

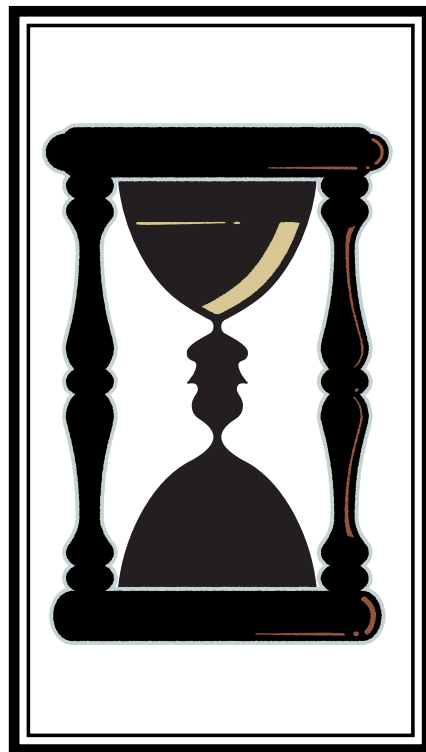


# MIGRAINE TREATMENT STRATEGIES THE RATIONALE FOR EARLY INTERVENTION



PRESENTED BY THE NATIONAL HEADACHE FOUNDATION

Supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals LP



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## NEEDS ASSESSMENT

Our understanding of the pathophysiologic events that lead to migraine has grown considerably in recent years. At the same time, a new class of migraine-specific drugs, the triptans, has revolutionized the acute treatment of migraine. In early trials and clinical use, the triptans were reserved for the treatment of moderate to severe head pain. It has subsequently been learned that this class of drugs is much more effective when used at the onset of headache, while head pain is mild. As a result, there is a need for both physicians and patients to understand the importance of early intervention in migraine.

## INTENDED AUDIENCE

This activity is intended for primary care and other physicians who treat patients with migraine headache.

## METHOD OF PARTICIPATION

The information is presented in a monograph and an audio program. The reader's knowledge is tested by the CME quiz. It is anticipated to take 1 hour to complete the activity.

## EDUCATIONAL OBJECTIVES

After listening to the audio program and reading this monograph, participants should be better able to:

- Describe the pathophysiology of migraine and its relationship to migraine phases.
- Understand the mode of action of the triptans and how it relates to migraine pathophysiology.
- Describe the advantages of the stratified-care approach to migraine.
- Better understand the importance of early intervention, at the onset of head pain, and how it relates to stratified care.
- Understand how early intervention may significantly alter the disability of migraine over a lifetime of care.

## EVALUATION

An evaluation form will provide the participants with the opportunity to review the activity content and method of delivery, and to help identify future educational needs and any possible bias in the monograph.

## FACULTY DISCLOSURE

Elizabeth W. Loder, MD, FACP:  
Research support, grants, consultant, and/or speakers' bureau for GlaxoSmithKline; AstraZeneca Pharmaceuticals LP; Merck & Co., Inc.; Pfizer Inc; Allergan, Inc.; Winston Laboratories, Inc.; Ortho-McNeil Pharmaceutical, Inc.

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## PROFESSIONAL CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Finch University of Health Sciences/The Chicago Medical School and the National Headache Foundation. Finch University of Health Sciences/The Chicago Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Finch University of Health Sciences/The Chicago Medical School designates this educational activity for a maximum of 1 hour toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she spent in the activity.

Finch University of Health Sciences/The Chicago Medical School is solely responsible for the content of this continuing medical education activity. This educational activity was planned and produced in accordance with the ACCME essentials and standards. This activity expires on May 30, 2005.

## EDUCATIONAL GRANT

This activity was supported, in part, by an unrestricted educational grant from AstraZeneca Pharmaceuticals LP.

