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## Advances in migraine management

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**SUMMARY** New drugs and better understanding of the pathogenesis of migraine are improving the outlook for patients with this debilitating disorder. This paper reviews recent advances and outlines our approach.

**KEY POINTS** Rational treatment of migraine begins with a detailed history to ascertain the frequency and severity of attacks and to identify "triggers" that can be eliminated.

■ Nonsteroidal anti-inflammatory drugs, isometheptene mucate, ergotamine, and metoclopramide remain the first-line agents to treat acute attacks; patients whose symptoms do not respond to these drugs may be candidates for subcutaneous sumatriptan or dihydroergotamine. Inhalable preparations of these drugs, when they become available, should simplify their use.

■ Patients whose attacks are frequent or interfere with their life-style should be offered prophylactic treatment with beta blockers without intrinsic sympathomimetic activity or calcium antagonists; nonsteroidal anti-inflammatory drugs, valproate, antidepressants, and biofeedback also may be used.

■ Corticosteroids and dihydroergotamine are mainstays of treatment for prolonged or intractable migraine.

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AS MANY AS 10 million Americans suffer some degree of disability from migraine.<sup>1</sup> Recent studies suggest that more than 15% of women have at least one migraine attack each year.<sup>2</sup> The lifetime prevalence of migraine may be as high as 25% in women.<sup>2</sup>

The study of existing therapies has led to a greater understanding of the underlying process,<sup>3</sup> which, in turn, has led to the development of new drugs. However, a great deal remains unknown about the pathogenesis of migraine. This paper reviews recent advances and outlines our approach to treating this debilitating disease.

### **PATHOGENESIS OF MIGRAINE**

A century ago, Osler<sup>4</sup> noted the similarity of migraine to epilepsy and speculated that vasodilation was the cause. Contemporary theories continue to implicate the interaction of blood vessels and nerves.<sup>5</sup> The trigeminovascular concept of Moskowitz<sup>6</sup> and others proposes that an intimate relationship exists between the fifth cranial nerve and certain cranial vessels. The *Figure* summarizes the steps thought to occur in a migraine attack.

Serotonin and its receptor subtypes (5HT-1D and 5HT-2) have been proposed as a possible link between the migraine cascade and various "triggers" and therapies.<sup>3,6,7</sup> Experimental evidence suggests that drugs used in acute migraine attacks stimulate 5HT-1D receptors,<sup>7</sup> inhibiting release of neuropeptides from the trigeminal axons.<sup>3,6,7</sup> Similar evidence suggests that drugs used in the prophylaxis of migraine inhibit 5HT-2 receptors<sup>7</sup>; this interaction may prevent vasospasm, perivascular inflammation, and the subsequent activation of the trigeminovascular pathway.<sup>3,6,7</sup>

#### DIAGNOSING MIGRAINE: IMPORTANCE OF THE HISTORY

The diagnosis of migraine and the exclusion of other primary or secondary headache syndromes begins with a detailed history.<sup>8</sup>

Therapeutic decisions in general will be based upon the information obtained in the interview. Illnesses, allergies, or other conditions likely to limit or contraindicate various therapies must be elucidated. Finally, recommending the exclusion of various migraine "triggers" from the patient's life-style is impossible without a detailed history elicited by a compassionate health care provider. The rapport borne of this clinical interaction may have therapeutic properties of its own.<sup>9-11</sup>

#### NONPHARMACOLOGIC MANAGEMENT

##### Avoiding 'triggers'

In Osler's words, "...the patient is fully aware of the causes which precipitate an attack. Avoidance of excitement, regularity in the meals, and moderation in diet are important rules. The treatment should be

