with their acute therapy because of insufficient efficacy, troublesome adverse events, or financial burden. If patients are overusing their acute medications, whether nonprescription or prescription, and are thus at risk for developing medication overuse headache, prevention should be recommended. Finally, the patient's preferences, expectations, needs, and goals should be considered. Patients should be offered preventive treatment if their lifestyle demands fewer and less severe attacks.

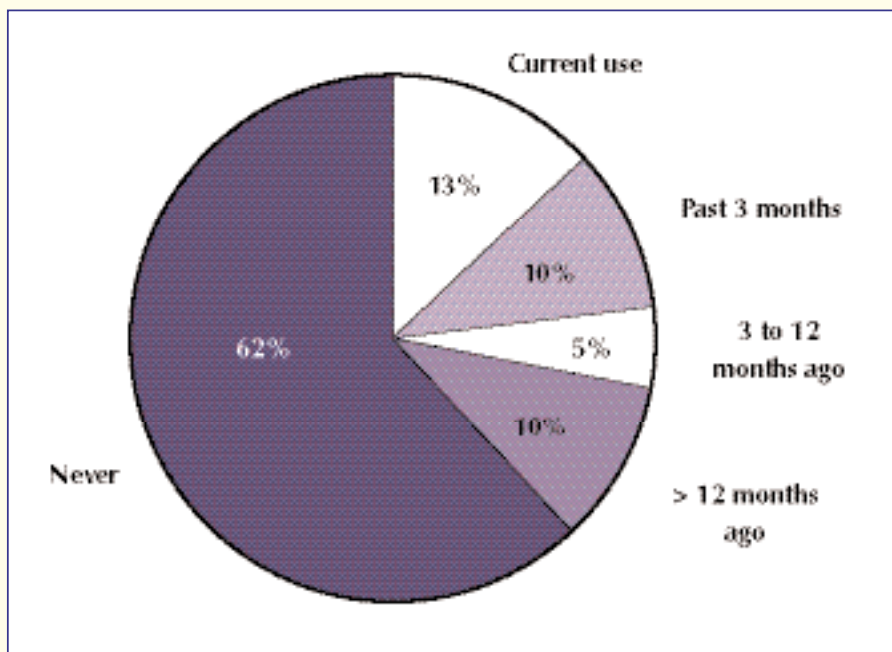
The American Migraine Study II, conducted in 1999, revealed that while 25% of migraineurs surveyed experienced one or more migraines per week and 53% reported severe impairment of activities or required bed

rest, only 5% were using preventive medication.^{2,3}

The more recent American Migraine Prevalence and Prevention Study showed that there has been some improvement, with 13% of migraineurs reporting current use of migraine preventives; 62% had never used preventives and 25% of patients had discontinued preventives (Figure).⁴ Thirty-nine percent of patients met consensus criteria for "offer" or "consider" preventive treatment (Table).

Hopefully, the increasing choice of effective and well-tolerated preventive agents and a greater understanding by clinicians of

Figure



Use of migraine preventive agents in the American Migraine Prevalence and Prevention Study.

Data adapted from Lipton et al. *Headache*. 2005.⁴

Table. Preventive Medication Need Among Migraine Cases

Past 3-month frequency based on MIDAS	Monthly migraine days (number of days in last 3 months)						Total
	≤ 1	2	3	4–5	6–10	≥ 11	
How are you usually affected by severe headaches?							
Able to work/function normally, %	4.4	0.6	0.7	<u>0.6</u>	0.5	0.4	7.2
Impaired to some degree, %	22.6	<u>3.5</u>	<u>4.4</u>	3.5	3.1	2.0	39.1
Severe impairment; bed rest required, %	33.0	<u>4.6</u>	5.2	4.1	3.9	2.9	53.7
Total	60.0	8.7	10.3	8.2	7.5	5.3	100.0
Offer preventive treatment = 25.6%							
<i>Consider preventive treatment = 13.1%</i>							
Preventive treatment not indicated = 61.3%							

MIDAS, Migraine Disability Assessment Scale.

Data adapted from Lipton et al. *Headache*. 2005.⁴

when to recommend prevention will reduce the disabling impact of migraine and improve patients' quality of life.

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What treatments are available for migraine prevention?

Frederick G. Freitag, DO, and Gayle Blake, PA-C

While a variety of agents are used for the prevention of migraine, only five are approved for use in the United States: propranolol, timolol, divalproex sodium, methysergide, and topiramate. The US Headache Consortium conducted an extensive review of the scientific literature and published its evidence-based recommendations on agents used for migraine prevention in 2000.¹ These recommendations were recently modified by others after the publication of several large randomized, double-blind, placebo-controlled clinical trials with topiramate (Table).^{2,3}

The agents given the highest scores in terms of efficacy, quality of evidence, and severity/frequency of adverse events are propranolol and timolol (both β -adrenergic blockers), amitriptyline (a tricyclic anti-

depressant), and divalproex sodium and topiramate (both antiepileptic agents). The selection of the most appropriate agent from among these should be based on individual patient characteristics, contraindications, adverse events, and comorbid conditions.

Whichever agent is selected, patients should be started on a low dose and the dosage should be increased slowly until therapeutic benefit is seen. All agents should be given an adequate trial (at least two to three months), after which time the therapy should be evaluated. If the migraines are well controlled after six to 12 months, the clinician should consider tapering the dosage and even attempting to discontinue the medication.