## NATIONAL HEADACHE FOUNDATION

The National Headache Foundation (NHF) is a non-profit organization established in 1970 to provide services to headache sufferers, their families and the healthcare professionals who treat them. Physician membership in the NHF provides the following benefits: *Standards of Care for the Diagnosis and Treatment of Headache*, the *Therapeutic Guide for the Treatment of Headache*, copies of *NHF Head Lines*, our award-winning bimonthly newsletter, patient education information, inclusion on the NHF physician membership list (if desired), listing in the NHF professional membership directory, opportunities to speak at public education seminars in your area, details on grants available through NHF, discounts on audio and videotapes, toll-free access to the NHF office, information via our Web site, assistance in organizing local support groups, and more. Take advantage of all these great membership benefits for only \$100 a year. To join as a professional member or learn more about the services we offer call 888-NHF-5552 or visit our Web site at [www.headaches.org](http://www.headaches.org).



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## PATHOGENESIS AND NATURAL HISTORY OF A MIGRAINE ATTACK

Our understanding of the pathophysiology of migraine has changed significantly in recent years, in large measure due to a growing knowledge of the functioning of the central and peripheral nervous systems. Migraine appears to originate from a strong genetic predisposition, which is best understood in familial hemiplegic migraine (FHM), a relatively rare form of migraine. Genes for this disorder have been mapped to chromosomes 19 and 1.<sup>1</sup> More common forms of migraine may also be associated with chromosome defects.<sup>2</sup> These genetic defects appear to impair the function of calcium channels that mediate 5-HT release, which predisposes the patient to migraine attacks.

The pathophysiologic events that lead to a migraine headache begin as much as 12 to 24 hours prior to the onset of pain (*Figure 1*). A dysfunction in the hypothalamus is thought to be involved in the first phase, the prodrome, which may be characterized by fatigue, sleepiness, elation, food cravings, depression, irritability, and a variety of other symptoms.<sup>3</sup> During the prodrome, patients are often vaguely aware that an attack is underway.

The prodrome is followed by an aura in patients who have migraine with aura (about 15% of migraineurs).<sup>4</sup> Aura symptoms include the perception of flashing lights that begin in the center of vision and expand in jagged patterns out into the periphery. Symptoms may be somatosensory, such as numbness and tingling in the lips or fingers. They may also involve a profound alteration of the perception of space and time (the “Alice in Wonderland” syndrome).<sup>4</sup>

The aura is generally associated with an electrical depolarization called cortical spreading depression (CSD); this phenomenon was first described in animal studies by Leao in 1944.<sup>5</sup> During CSD, a depression in neuronal activity is followed by a reduction in blood flow, usually beginning in the occipital region, which moves across the cerebral cortex at a rate of 2-3 mm per minute.<sup>6</sup> A preliminary study by Hadjikhani et al employed high-field functional magnetic resonance imaging (MRI) to demonstrate this phenomenon in three human subjects who had migraine with aura.<sup>7</sup> They

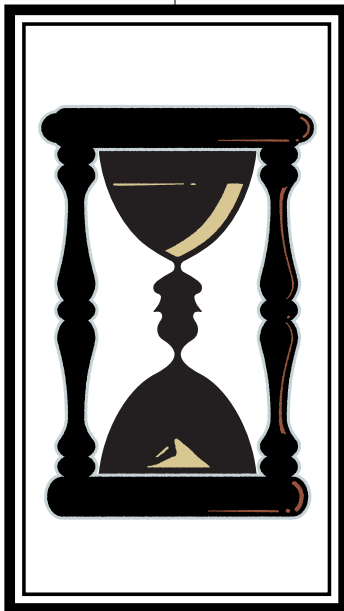
observed blood oxygenation-level dependent changes highly characteristic of CSD that were coincident with the onset of the aura. The investigators noted that their results strongly suggest that the neuronal-mediated electrophysiological events of CSD generate the aura in human visual cortex.

There is a considerable debate on the relationship between the aura and the initiation of the pain phase of migraine. Bolay et al recently demonstrated a neural mechanism in mi-

