Review Article

Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

MIGRAINE — CURRENT UNDERSTANDING AND TREATMENT

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MIGRAINE is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms.[1,2] Recent advances in basic and applied clinical neuroscience[3] have led to the development of a new class of selective serotonin (5-hydroxytryptamine [5-HT]) receptor agonists that activate 5-HT_{1B} and 5-HT_{1D} (5-$HT_{1B/1D}$) receptors and are known as the triptans; these agents have changed the lives of countless patients with migraine. Despite such progress, migraine remains underdiagnosed and the available therapies underused.[4] In this article, we review the current understanding of the epidemiology, pathophysiology, and treatment of migraine.

CLINICAL MANIFESTATIONS

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine), attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement.[5] When untreated, these attacks typically last 4 to 72 hours.[6] A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient (Table 1).

These symptoms distinguish migraine from tension-type headache, the most common form of primary headache, which is characterized by the lack of associated features. Any severe and recurrent headache is most likely to be a form of migraine and to be responsive to antimigraine therapy.[8] In 15 percent of patients, migraine attacks are usually preceded or accompanied by transient focal neurologic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine).[9] In a recent large, population-based study, 64 percent of patients with migraine had only migraine without aura, 18 percent had only migraine with aura, and 13 percent had both types of migraine (the remaining 5 percent had aura without headache). Thus, up to 31 percent of patients with migraine have aura on some occasions,[10] but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases.

We find it useful to assess the severity and effects of migraine by asking about time lost because of migraine at work or school, in performing household work or chores, or in family, social, and leisure activities. One can ask patients directly about temporary disability, have them keep a diary, or get a quick but accurate estimate with the use of the Migraine Disability Assessment Scale (MIDAS) (Table 2), a well-validated five-item questionnaire that is easy to use in practice.[11]

Although attacks of migraine may start at any age, the incidence peaks in early to mid-adolescence. In the United States and Western Europe, the one-year prevalence of migraine is 11 percent overall: 6 percent among men and 15 to 18 percent among women.[12-14] The median frequency of attacks is 1.5 per month, and the median duration of an attack is 24 hours; at least 10 percent of patients have weekly attacks, and

TABLE 1. MODIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE.*

Migraine is defined as episodic attacks of headache lasting 4 to 72 hr
With two of the following symptoms:
Unilateral pain
Throbbing
Aggravation on movement
Pain of moderate or severe intensity
And one of the following symptoms:
Nausea or vomiting
Photophobia or phonophobia

*Criteria are those specified for migraine without aura by the International Headache Society.[6,7]

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TABLE 2. MIGRAINE DISABILITY ASSESSMENT SCALE (MIDAS) QUESTIONNAIRE.*

Instructions: Please answer the following questions about all the headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months. (Please refer to the calendar below, if necessary.)	
1. On how many days in the last 3 months did you miss work or school because of your headaches?	□□ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)	□□ days
3. On how many days in the last 3 months did you not do household work because of your headaches?	□□ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)	□□ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?	□□ days
A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than one day, count each day.)	□□ days
B. On a scale of 0–10, on average how painful were these headaches (where 0=no pain at all, and 10=pain as bad as it can be)?	□□

*The questionnaire is from Stewart et al.[11]

20 percent have attacks lasting two to three days.[12] Thus, 5 percent of the general population have at least 18 days of migraine per year, and at least 1 percent — that is, more than 2.5 million persons in North America — have at least 1 day of migraine per week. The lifetime prevalence of migraine is at least 18 percent,[13] although among older subjects the figures are deflated by recall bias. In the United States, most patients with migraine have not seen a physician for headache during the previous year, have never received a medical diagnosis of migraine, and use over-the-counter medications to the exclusion of prescription drugs.[15] A recent survey by the World Health Organization (WHO) rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders.[16] This ranking suggests that in the judgment of the WHO, a day with severe migraine is as disabling as a day with quadriplegia.

PATHOPHYSIOLOGY

Migraine is best understood as a primary disorder of the brain.[17] It is a form of neurovascular headache: a disorder in which neural events result in the dilation of blood vessels, which, in turn, results in pain and further nerve activation.[18] Migraine is not caused by a primary vascular event. Migraine attacks are episodic and vary within and among patients. We may best explain this variability by considering the basic biologic problem in migraine to be the dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels.[17]

In patients with familial hemiplegic migraine, missense mutations in the α_1 subunit of the voltage-gated P/Q-type calcium channel have been identified.[19] It is possible that other ion-channel mutations contribute to migraine without aura, since it is primarily cases of migraine with aura that have been linked to the familial-hemiplegic-migraine locus.[20] It thus seems possible that the aura of migraine is separate from the headache,[21] with aura susceptibility genes as its determinant[22]; the pain and associated features of migraine itself may be determined by another gene or genes.