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Table. Medications Used for Migraine Prevention

Drug	Contraindications	Adverse events	Quality of evidence summary*	Efficacy rating†
β-Adrenergic blockers				
Atenolol	Asthma, Raynaud's disease,	Drowsiness, fatigue,	B	2
Metoprolol	severe heart failure, type 1	nightmares, depression,	B	2
Nadolol	diabetes, peripheral vascular	cognitive disturbance,	B	2
Propranolol	disease, basilar migraine,	exercise intolerance,	A	1
Timolol	prolonged neurologic symptoms	impotence	A	1
Tricyclic antidepressants				
Amitriptyline	Hypotension, cardiac	Sedation, dry mouth,	A	1
Desipramine	dysrhythmia, bowel	constipation, fatigue,		
Doxepin	obstruction, urinary bladder	weight gain, decreased	C	3a
Nortriptyline	retention, angle-closure	libido, delayed orgasm	C	3a
Protriptyline	glaucoma		C	3a
Other antidepressants				
Fluoxetine	Mania			2
Nefazodone			B	
Venlafaxine			B	
Antiepileptic agents				
Divalproex sodium	Divalproex: liver disease,	Divalproex: nausea, hepatotoxicity,	A	1
Gabapentin	bleeding disorders	hemorrhagic pancreatitis, weight gain,	B	2
Topiramate		tremor, hair loss, polycystic ovary syndrome, cognitive changes	A	1
		Gabapentin: fatigue, somnolence, dizziness, weight gain, cognitive dysfunction		
		Topiramate: paresthesia, taste perversion, anorexia, rapid weight loss, renal lithiasis, cognitive dysfunction, angle-closure glaucoma		
Calcium-channel blockers				
Diltiazem HCl	Heart failure, cardiac	Constipation, dizziness, fatigue,	C	3a
Verapamil	conduction block	peripheral edema	B	2
Serotonin antagonists				
Ergot derivatives	Basilar or brainstem-related	Serious: fibrotic complications		
Methylergonovine	neurologic symptoms,	(retroperitoneal, pericardial, pleural,	C	3b
Methysergide	prolonged aura, migraine-	subendocardial fibrosis), coronary	A	4
Cyproheptadine	related stroke, peripheral	vasoconstriction (resulting in angina	C	3a
	vascular disease, coronary	or myocardial infarction), peripheral		
	artery disease, cerebrovascular	vasoconstriction (resulting in claudication)		
	disease, uncontrolled	Other for ergot derivatives: nausea,		
	hypertension, pulmonary	vomiting, abdominal pain, diarrhea,		
	fibrotic disorders	leg cramps, dizziness, drowsiness		
		Other for cyproheptadine: sedation,		
		fatigue, dry mouth, weight gain		
Monoamine oxidase inhibitors				
Phenelzine	Unreliable patient	Orthostatic hypotension,	C	3b
Tranylcypromine		constipation, weight gain,	C	
		peripheral edema, sexual dysfunction		
Nonsteroidal anti-inflammatory drugs				
Aspirin	Ulcer disease, gastritis	Gastritis, bleeding, GI ulcers,	B	2
Ibuprofen		renal failure	C	3a
Naproxen sodium			B	2

*A, multiple, well-designed, randomized controlled trials (RCTs) yielding a consistent pattern of findings; B, some evidence from RCTs but scientific support not optimal; C, recommendation in the absence of RCTs.

†1, medium to high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency of adverse events (AEs); 2, lower efficacy than #1, or limited strength of evidence, and mild to moderate AEs; 3, clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy: (a) mild to moderate AEs (b) AE concerns; 4, medium to high efficacy, good strength of evidence but with AE concerns.

Adapted with permission from Loder and Biondi. *Headache*. 2005.³ Copyright © 2005, Blackwell Publishing.

How do you optimize the use of migraine prevention agents?

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When migraine prevention is indicated, the medication should be chosen from among those with the best efficacy and tolerability profile (see previous Table).^{1,2} Patient preferences, lifestyle, and coexistent conditions should also be taken into consideration.³ For example, β -blockers (eg, propranolol, timolol) may not be a good choice for an athlete because they are associated with exercise intolerance, and tricyclic antidepressants (eg, amitriptyline) may not be a good choice for overweight patients as they are associated with weight gain.

Most migraine preventive agents were originally developed to treat other disorders. Clinicians can use this to their advantage in the case of migraineurs with comorbid conditions. In treating such patients, the best available agent for each of the comorbid conditions should be considered the optimal agent. In some situations, the optimal agent for treating an illness comorbid with migraine, such as propranolol for a patient with hypertension, may also be the optimal agent for the treatment of migraine. Another example of selecting a single agent to treat more than one disorder may occur in a patient with comorbid depression. In this case, tricyclic antidepressants or selective serotonin reuptake inhibitors would be good choices for migraine prevention. In other cases, the optimal agent for each of the comorbid conditions may be different. Using the example of the patient with hyper-

tension and migraine, an angiotensin-converting enzyme inhibitor may be the optimal therapy for hypertension, while topiramate may be the optimal treatment for migraine.

In cases where more than one agent is prescribed, clinicians must be careful not to treat one condition with a drug contraindicated for, or which can exacerbate, the other condition. For example, β -blockers should not be used for migraine prevention in patients with comorbid asthma, diabetes, depression, cardiac conduction defects, or low blood pressure, and tricyclic antidepressants, which can lower seizure threshold, should be avoided in patients with comorbid epilepsy.

Care must also be taken to avoid combinations that will result in drug interactions. It must be kept in mind that patients receiving preventive treatment will still experience breakthrough migraines and some acute migraine agents may be contraindicated with specific preventive agents. For example, triptan use is contraindicated with ergot alkaloids, as is concomitant use of sumatriptan, rizatriptan, and zolmitriptan with monoamine oxidase inhibitors; eletriptan should not be used within at least 72 hours of treatment with potent CYP3A4 inhibitors such as verapamil and a dose adjustment is recommended for rizatriptan in patients taking propranolol. ■

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