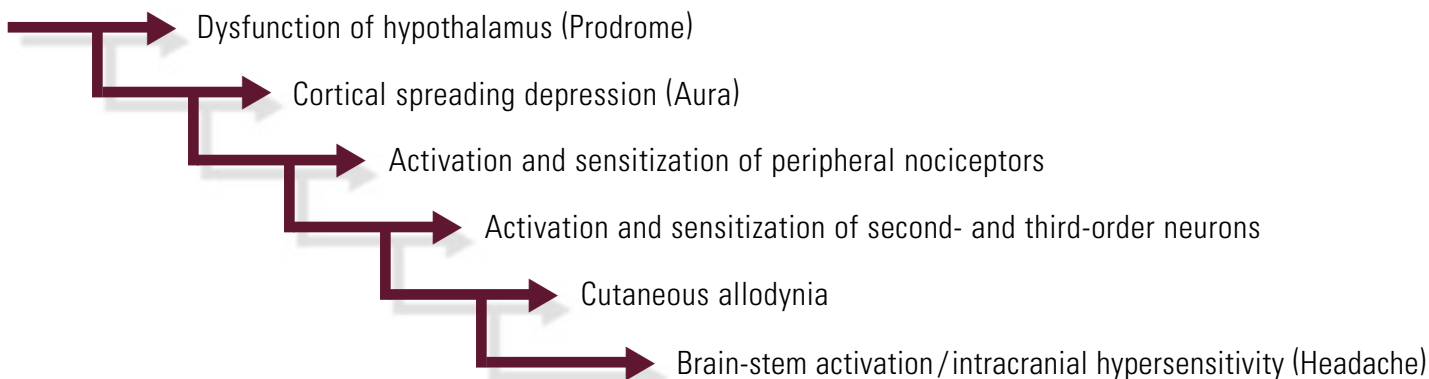
graine that couples extracerebral blood flow to brain events. They showed that CSD activates trigeminovascular afferents that lead to cortical meningeal and brainstem events consistent with the development of headache.<sup>8</sup> Moskowitz et al demonstrated that CSD results in the release of neuropeptides, such as substance P, CGRP, and neurokinin A, that produce sterile neurogenic inflammation.<sup>9</sup> This inflammation sensitizes first-order neurons to respond to previously innocuous stimuli.<sup>10</sup> Impulses coming from sensitized peripheral nociceptors then activate second-order neurons and initiate their sensitization; this process may mediate the development of ipsilateral cutaneous allodynia. The sensitized second-order neurons then activate and sensitize third-order neurons, which subsequently mediate cutaneous allodynia on the contralateral head and ipsilateral forearm.

Burstein et al observed that this peripheral sensitization may provoke subsequent intracranial hypersensitivity that contributes to the headache phase, although the relationship is not fully understood.<sup>11</sup>

Intracranial sensitization appears to be related to activation of an area of the brain stem. Using positron emission tomography (PET), Weiller et al discovered a “migraine generator” in the dorsal raphé of the brain stem.<sup>12</sup> Activation of this brain stem region is specific to migraine and is not present in cluster headache or other types of head pain. Significantly, the brain-stem activation observed by Weiller et al persisted after the administration of sumatriptan relieved the headache, photophobia, phonophobia, and other autonomic symptoms.<sup>12</sup> This phenomenon suggests a mechanism for migraine recurrence when a drug with a short duration of action is used.



**FIGURE 1 THE NATURAL HISTORY OF A MIGRAINE ATTACK**



The headache phase may last from four to 72 hours; headache duration may be related to continued brain-stem activation. Once the pain has run its course, there is a post-drome, where the pain is resolved but other symptoms may linger. Patients often describe a feeling of being “hung over.” Sensory perception and cognition may remain impaired and GI symptoms (nausea, queasiness, and anorexia) and sore muscles may persist for a day or two. Postdrome symptoms may require treatment in some patients. ■■■

**MIGRAINE TREATMENT STRATEGIES:  
STEP CARE VS. STRATIFIED CARE**

Our growing understanding of the pathophysiology of a migraine attack has important implications for treatment. Since a migraine attack involves a complex cascade of neurochemical processes, the effectiveness of a particular therapy would appear to depend on which process is underway when the therapy is administered.