Migraine and the Brain

As noted above, migraine probably results from a dysfunction of brain-stem or diencephalic nuclei that are involved in the sensory — particularly nociceptive — modulation of craniovascular afferents. Activation in the brain stem during attacks of migraine has been detected with the use of positron-emission tomography.[23,24] Moreover, the aura of migraine is likely to be the human counterpart of the animal phenomenon of Leão's spreading depression.[25] Aura is characterized by a wave of oligemia that passes across the cortex[26-29] at the characteristically slow rate of 2 to 6 mm per minute.[30] A short phase of hyperemia precedes this oligemia[31] and is likely to be a correlate of such symptoms as flashing, jagged lights. Oligemia is a response to depressed neuronal function and is still clearly present when the headache starts.[29,32] These findings, together with direct evidence that the local oxygen supply is more than adequate,[33] make the notion that migraine is simply a vascular headache untenable (Fig. 1).

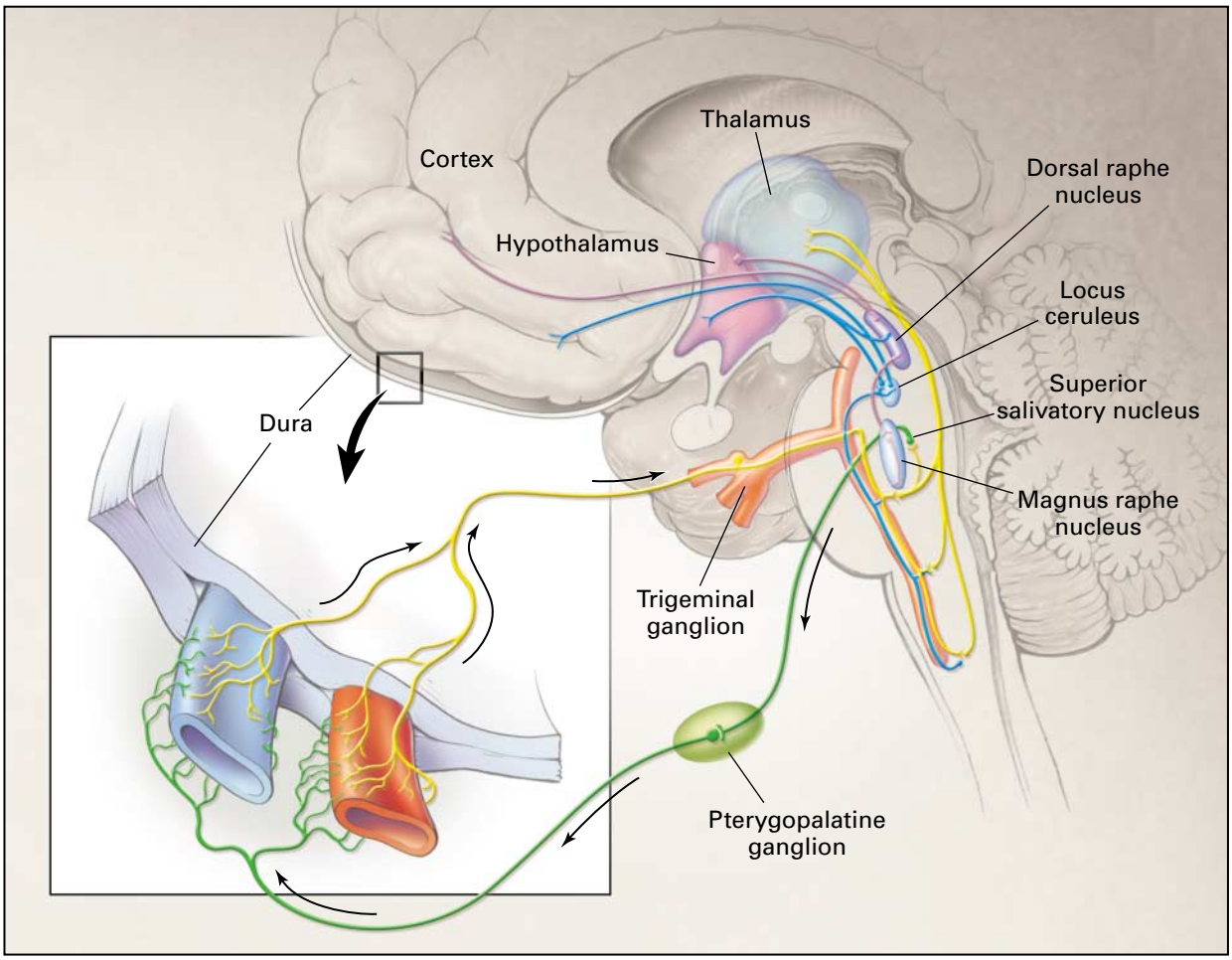

Figure 1. Pathophysiology of Migraine.

Migraine involves dysfunction of brain-stem pathways that normally modulate sensory input. The key pathways for the pain are the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex. These neurons, in turn, project through the quintothalamic tract, and after decussating in the brain stem, form synapses with neurons in the thalamus. There is a reflex connection between neurons in the pons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal–autonomic reflex is present in normal persons[34] and is expressed most strongly in patients with trigeminal–autonomic cephalgias, such as cluster headache and paroxysmal hemicrania; it may be active in migraine. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus.