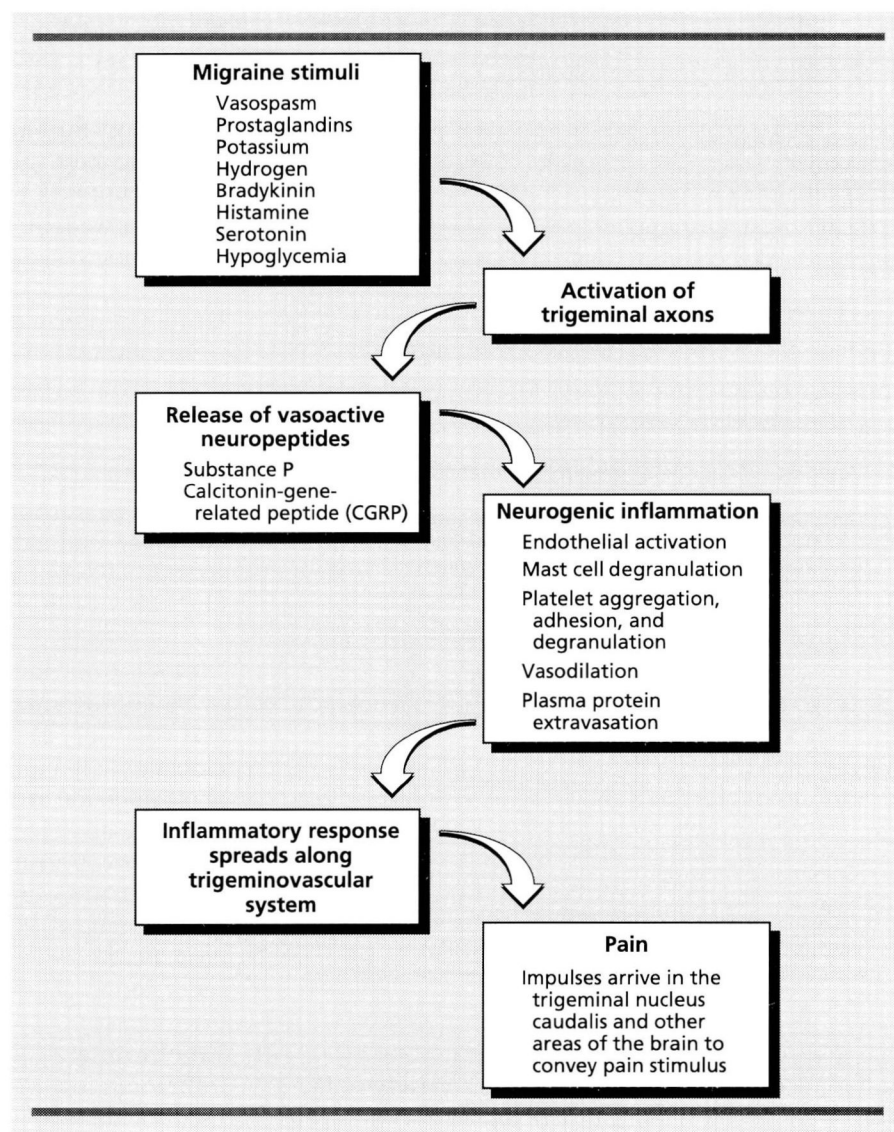


FIGURE. The migraine cascade.

directed toward the removal of the conditions upon which the attacks depend..."<sup>14</sup>

Blau<sup>12</sup> reported that approximately 50% of patients with previously intractable migraine could reduce the frequency of their attacks by 50% by eliminating various triggering factors. A single factor is seldom enough to trigger an attack by itself<sup>13</sup>; it has been hypothesized that they interact in some way to lower the threshold for trigeminovascular stimulation.<sup>3,14</sup> In addition, a migraine trigger may be variably effective in causing a migraine attack at

**TABLE**  
COMMON TRIGGERS FOR MIGRAINE

<b>Foods</b>
Aged cheese
Alcohol
Monosodium glutamate
Chocolate
Caffeinated beverages
Nitrites and nitrates (hot dogs, sausages, luncheon meats)
Avocado
Smoked or pickled fish or meats
Yeast or protein extracts (brewer's yeast, marmite)
Onions
Nuts
Aspartame (dietary sweetener)
<b>Medications</b>
Antibiotics (trimethoprim-sulfamethoxazole, griseofulvin)
Antihypertensives (nifedipine, captopril, atenolol, metoprolol, prazosin, reserpine, minoxidil)
Histamine-2 blockers (cimetidine, ranitidine)
Hormones (oral contraceptives, estrogens, clomiphene, danazol)
Nonsteroidal anti-inflammatory drugs (indomethacin, diclofenac, piroxicam)
Vasodilators (nitroglycerin, isosorbide dinitrate)
Others (isotretinoin, erythropoietin)
<b>Life-style</b>
Fasting or skipping meals
Sleeping late or changes in sleep patterns (shift changes or jet lag)
Letdown following stress (weekends, vacations, after exams)
Caffeine withdrawal
<b>Others</b>
Weather changes
High altitude (air travel, mountain climbing)