There are currently two major approaches to the acute treatment of migraine: traditional step care, and the stratified-care approach. In the step-care approach, patients are started at the bottom of a therapeutic pyramid and, if treatments fail, therapy is escalated. If the patient is satisfied with first-line treatment (usually simple analgesics), he or she continues on that treatment. If the treatment fails or if the patient is not satisfied, a second-line treatment is prescribed, usually

combination analgesics. If the second line of treatment fails, the patient is switched to more potent migraine-specific medications, such as the triptans. If the patient responds to first-line treatment, this is a cost-effective approach. However, a fundamental but erroneous assumption of step care is that all headache attacks and all patients have the same therapeutic requirements. In practice, step care has several disadvantages:

- 1** Successful treatments may be delayed, resulting in unnecessary suffering.
- 2** Resources may be wasted on follow-up visits and failed prescriptions.
- 3** Patients and physicians may become discouraged and the patient may lapse from care.
- 4** Overuse of medications may lead to chronic daily headache or rebound headache.

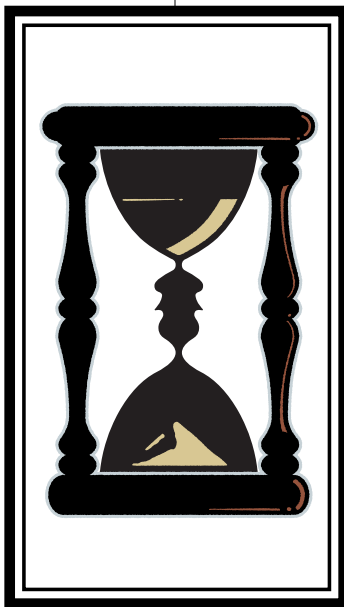
Stratified care is a more logical approach to migraine treatment. In this approach, the physician stratifies the attacks and the patients according to specific therapeutic needs. Patients with severe, disabling headaches would be prescribed highly effective, migraine-specific medications at the onset of pain. Patients with mild attacks may require simple analgesics or NSAIDs. Moderate attacks may require an oral triptan. Attacks with a rapid time to peak pain may require a rapid-acting triptan, such as a subcutaneous injection (sumatriptan),

or a triptan nasal spray (sumatriptan or zolmitriptan). Patients who have slow-building, prolonged migraine, or who tend to experience migraine recurrence may be treated with a long half-life triptan, such as frovatriptan or naratriptan. Extremely severe migraine that presents in a hospital emergency department may be treated with parenteral dihydroergotamine (DHE) plus metoclopramide. Patients with an early onset of nausea may not be able to take oral tablets and may need medications with injectable, nasal spray, rapid-dissolving or suppository dosage forms. The stratified-care approach should also take into account patient wishes and expectations. Most patients prefer medications they can swallow. However, patients who get inconsistent results from their oral tablets or who end up in the emergency department are usually willing to try nasal spray or injectable formulations. A patient who cannot predict when a headache will be severe might also prefer the extra margin provided by a rapid-acting injection. Triptan nasal sprays offer an attractive middle option for patients who don't get consistent or sufficiently rapid relief from an oral formulation. Thus, there are a variety of ways to stratify migraine attacks and patient needs and the clinician should attempt to prescribe the appropriate medication for the patient's specific needs.

The superiority of stratified care was confirmed in a large-scale randomized, multicenter study conducted by Lipton et al.<sup>13</sup> The efficacy analysis population included 835 adult migraine patients at 88 clinical centers in 13 countries. Enrolled patients had Migraine Disability Assessment Questionnaire (MIDAS) grades of II, III, or IV. A safety analysis was conducted in 930 patients. Patients were randomly assigned to receive either stratified care (n=279), step care across attacks (n=271), or step care within attacks (n=285). MIDAS grade II stratified-care patients treated up to six attacks with aspirin, 800 to 1000 mg, plus metoclopramide 10 mg. MIDAS grades III and IV stratified-care patients treated up to six attacks with zolmitriptan 2.5 mg. For step-care-across-attack patients, initial treatment was aspirin 800 to 1000 mg, plus metoclopramide 10 mg. Patients not responding in at least two of the first three attacks switched to zolmitriptan 2.5 mg to treat the remaining three attacks. For step-care-within-attack patients, initial treatment for all attacks was aspirin, 800 to 1000 mg, plus metoclo-

pramide 20 mg. Patients not responding after two hours escalated treatment to zolmitriptan 2.5 mg. The main outcome measures were headache response at two hours and disability time at four hours across six attacks. The headache response at two hours was significantly greater across six attacks in the stratified-care treatment group (52.7%) than in either the step-care-across-attack group (40.6%;  $p<0.001$ ) or the step-care-within-attack group (36.4%;  $p<0.001$ ). Disability time across six attacks was significantly lower in the stratified-care group than in either the step-care-across-attack group ( $p<0.001$ ) or the step-care-within-attack group ( $p<0.001$ ). The incidence of adverse

events was higher in the stratified-care group compared with both step-care groups, although most events were of mild to moderate severity. The investigators concluded that stratified care provides better clinical outcomes than either step-care approach. ■ ■ ■