Pain Mechanisms

We do not completely understand the pathogenesis of pain in migraine, but three key factors merit consideration: the cranial blood vessels, the trigeminal innervation of the vessels, and the reflex connections of the trigeminal system with the cranial parasympathetic outflow. The substance of the brain is largely insensate; pain can be generated by large cranial vessels,[35] proximal intracranial vessels,[36,37] or by the dura mater.[38-40] These vessels are innervated by branches of the ophthalmic division of the trigeminal nerve,[40] whereas the structures of the posterior fossa are innervated by branches of the C2 nerve roots.[41]

In nonhuman primates, stimulation of vascular afferents leads to the activation of neurons in the superficial layers of the trigeminal nucleus caudalis in the region of the cervicomedullary junction and the superficial layers of the dorsal horns of the C1 and

C2 levels of the spinal cord[42,43] — the trigeminocervical complex. Similarly, stimulation of branches of C2 activates neurons in the same regions of the brain.[44-46] The involvement of the ophthalmic division of the trigeminal nerve and the overlap with structures innervated by C2 explain the common distribution of migraine pain over the frontal and temporal regions, as well as the involvement of parietal, occipital, and high cervical regions by what is, in essence, referred pain.

Peripheral trigeminal activation in migraine is evidenced by the release of calcitonin-gene–related peptide, a vasodilator,[47] but the mechanism of the generation of pain is not clear. Studies in animals suggest that the pain may be caused by a sterile neurogenic inflammatory process in the dura mater,[48] but this mechanism has no clearly demonstrated correlate in humans.[49] The pain may be a combination of an altered perception — as a result of peripheral or central sensitization — of craniovascular input that is not usually painful[34] and the activation of a feed-forward neurovascular dilator mechanism that is functionally specific for the first (ophthalmic) division of the trigeminal nerve.[50]

DRUG THERAPY

Approaches to treating migraine can be divided into nonpharmacologic therapies and pharmacologic therapies. Nonpharmacologic therapies include education of the patient about the disorder, its mechanisms, approaches to treatment, and changes in lifestyle involved in the avoidance of triggers of migraine. In patients with migraine, the brain does not seem to tolerate the peaks and troughs of life well. Thus, regular sleep, regular meals, exercise, avoidance of peaks of stress and troughs of relaxation, and avoidance of dietary triggers can be helpful. The crucial message is that the patient should aim for a certain regularity of habits, rather than adhere to a long list of prohibitions of foods and activities. What cannot be known is the sensitivity of the brain to such triggers at any given time. This uncertainty leaves many patients frustrated by the fact that the same manipulations intended to avoid triggering migraine will lead to different outcomes on different days. It can be helpful to explain the nature of this variability to patients. An evidence-based review of nonpharmacologic approaches to treatment of migraine was recently published.[51]

Drugs for the treatment of migraine can be divided into drugs that are taken daily whether or not headache is present to reduce the frequency and severity of attacks[52] and drugs that are taken to treat attacks as they arise. Treatments for attacks can be further divided into nonspecific and migraine-specific treatments. Nonspecific treatments, such as aspirin, acetaminophen, nonsteroidal antiinflammatory drugs, opiates, and combination analgesics, are used to treat a wide range of pain disorders. Specific treatments,[7] including ergotamine, dihydroergotamine, and the triptans, are effective for treating neurovascular headaches, such as migraine and cluster headache, but not for treating other types of pain, such as pure tension-type headache[53] or atypical facial pain.[54] Given that there are responses to placebo in patients with migraine,[55] that there is a significant rate of nonresponse to oral drugs, and that triptans have not been studied systematically in patients with such problems as subarachnoid hemorrhage or meningitis, triptans should not be used as diagnostic testing agents in patients with headache.

PREVENTIVE THERAPY

The decision to start a preventive therapy in a patient with migraine is best made collaboratively. On the basis of a combination of the frequency, duration, severity, and tractability of acute attacks, as well as the preference of the patient, a sensible selection can be made. Patients who have attacks that are unresponsive to acute-attack medications and that cause substantial disability are candidates for preventive therapy. If attacks occur at least twice a month, if the patient may be at risk for rebound headache, or if the migraine diary kept by the patient reveals a clear trend toward an increasing frequency of attacks, it is probably better to consider prevention than to wait for the problem to become more troublesome. It is not clear how preventive therapy works, although it seems likely that it modifies the sensitivity of the brain that underlies migraine.

In general, if headaches occur one to two days per month, there is usually no need for preventive therapy; if they occur three to four days per month, preventive therapy should be considered; if the patient has five or more attacks per month, preventive therapy should be considered seriously. The available options are listed in Table 3, and the evidence regarding their use has been extensively reviewed.[50] Often, the doses required to reduce the frequency of headache cause marked and intolerable side effects. Each drug should be started at a low dose, and the dose should be gradually increased to a reasonable maximum; patients should be reminded that this approach often entails some delay in achieving efficacy.