different times in a given patient. A variety of factors seem to be important, including recent sleep habits and timing within the menstrual cycle. Since predicting which trigger will cause an attack at what time can be quite difficult, it seems prudent to advise patients to avoid all rationally determined migraine triggers (Table).<sup>15</sup>

#### PHARMACOLOGIC TREATMENT: TREATING ACUTE ATTACKS

For most patients, the initial drug to try for aborting migraine attacks should be an oral one that will not lead to analgesic-rebound headache and that causes few significant adverse effects. Several nonsteroidal anti-inflammatory drugs (NSAIDs) and isometheptene mucate fit these criteria and are excellent first-line drugs.

#### Nonsteroidal anti-inflammatory drugs (NSAIDs)

Of the NSAIDs used to treat migraine attacks, naproxen,<sup>16</sup> flurbiprofen,<sup>17</sup> and meclofenamate<sup>18</sup> have been the best studied. Several new studies have found ibuprofen,<sup>19</sup> diclofenac,<sup>20</sup> and ketorolac<sup>21,22</sup> effective as well. NSAIDs should generally be avoided in patients with peptic ulcer disease.

#### Isometheptene mucate

Isometheptene mucate, a sympathetic agent, appears to have efficacy in acute migraine by virtue of its vasoconstrictive properties. It is currently available in combination with acetaminophen and dichloralphenazone, a mild sedative. This combination has been shown to be effective in double-blind crossover studies.<sup>23,24</sup> The Food and Drug Administration (FDA) has classified this product as "possibly" effective in the treatment of migraine.<sup>25</sup>

#### Metoclopramide

Since migraine is often accompanied by nausea and vomiting, in part caused by gastroparesis, metoclopramide is a useful adjunct to medications used to abort migraine attacks. In addition to having its own migraine-abortive effect,<sup>26</sup> metoclopramide speeds the gastric transit of the abortive medication and relieves nausea and vomiting. Phenothiazine antiemetics, some of which possess migraine-abortive efficacy, neither relieve gastroparesis nor speed the onset of action of other abortive agents.

#### Ergotamine

Ergotamine was isolated in 1920 and was first used for treating migraine in 1926. Its effects have been thought to stem from constriction of cranial and peripheral blood vessels,<sup>27</sup> or from interaction with the serotonergic system.<sup>28</sup> This agent has several potential side effects that limit its usefulness, including headache "rebound" (increased frequency of headache induced by frequent ergot use), nausea and vomiting, and peripheral ischemia.

Rectal suppositories and sublingual formulations of ergotamine have replaced the parenteral forms that were popular until recently, and have much greater bioavailability than oral tablets.<sup>28-32</sup> We recommend that patients use only one fourth to one third of a 2-mg rectal suppository at the onset of an attack, followed by additional doses every 30 minutes (limit 4 mg per day). We generally limit ergotamine use to no more than every 4 days, regardless of dose.

## Sumatriptan

Patients whose symptoms fail to respond to the drugs discussed above may be candidates for therapy with subcutaneous injections of sumatriptan or dihydroergotamine (DHE). The cost of these drugs and the inconvenience of parenteral administration, rather than problems with efficacy or adverse effects, preclude their use as first-line therapy. Intranasal preparations, when they become available in the United States, will be valuable options.