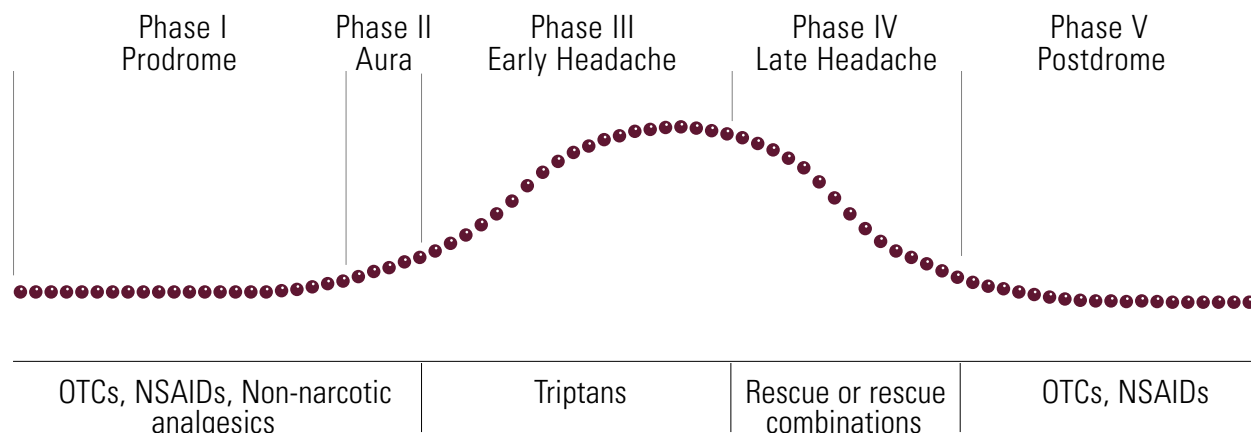


## THE TRIPTANS AND PHASE-SPECIFIC TREATMENT

Phase-specific migraine intervention is a variant of the stratified-care approach, where the clinician tailors the therapy to the phase of migraine the patient is experiencing (Figure 2). If the patient can begin treatment during the prodrome, simple nonpharmacologic approaches, such as exercise, sleep, rest, or biofeedback may actually stop the

migraine process. Most physicians have heard some patients say that if they took their ibuprofen early enough or applied an ice pack soon enough they can “nip that migraine in the bud.”

In the context of phase-specific intervention, the work of Burstein et al on cutaneous allodynia in migraine has important clinical implications.<sup>11</sup> They observed that initiation of central sensitization appears to depend on impulses from peripheral nociceptors. These nociceptors contain numerous 5-HT<sub>1D</sub> receptors, the stimulation of which causes a reduction in the release of vasoactive neuropeptides responsible for neurogenic inflammation.<sup>14</sup> The 5-HT<sub>1D</sub> receptors in trigeminal nerves project peripherally to the dural vasculature and centrally to the brain stem trigeminal nuclei. Peripherally, these receptors are ideally placed to inhibit

**FIGURE 2 PHASE-SPECIFIC TREATMENT OF MIGRAINE<sup>4</sup>**

activated trigeminal nerves and prevent the release of vasoactive peptides. Centrally, they are ideally placed to inhibit pain transmission from the blood vessels to second-order sensory neurons in the brain stem.<sup>15</sup> The 5-HT<sub>1B</sub> receptors occur in large numbers on the smooth muscle of meningeal blood vessels that mediate vasoconstriction; thus, they are ideally placed to reverse the meningeal vasodilation that occurs during a migraine attack.<sup>14,16-18</sup> The triptans are selective 5-HT<sub>1B/1D</sub> agonists; they target the peripheral nociceptors and have no effect on second- and third-order neurons. Therefore, the triptans (and other drugs that target peripheral nociceptors) should be most effective in aborting the headache when used early in the pain phase, before the development of central sensitization and cutaneous allodynia.<sup>11</sup> This may explain why many patients who treat migraine early find they are able to “nip it in the bud” and achieve a pain-free state. ■ ■ ■