On average, about two thirds of the patients given any of the drugs listed in Table 3 will have a 50 percent reduction in the frequency of headaches. It is our practice to explain the side effects of these drugs and engage the patient in the decision-making process. We avoid methysergide, at least initially, because of its fibrotic complications,[58,59] and we carefully explain the teratogenicity of divalproex (valproate).[60]

TABLE 3. PREVENTIVE THERAPY FOR MIGRAINE.*

DRUG	DOSE	SELECTED SIDE EFFECTS
Proven or well accepted		
β-Adrenergic–receptor antagonists		
Propranolol	40–120 mg twice daily	Reduced energy, tiredness, postural symptoms; contraindicated in patients with asthma
Metoprolol	100–200 mg daily	
Amitriptyline	25–75 mg at bedtime†	Drowsiness
Divalproex (valproate)	400–600 mg twice daily	Drowsiness, weight gain, tremor, hair loss, fetal abnormalities, hematologic and liver abnormalities
Flunarizine	5–15 mg daily	Tiredness, weight gain, depression, parkinsonism
Serotonin antagonists		
Pizotyline (pizotifen)	0.5–3 mg daily	Drowsiness, weight gain
Methysergide‡	1–6 mg daily	Drowsiness, leg cramps, hair loss, retroperitoneal fibrosis
Widely used but with poor evidence of benefit		
Verapamil	160–320 mg daily	Constipation, leg swelling, atrioventricular conduction disturbances
Selective serotonin-reuptake inhibitors		Anxiety, insomnia
Promising§		
Gabapentin	900–2400 mg daily	Tiredness, dizziness
Topiramate	25–200 mg daily	Confusion, paresthesias, weight loss

*Commonly used preventive therapies are listed with reasonable doses and common side effects. Local prescribing information should be consulted before use.

†In some patients, only 10 mg is needed, although often 1 mg/kg of body weight is required.

‡Treatment must be discontinued for one month every six months.

§There have been positive placebo-controlled studies of these drugs,[56,57] but more data are required.

TREATMENT OF ACUTE ATTACKS

Analgesic and Nonsteroidal Antiinflammatory Drugs

In many patients, migraine responds well to simple treatment at the time of an attack. There are several key features of the successful use of such treatments, after the preference of the patient and any contraindications have been taken into consideration. The drug should be taken as soon as the headache component of the attack is recognized.[61] The dose of drug should be adequate; for example, 900 mg of aspirin,[62,63] 1000 mg of acetaminophen,[64] 500 to 1000 mg of naproxen,[65] 400 to 800 mg of ibuprofen,[66] or appropriate doses of a combination of these drugs.[67,68] The administration of antiemetic drugs or drugs that increase gastric motility is likely to facilitate the absorption of the primary drug and thus help to ameliorate the attack.[63,69,70] Overuse of these drugs should be avoided; for example, intake should be restricted to no more than two to three days a week, and a headache diary should be kept and monitored for any escalation in drug use. It is important to remember that the severity of migraine attacks and their response to treatment may vary; patients may therefore require only one drug for some attacks but several drugs for more bothersome attacks.

As a rule, we avoid the use of opiates. These drugs seem to mask the pain without suppressing the pathophysiologic mechanism of the attack, often leaving the patient cognitively impaired. Their use may lead to addiction, and for most patients, they offer no advantages over more migraine-specific therapy.

Ergot Derivatives

The main advantages of the ergotamine and dihydroergotamine ergot derivatives are their low cost and the long experience with their use.[71,72] The major disadvantages are their complex pharmacology, their erratic pharmacokinetics, the lack of evidence regarding effective doses, their potent and sustained generalized vasoconstrictor effects, which are associated with adverse vascular events, and the high risk of overuse syndromes and rebound headaches.[72]

The Triptans

In comparison with the ergot derivatives, the triptans (Table 4) have distinct advantages — notably, selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescription instructions, established efficacy based on well-designed controlled trials, moderate side effects, and a well-established safety record.[5,87] The most important disadvantages of the triptans are their higher cost and the restrictions on their use in the presence of cardiovascular disease.

Pharmacology and Mechanisms of Action

The triptans are serotonin 5-$HT_{1B/1D}$–receptor agonists. They were discovered[88] as a result of studies of serotonin and migraine[89-93] that led to the identification of an atypical 5-HT receptor. Activation of the novel receptor can close cranial arteriovenous anastomoses,[94] and its anatomical distribution is restricted in vivo.[95] Seven major subclasses of 5-HT receptors — classes 1 through 7 — are now recognized.[96,97] The triptans all activate the 5-$HT_{1B/1D}$ receptor and, to a lesser extent, the 5-HT_{1A} or 5-HT_{1F} receptor. It is likely that the 5-$HT_{1B/1D}$–agonist activity is the primary mechanism of the therapeutic effects of these drugs, although a therapeutic action at the 5-HT_{1F} receptor has not been excluded.[98] Exclusively 5-HT_{1D}–mediated effects were studied with the use of PNU142633,[99] but the results were inconclusive.[100] This compound, which has exclusively neural action, produced some chest symptoms remarkably similar to those that occur with triptans.[101] We define a triptan as a 5-$HT_{1B/1D}$–receptor agonist.[102]

Triptans have three potential mechanisms of action: cranial vasoconstriction,[88] peripheral neuronal inhibition,[48] and inhibition of transmission through second-order neurons of the trigeminocervical complex.[102] Which mechanism is the most important is as yet unclear.[103] These actions inhibit the effects of activated nociceptive trigeminal afferents and, in this way, control acute attacks of migraine (Fig. 2).