Developed as a selective constrictor of intracranial blood vessels,<sup>6</sup> sumatriptan constricts large cerebral vessels and arteriovenous anastomoses without reducing cerebral or extracranial blood flow.<sup>25,33-35</sup> Sumatriptan is structurally related to serotonin and is a potent and selective agonist of the 5HT-1D receptor.<sup>36</sup> It is well absorbed intranasally, rectally, and subcutaneously, but not orally. Food does not affect sumatriptan's pharmacokinetics, nor does the migrainous state.<sup>36</sup>

The clinical efficacy of sumatriptan has been documented in several placebo-controlled trials using oral,<sup>37</sup> subcutaneous,<sup>38,39</sup> and intranasal<sup>40</sup> formulations. Approximately 70% of patients treated with subcutaneous or intranasal medication obtained clinically significant relief; approximately 50% of patients treated with oral medication obtained such relief. Headache recurred within 24 hours in about 40% of patients who obtained relief with sumatriptan, perhaps reflecting the short half-life of the drug. Further treatment strategies will need to be developed to overcome the problem of migraine recurrence. A second injection of sumatriptan will usually abort a recurrent attack.

Our experience with more than 500 patients treated with sumatriptan is similar to the results of published trials. Adverse effects have been minimal, and complaints of chest tightness or pressure have been uncommon. Patients rarely find it difficult to give themselves subcutaneous injections using the autoinjector system. The approximate price of sumatriptan in the Cleveland area is just over \$26 wholesale and \$30 to \$35 retail per injection.

## Dihydroergotamine

A potent venoconstrictor with fewer arterial constrictive properties than ergotamine,<sup>27,41,42</sup> DHE may also inhibit the neurogenic inflammation process by activating the 5HT-1D receptor.<sup>43</sup> DHE has been shown useful for treating acute migraine when administered intravenously,<sup>44,45</sup> intramuscularly,<sup>46</sup> sub-

cutaneously,<sup>47</sup> intranasally,<sup>48</sup> and rectally.<sup>49</sup> The most common side effects are nausea and vomiting, particularly with intravenous administration. Recurrence of headache within 24 hours does not seem to be common.

An intranasal formulation of DHE is expected to be approved by the FDA in 1995. This formulation has the advantages of ease of administration and rapid onset of activity.

## Phenothiazines

Several phenothiazines have been proven effective in aborting migraine headaches, including chlorpromazine<sup>50</sup> and methotrimeprazine.<sup>51</sup> We usually give 10 mg of prochlorperazine via a slow intravenous infusion. Adverse effects include dystonic reactions, orthostatic hypotension, and sedation. This approach is most useful in patients with prolonged migraine and significant nausea or vomiting who desire sedation and sleep. Unlike sumatriptan or DHE, phenothiazines are not useful for patients who need to drive or engage in other activities requiring alertness and motor coordination.

## Butorphanol

In one study, transnasal butorphanol provided more rapid analgesia and higher pain-relief scores than methadone or placebo.<sup>52</sup> Sedation and gastrointestinal upset were the major adverse effects.

Our experience with transnasal butorphanol suggests that it may carry a significant risk of overuse and habituation: we have seen several patients who have abused this medication. The spray bottle requires priming of the pump, and the number of doses in each bottle will vary depending on the number of times the pump is primed. This makes it particularly difficult to calculate the number of doses a patient uses. We limit use of transnasal butorphanol to occasional patients who fail to respond to usual abortive medications and require an opiate analgesic, and who cannot tolerate an oral opiate preparation.

## TREATING INTRACTABLE MIGRAINE

For patients with prolonged (status) or intractable migraine, corticosteroids and intravenous infusions of DHE are the mainstays of treatment.<sup>53,54</sup> Whether sumatriptan will be valuable in this setting has not been evaluated, but preliminary experience suggests it has some efficacy. The value of glucocor-

ticoids in the management of status migraine is well accepted, though controlled studies are lacking. The salutary effects of glucocorticoids may relate to the reduction of perivascular inflammation.

Opioid analgesics should rarely be used, owing to their poor rate of efficacy (approximately 30%), the risk of habituation, and adverse effects of sedation and nausea. Transnasal butorphanol may be useful for the rare migraine patient needing opioid therapy, since it has a rapid onset of analgesic activity and can be taken by a patient who has nausea and vomiting.

#### PROPHYLACTIC MEDICATIONS

Prophylactic therapy should be considered for any patient with frequent or incapacitating migraine. Although some clinicians base the decision to prescribe prophylaxis purely on the frequency of migraine attacks, prophylactic therapy should be offered to all patients who find their life-style adversely affected by migraine.