### TRIPTAN PHARMACOKINETICS AND CLINICAL PERFORMANCE

The chemical structures of available triptans share a basic indole ring but have different side chains that are responsible for the different pharmacokinetic properties of these drugs. Pharmacokinetic parameters that may have a bearing on the clinical performance of these drugs include T-max (time to maximum concentration), T<sub>1/2</sub> (half-life), and bioavailability. The pharmacokinetic differences among the triptans may or may not be significant in individual patients in clinical practice; frequently, however, there is a correlation between pharmacokinetics and clinical performance. A short T-max generally

equates with a rapid onset of action, a characteristic that may be important in the context of early intervention. The mean T-max for subcutaneous sumatriptan is 12 minutes<sup>19</sup>, while the shortest T-max for an oral triptan (rizatriptan) is 1-1.5 hrs.<sup>20</sup> The T-max's for zolmitriptan and sumatriptan nasal sprays are intermediate between the subcutaneous and oral dosage forms. In a pharmacokinetic study of 12 healthy volunteers, plasma drug concentrations of zolmitriptan nasal spray were detectable within five minutes of dosing.<sup>21</sup>

### STUDIES ON EARLY INTERVENTION

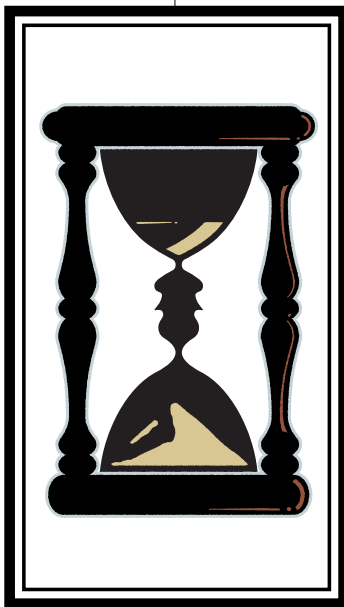
Studies have confirmed that intervention early in the headache phase tends to be far more effective than later intervention. Early triptan trials instructed patients to wait until head pain was moderate to severe before treatment with the investigational drug. Migraine, by definition, produces moderate to severe head pain, so this was a defensible strategy. However, the results observed in protocol violators, who treated their migraines when pain was mild, suggested that this wasn't the best strategy.

In 1998, the first report was published suggesting that headache outcomes improved when mild pain was treated compared to moderate or severe pain.<sup>22</sup> Specifically, pain-free response rates doubled when mild pain was treated with zolmitriptan 5 mg compared with severe pain (80% vs. 35%). Although 29,808 attacks were treated over a 12-month period, the study was unblinded and not randomized. The subsequent Spectrum trial was a large-scale study that evaluated the effectiveness of sumatriptan 50-mg tablets across the

spectrum of headaches (migraine, migrainous, and episodic tension-type) experienced by IHS-diagnosed migraineurs with disabling headaches.<sup>23</sup> A post-hoc analysis was conducted in a subgroup of patients (violators of the original protocol) who treated their headaches while pain was mild.<sup>24</sup> Across all headaches treated while pain was mild, pain-free responses were higher for sumatriptan than placebo at four hours (85% vs. 17%) and two hours (50% vs. 0%) postdose compared with placebo. When the same patients treated headaches while pain was moderate or severe, pain-free rates were lower than those reported for treatment during mild pain. In addition, there was a trend toward lower headache recurrence rates in headaches treated while pain was mild compared with moderate or severe pain. The post-hoc analysis included a small number of patients, but it confirmed the earlier report of improved outcomes with treatment of mild pain.