There are five triptans in routine clinical use: sumatriptan, naratriptan, rizatriptan, zolmitriptan, and almotriptan. Eletriptan was recently approved in Europe; frovatriptan is awaiting approval; and donitriptan is in preclinical development.[104] During migraine attacks, the oral absorption of many drugs is delayed,[69] so there may be an advantage to nonoral methods of administration, such as the use of nasal sprays, inhalers, suppositories, or injections. Most patients, however, prefer oral formulations,[105] which account for 80 percent of all triptan prescriptions; we therefore focus on the oral formulations. Sumatriptan is also available in subcutaneous,[106] rectal,[107] and intranasal[108] formulations; these will be discussed separately. The pharmacokinetic properties of the triptans are summarized in Table 4.

Safety and Tolerability

It is crucial to distinguish between safety and tolerability in discussing studies of treatments for acute migraine. Tolerability refers to the extent of medically unimportant but clinically irritating side effects of drugs, such as tingling, flushing, and sensations of pressure; safety is assessed on the basis of records of medically important side effects. Because the latter type of effects may be rare, safety is best assessed after large-scale clinical exposure. The triptans differ from one another in terms of tolerability but not in terms of safety. The most frequent side effects are tingling, paresthesias, and sensations of warmth in the head, neck, chest, and limbs; less frequent are dizziness, flushing, and neck pain or stiffness. Triptans can constrict coronary arteries and may cause chest symp-

TABLE 4. PHARMACOKINETIC CHARACTERISTICS OF TRIPTANS.*

VARIABLE	SUMATRIPTAN	ALMOTRIPTAN	ELETRIPTAN	FROVATRIPTAN	NARATRIPTAN	RIZATRIPTAN	ZOLMITRIPTAN
Half-life (hr)	2.0	3.5	5.0	25.0	5.0–6.3	2.0	3.0
Time to maximal concentration (hr)							
During attacks	2.5	2.0–3.0	2.8	3.0	—	1.0	4.0
At other times	2.0	1.4–3.8	1.4–1.8	3.0	2.0–3.0	1.0	1.8–2.5
Oral bioavailability (%)	14	69	50	24–30	63–74	40	40
Metabolism and excretion							
Primary route	MAO	CYP450 and MAO	CYP3A4	Renal, 50%	Renal, 70%	MAO	CYP450
Secondary route	—	—	—	—	CYP450	—	MAO

*Data are derived from multiple studies.[73-86] MAO denotes monoamine oxidase, CYP450 cytochrome P450, and CYP3A4 the 3A4 isoform of cytochrome P450.