#### Beta blockers

Propranolol and timolol are the only beta blockers approved by the FDA for migraine prophylaxis, but nadolol, metoprolol, and atenolol have also been shown to be effective. Beta blockers with intrinsic sympathomimetic activity, such as pindolol and acebutolol, have not been found useful in migraine prophylaxis.

While generally well tolerated, beta blockers are contraindicated in patients with congestive heart failure, bronchospastic disease (ie, asthma, emphysema, chronic bronchitis), diabetes mellitus, and Wolff-Parkinson-White syndrome. Beta blockers may also exacerbate Raynaud's phenomenon, a condition found more commonly in migraine sufferers than in the general public. Side effects of beta blockers include depression, fatigue, and sleep disorders. Depression is more commonly reported with propranolol than with other beta blockers. Patients should not abruptly discontinue beta blocker therapy, since doing so may lead to myocardial infarction even in patients with no history of heart disease.<sup>55</sup>

Although propranolol has long been valued as a prophylactic drug for migraine, two studies found it ineffective for treating acute migraine attacks.<sup>56,57</sup>

#### Calcium antagonists

Several calcium antagonists have been shown to

be effective in migraine prophylaxis, including verapamil, diltiazem, flunarizine,<sup>58</sup> nimodipine, and nifedipine.<sup>59</sup> Nifedipine is either weakly effective or ineffective for migraine prophylaxis and can exacerbate migraine in some patients because of profound vasodilation. In the United States, verapamil is considered the calcium antagonist of choice for migraine and cluster headache prophylaxis<sup>60</sup>; in Europe, flunarizine is the agent of choice.

Verapamil and diltiazem have negative inotropic effects and slow conduction through the atrioventricular node. Therefore, these agents should be avoided in patients with congestive heart failure, advanced heart block, or sick sinus syndrome. The dihydropyridine antagonists (ie, nifedipine, nifedipine, and nimodipine) have no effect on cardiac conduction, but can cause marked vasodilation.

Adverse effects of calcium antagonists include constipation with verapamil; sedation, weight gain, and parkinsonism with flunarizine; flushing and edema with nifedipine; and gastrointestinal upset and parkinsonism with diltiazem.

#### NSAIDs as prophylaxis

NSAIDs are valuable in both prophylaxis of migraine headache and adjunctive therapy for tension-type headache.<sup>61</sup> This dual effect allows NSAIDs to be used as single-drug therapy in some patients with the mixed headache syndrome.

Aspirin, naproxen,<sup>62-64</sup> flurbiprofen,<sup>65</sup> ketoprofen, flufenamic acid, tolfenamic acid, and fenoprofen are among the NSAIDs reported to have prophylactic activity in migraine. For reasons of safety and tolerability, flurbiprofen and naproxen are the NSAIDs we prescribe most frequently for headache prevention.

Adverse effects of long-term NSAID use are relatively common and may include gastrointestinal symptoms such as dyspepsia, heartburn, nausea, vomiting, diarrhea, constipation, and generalized abdominal pain. Most NSAIDs can cause bleeding of the upper gastrointestinal tract. Renal effects of NSAIDs may include decreased glomerular filtration with sodium, chloride, and water retention. These renal problems are most likely to occur in patients who are elderly, who are hypertensive, who have renovascular or advanced atherosclerotic disease, or who take diuretics. Indomethacin and fenoprofen appear to be more nephrotoxic than other NSAIDs. Analgesic nephropathy, the most com-

mon cause of drug-induced renal failure, has been associated with excessive use of NSAIDs along with phenacetin or acetaminophen.

For patients for whom therapy with beta blockers, calcium antagonists, and NSAIDs has failed, the combination of either a beta blocker or a calcium antagonist with an NSAID may be worthwhile. A tricyclic or specific serotonin reuptake inhibitor (SSRI) antidepressant may also be added.