As a result of these data, retrospective analyses were conducted of three other studies that treated migraine attacks with sumatriptan 50- and 100-mg tablets.<sup>25</sup> They measured pain-free response at two and four hours in headaches treated during mild vs. moderate/severe pain. In the first study, 92 patients treated 118 headaches during mild pain. With sumatriptan 50 mg, rates of pain-free response at two hours were higher with early treatment of mild pain (51%) compared with treatment of moderate/severe pain (31%;  $p < 0.05$ ). With sumatriptan 100 mg, the pain-free response at two hours was 67% for treatment during mild pain and 36% for treatment during moderate/severe pain. Pain-free response at four hours for both doses also favored early treatment ( $p < 0.05$ ). Early intervention also resulted in less redosing than when moderate/severe pain was treated. In the second and third studies, early treatment with sumatriptan 100 mg produced significantly higher pain-free rates at two hours than did ergotamine plus caffeine (69% vs. 34%;  $p < 0.001$ ) or aspirin plus metoclopramide (73% vs. 25%;  $p < 0.001$ ). The investigators concluded that sumatriptan 50- and 100-mg tablets are effective whether pain is mild or moderate/severe; however, treatment while pain is mild or moderate provides higher pain-free response rates while reducing the need for redosing.

An additional prospective study evaluated the effect of early treatment in a subgroup of migraineurs with severely disabling headaches (MIDAS grade III or IV).<sup>26,27</sup> In this study, a total of 302 patients from 24 centers in the U.S., France, and Norway were randomized to zolmitriptan 2.5 mg ( $n = 138$ ) or placebo ( $n = 142$ ). After treatment of one mild migraine attack, significantly more patients in the zolmitriptan group were pain-free at two hours compared with placebo (43% vs. 18%;  $p < 0.0001$ ). The majority of patients in this study chose to treat their mild migraine attacks early. In the intent-to-treat (ITT) population, 38.4% of the zolmitriptan group and 39.4% of the placebo group treated their attacks within 15 minutes, while 54% of the zolmitriptan group and 56% of the placebo group treated their attacks within 30 minutes. The pain-free rate increased to 57% in the zolmitriptan group and 20% in the placebo group (an increase of 33%) when the attack of mild pain was treated within the first 15 minutes. ■ ■ ■



## TREATMENT DURING THE AURA

Will a triptan be effective if it is administered still earlier, during the aura phase of migraine? Studies by Moskowitz et al<sup>9</sup> and Burstein et al<sup>11</sup> discussed above suggest that administering a triptan during the aura, prior to the activation of peripheral nociceptors, would not be effective in preventing the headache phase. Bates et al conducted a double-blind, placebo-

controlled, multicenter, parallel-group study to determine whether subcutaneous sumatriptan 6 mg administered during the migraine aura would prolong or modify the aura and prevent or delay the headache.<sup>28</sup> Patients were randomized to receive either subcutaneous sumatriptan 6 mg ( $n = 88$ ) or placebo ( $n = 83$ ). They treated a single attack of migraine at home, during the aura phase, by self-injection. The median duration of aura following the first injection was 25 minutes for the sumatriptan group and 30 minutes for the placebo group; the difference was not statistically significant. The percentage of patients who developed a moderate or severe headache within six hours after dosing was also similar between the two groups: 68% for those receiving sumatriptan and 75% for those receiving placebo; the difference was not statistically significant. The authors concluded that sumatriptan given during the aura phase of migraine does

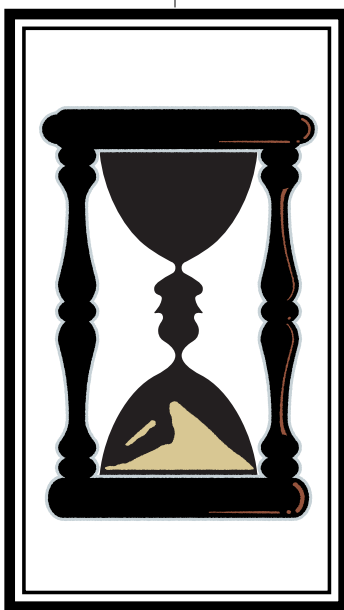
not prolong or alter the nature of the aura and does not prevent or delay the development of headache.