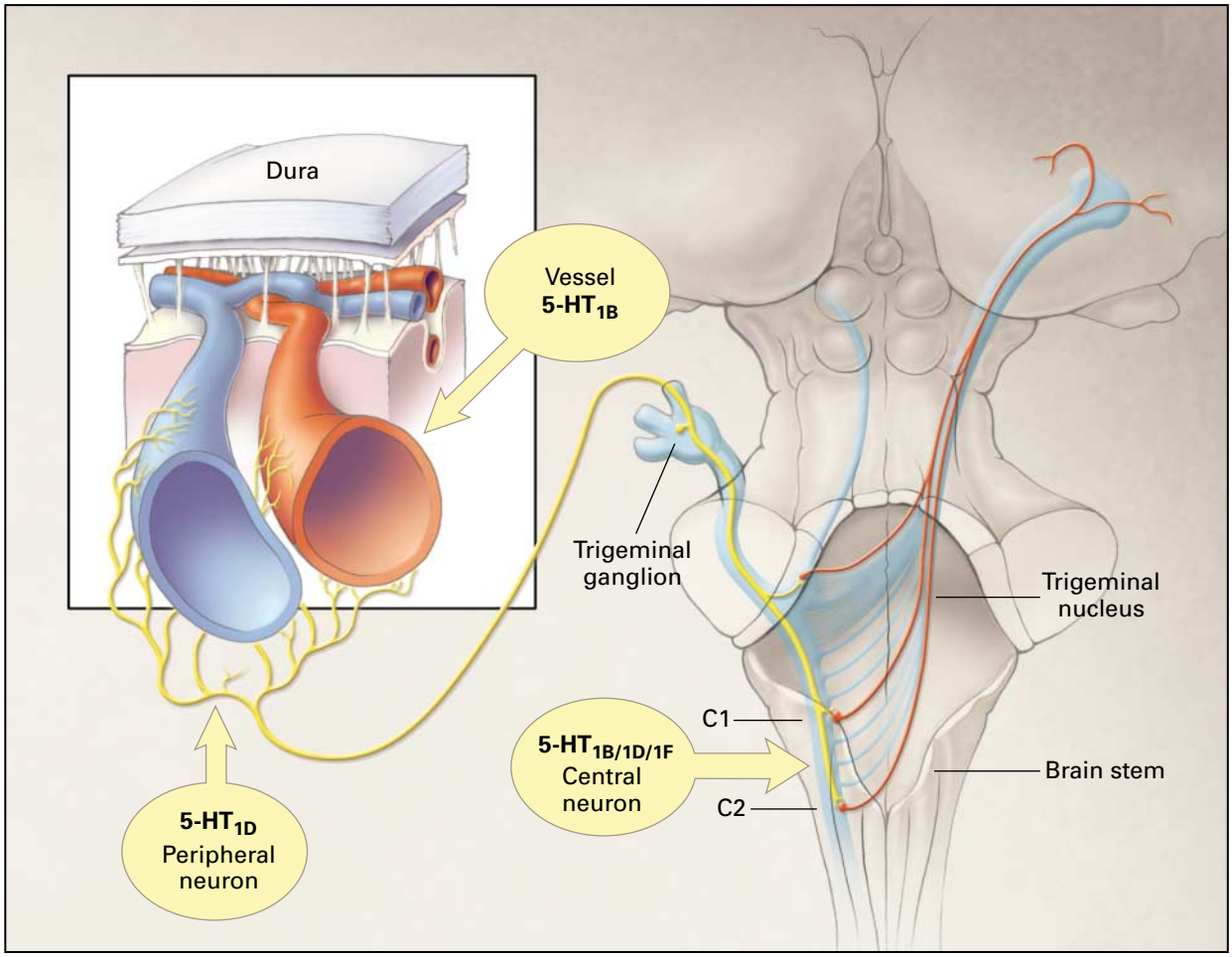

Figure 2. Possible Sites of Action of Triptans in the Trigeminovascular System.

toms, sometimes closely mimicking angina pectoris. Such symptoms may cause alarm, so the cardiovascular issues warrant discussion. When patients are warned about these symptoms, they rarely cause problems.

In rare instances, however, triptan therapy has been associated with myocardial infarction.[87] There has thus been general concern about the safety of triptans. This concern is supported by in vitro pharmacologic studies that demonstrate the potential of the triptans to constrict the coronary vessels of humans, although ergotamine and dihydroergotamine have a more potent and longer-lasting effect than the triptans.[109] It is clear from anatomical studies using antibodies selective for human 5-HT_{1B} or 5-HT_{1D} receptors[110] that 5-HT_{1B} receptors are located primarily in the cranial circulation but are also found in the coronary circulation.[111] There have been relatively few reports of clinically important myocardial ischemia or infarction, despite the now very substantial human exposure to triptans, particularly to sumatriptan.[87] However, all triptans are 5-HT_{1B} agonists, and thus the sensible contraindications of ischemic heart disease, uncontrolled hypertension, and cerebrovascular disease apply to the entire class.

META-ANALYSIS OF STUDIES OF ORAL TRIPTAN THERAPY

Most trials of triptans have been similar in design[112] and in the population of patients studied — factors that facilitate meta-analysis. We recently performed such a meta-analysis, using data from 24,089 patients in 53 controlled clinical trials of triptans.[113,114]

We subtracted the rate of response in the placebo group from that in the active-drug group and used this difference, the therapeutic gain, as another means of comparing the results of the trials.[115] All doses of all drugs have been compared with the standard of sumatriptan at a dose of 100 mg.

Improvement at Two Hours

The headache (pain) response at two hours was the primary end point in nearly all trials of triptans. As compared with 100 mg of sumatriptan, 10 mg of rizatriptan and 80 mg of eletriptan were significantly more effective, whereas 2.5 mg of naratriptan, 20 mg of eletriptan, and 2.5 mg of frovatriptan were less effective (data were obtained from abstracts only) (Fig. 3A).

Although the freedom from pain is the currently recommended primary end point,[116] it was a secondary end point in most trials. In terms of this end point, 80 mg of eletriptan, 12.5 mg of almotriptan, and 10 mg of rizatriptan were more effective than 100 mg of sumatriptan, whereas 25 mg of sumatriptan, 2.5 mg of naratriptan, and 20 mg of eletriptan were less effective than 100 mg of sumatriptan (Fig. 3B).

Sustained Freedom from Pain

The percentages of patients with sustained freedom from pain (freedom from pain at 2 hours with no rescue medication and with no recurrence of headache within 24 hours) are shown in Figure 4. These rates were higher with 10 mg of rizatriptan, 80 mg of eletriptan, and 12.5 mg of almotriptan than with 100 mg of sumatriptan, and lower with 20 mg of eletriptan than with 100 mg of sumatriptan.