### Antidepressants

A valuable group of agents in migraine prophylaxis are the antidepressants. Although the mechanism of action of these agents is not known with certainty, an attractive explanation may again involve serotonin receptors.<sup>7</sup>

Amitriptyline is the best studied antidepressant for migraine, but a variety of others have been used.<sup>25,66-70</sup> Extensive clinical experience and relatively low cost are the potential benefits that must be weighed against the various well-known side effects of tricyclic antidepressants.<sup>25</sup>

SSRIs have been introduced only recently for the treatment of depression. Both controlled studies and extensive clinical experience are lacking in their application to migraine. These agents offer potentially fewer side effects at significantly greater cost.

The monoamine oxidase inhibitors, although effective for preventing migraine, have limited application due to their well-known side effects and drug interactions.<sup>71</sup>

### Valproate

Gamma aminobutyric acid (GABA), an inhibitory neurotransmitter, dilates the cerebral arteries, influences human circadian rhythm, and may help regulate secretion of hormones from the anterior pituitary gland. Valproate, a GABA agonist anticonvulsant, has been evaluated for efficacy in migraine<sup>72-74</sup> and "chronic daily headache."<sup>74</sup> It may affect migraine through influence on cerebral arteries and circadian rhythms.<sup>73</sup>

Recent data have helped to elucidate the circadian rhythm of migraine. In a 20-week study of 15 patients, one of us (Solomon) found a circadian variation in migraine onset, with a marked increase in attacks between 6 AM and 8 AM, peak frequency between 8 AM and 10 AM, and a dramatic decrease in frequency between 8 PM and 4 AM.<sup>75</sup> The circadian rhythm of migraine onset parallels that of myocardial infarction, platelet aggregability, and plasma concen-

trations of cortisol and catecholamines. An attractive hypothesis that vasoconstriction or ischemia or both play a role in the onset of migraine has yet to be proven.

### BIOFEEDBACK

Biofeedback for migraine headache includes electromyographic (EMG) and, more commonly, thermal techniques. In EMG biofeedback, patients learn to decrease the tension in the frontalis muscle or in the most tense muscle in the head or neck; in thermal biofeedback, they learn to increase the surface temperature of the hands, causing a reduction in sympathetic tone.<sup>76</sup> Daily home practice of these skills is encouraged.<sup>76</sup>

The appropriate role of biofeedback in headache remains uncertain. Although biofeedback has been found effective in clinical trials,<sup>77,78</sup> the American College of Physicians, in its 1985 position paper,<sup>76</sup> concluded that biofeedback lacks sufficient evidence of efficacy to recommend it for the treatment of mixed (migraine plus tension-type) headache. However, it may be useful adjunctively in some patients with tension-type or migraine headache to assist relaxation, or in patients whose headaches are refractory to other forms of therapy. The report also concluded that biofeedback was no more effective than other relaxation techniques.<sup>76</sup> It is uncertain whether biofeedback and pharmacotherapy offer additive benefits.<sup>77-79</sup>

Patient acceptance of biofeedback and ancillary approaches such as relaxation techniques is highly variable. Any interested patient with migraine attacks frequent or severe enough to merit prophylaxis should probably be referred to a qualified biofeedback therapist for evaluation.

### FUTURE TRENDS IN MIGRAINE THERAPY

As medical science gains understanding of the neurochemical pathways of migraine, specific therapies are being developed. Medications under study include serotonin receptor agonists, neurokinin (NK-1) receptor antagonists, nitric oxide synthase inhibitors, cyclooxygenase-2 (COX-2) selective inhibitors, and cholecystokinin-B (CCK-B) receptor antagonists.

Serotonin receptor agonists such as sumatriptan work at the 5HT-1D receptor. Several new agents currently in phase II studies may obviate the prob-

lems of headache recurrence and adverse effects that limit the utility of sumatriptan.

The NK-1 receptor, the physiologic receptor for substance P, may mediate the nociceptive and inflammatory response in migraine. At least four pharmaceutical companies are currently evaluating agents that block the NK-1 receptor to abort migraine attacks.

Nitric oxide synthase inhibitors, COX-2 selective inhibitors, and CCK-B receptor antagonists are in early stages of development as migraine therapy.

These agents appear to act as vasoactive mediators and as anti-inflammatory agents.

#### SUMMARY

Several major pharmacologic advances in migraine therapy have taken place in the last few years. As our understanding of the pathophysiology and receptor pharmacology of migraine improves, so does the likelihood of finding more effective therapy.

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