A second study of migraine treatment during an aura had more equivocal results. Dowson conducted a pilot study to determine whether 20 mg oral zolmitriptan can prevent the development of headache when taken during an aura.<sup>29</sup> This was an outpatient, double-blind, placebo-controlled, two-period crossover trial of 40 patients (31 females and nine males). Most of the patients studied experienced a migraine headache after the aura phase. During the study, patients treated two migraine attacks during the aura phase in a random order with either zolmitriptan 20 mg or placebo. The primary outcome measure was the absence of head pain during the 24-hour period following the dose of study medication. Of the 40 patients entering the study, 20 completed the study by treating two attacks and 16 were fully compliant with the study protocol. Three of the 16 patients (19%) responded to zolmitriptan (reporting no pain following treatment), while all patients developed a migraine headache after taking placebo. Two patients who did not respond to active treatment developed headaches they described as “non-migraine.” There were no reports of zolmitriptan-related adverse effects on the aura symptoms. The investigator concluded that oral zolmitriptan 20 mg may be of value in preventing a migraine headache and is safe

when taken during the aura phase. It is possible, however, that the three patients who responded had blood levels of the study drug immediately prior to the pain phase sufficient to prevent the development of headache. One of the current faculty (EL) noted that, when patients have severe headaches following relatively brief auras (i.e., approximately 30 minutes), she allows them to take an oral triptan during the aura. This enables the drug’s onset of action to roughly coincide with the onset of pain. ■ ■ ■

### SUMMARY AND CONCLUSIONS

There is compelling evidence supporting intervention early in the pain phase of migraine with migraine-specific medications. Pain-free response is significantly higher; furthermore, migraineurs who progress to the late headache phase often end up in hospital emergency departments or acute care centers. These patients present a considerable cost burden. Over years of migraine attacks, early intervention may also ease the substantial burden of disability, with fewer missed days of school and work and fewer trips to emergency departments. It may mean a patient performs better at work and isn’t exposed to barbiturate or opiate rescue medications. During a single attack, early intervention can save hours of unnecessary pain. Over a lifetime, it can have a cumulative and very important benefit on a patient’s quality of life.<sup>30</sup>



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**POST-TEST** *Seven correct answers are required for credit*

1. The pathophysiologic events that lead to a migraine headache begin
  - A. three to six hours prior to the onset of pain.
  - B. six to eight hours prior to the onset of pain.
  - C. as much as 12 to 24 hours prior to the onset of pain.
2. What percentage of migraineurs experience aura?
  - A. 15%
  - B. 25%
  - C. 35-40%
3. Which of the following statements about cortical spreading depression (CSD) is correct?
  - A. CSD results in the release of neuropeptides that produce sterile inflammation.
  - B. CSD activates trigeminal afferents that lead to cortical meningeal and brainstem events consistent with the development of headache.
  - C. Both of the above
  - D. Neither of the above
4. Weiller et al discovered a “migraine generator” in
  - A. peripheral nociceptors.
  - B. the hypothalamus.
  - C. the dorsal raphé of the brainstem.
5. Which of the following is a disadvantage of the step-care approach to migraine?
  - A. Successful treatments may be delayed, resulting in unnecessary suffering.
  - B. Resources may be wasted on follow-up visits and failed prescriptions.
  - C. Patients and physicians may become discouraged and the patient may lapse from care.
  - D. Overuse of medications may lead to chronic daily headache or rebound headache.
  - E. All of the above
  - F. A and B above
6. The stratified-care approach takes into account patients’ wishes and expectations from therapy.
  - A. True
  - B. False
7. The stimulation of 5-HT<sub>1D</sub> receptors causes
  - A. an increase in the release of vasoactive neuropeptides.
  - B. a decrease in the release of vasoactive neuropeptides.
  - C. the initiation of the process of central sensitization.
8. The triptans target peripheral nociceptors and have no effect on second- and third-order neurons.
  - A. True
  - B. False
9. In the Spectrum study, what was the pain-free response at two hours for treatment during mild pain vs. moderate/severe pain, respectively?
  - A. 40% vs. 26%
  - B. 51% vs. 42%
  - C. 51% vs. 31%
10. Administering a triptan during the aura phase of migraine can shorten the aura and delay or prevent the onset of headache.
  - A. True
  - B. False