Intrapatient Consistency of Response

Efficacy in at least two out of three treated attacks can be considered a reasonable estimate of consistency. Such consistency was found in 67 percent of patients given 100 mg of sumatriptan and 65 percent of those given 50 mg of sumatriptan. The consistency of 10 mg of rizatriptan was evaluated in a novel double-blind, crossover study encompassing four attacks in each patient, with placebo given during one randomly chosen attack in four of five groups of patients; the fifth group received 10 mg of rizatriptan for each of four attacks.[117] The unusual design, with the inclusion of placebo, makes it difficult to compare this study with others, but it seems unlikely that the inclusion of placebo would increase consistency. The rates of consistency in the three attacks for which patients received rizatriptan were the highest for any of the triptans; the rates of response and freedom from pain were 86 percent and 48 percent, respectively, in at least two out of three attacks and 60 percent and 20 percent, respectively, in three of three attacks.

Tolerability

Differences among studies in the methods of collecting data on adverse events and in the definitions of such events complicate comparisons. The rates of adverse events with most triptans other than sumatriptan overlap with those found with 100 mg of sumatriptan; there were lower values for 2.5 mg of naratriptan and 12.5 mg of almotriptan. The rates in the latter instances did not differ from those found with placebo.

Direct Comparisons

In general, trials involving direct comparisons provide the optimal comparison between drugs, although encapsulation of treatments, selection bias, and population size may influence results. Some direct comparisons between triptans have been conducted, and the overall results of those to which we had access were consistent with the results of the studies of single triptans.[113] Comparisons between the main pharmacologic and clinical characteristics of the new oral triptans and those of 100 mg of oral sumatriptan are summarized in Table 5; information on these characteristics is derived from a synthesis of both types of studies.[113]

Parenteral Sumatriptan

Subcutaneous sumatriptan, at a dose of 6 mg, has the best pharmacokinetic profile (time to maximal concentration, 10 minutes; bioavailability, 96 percent),[118] clinical efficacy (a response rate of 76 percent and a rate of freedom from pain of 48 percent at 60 minutes after administration),[106] and intrapatient consistency in multiple attacks (up to 90 percent).[119] The main limitations are that patients must inject themselves and that the incidence of adverse events is higher and their intensity is greater than with oral sumatriptan. This adverse-event profile may be related to the fixed 6-mg dose, among other factors, since 3 to 4 mg may suffice in many patients.[120] Subcutaneous sumatriptan is also highly effective in the treatment of acute attacks of cluster headache.[121] The efficacy and tolerability profiles of rectal and intranasal sumatriptan are very similar to those of the oral formulation.[107,108] These formulations may be useful in patients with nausea. Intranasal sumatriptan in a dose of 20 mg is the only triptan with demonstrated efficacy in adolescents,[122,123] in whom migraine attacks are usually of relatively short duration and are associated with more prominent gastrointestinal symptoms and a high rate of response to placebo.[124,125]

SELECTING INITIAL TREATMENT FOR ACUTE ATTACKS

Migraine is a heterogeneous disorder, so the selection of initial treatment for acute attacks depends on the severity and frequency of the attacks, the associ-

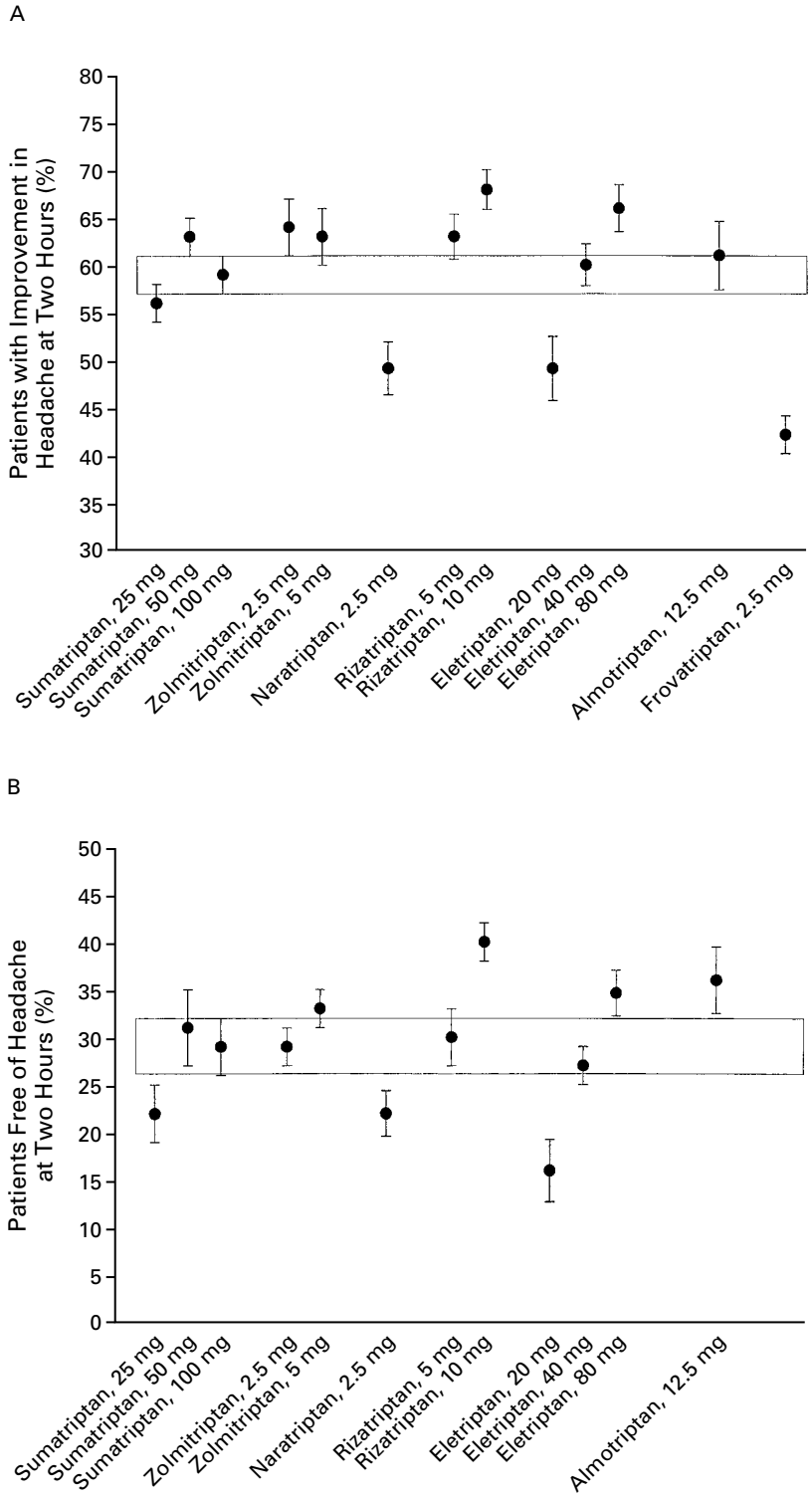

Figure 3. Effects of the Various Triptans in Patients with Migraine.

The mean rates and 95 percent confidence intervals of improvement in headache pain at two hours (Panel A) and freedom from headache pain at two hours (Panel B) are shown for each triptan at each dose tested. The box represents the 95 percent confidence interval for 100 mg of sumatriptan — the reference treatment. Adapted from Ferrari et al.[113]

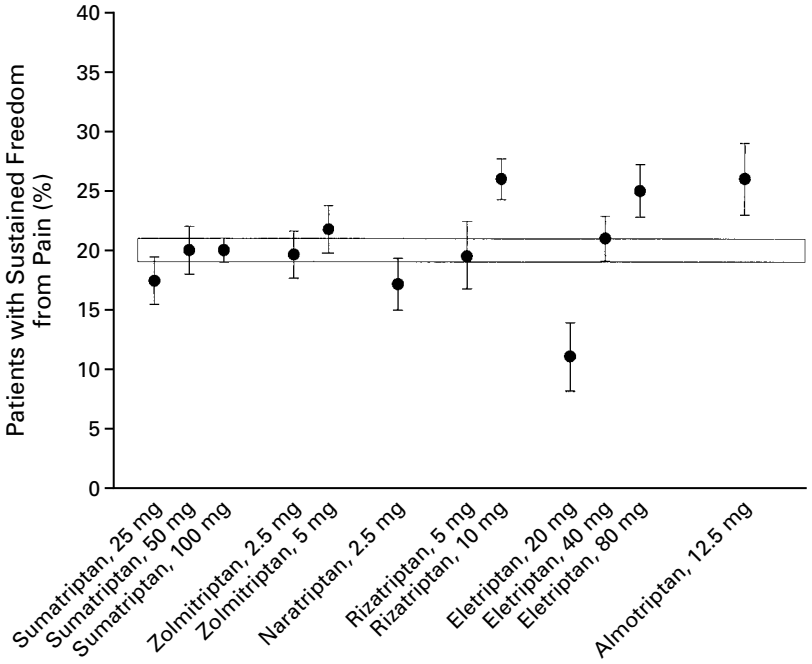

Figure 4. Effects of the Various Triptans in Inducing Sustained Freedom from Headache Pain.

The mean rates and 95 percent confidence intervals of sustained freedom from headache pain (defined as freedom from pain at 2 hours, no use of rescue medication, and no recurrence of headache within 24 hours) are presented. The box represents the 95 percent confidence interval for 100 mg of sumatriptan.

TABLE 5. PHARMACOLOGIC AND CLINICAL CHARACTERISTICS OF ORAL TRIPTANS, IN COMPARISON WITH 100 mg OF SUMATRIPTAN.*

DRUG AND DOSE	PHARMACOKINETIC PROFILE†	RELIEF AT 2 HR	SUSTAINED FREEDOM FROM PAIN	CONSISTENCY OF EFFECT‡	TOLERABILITY
Sumatriptan					
50 mg	=	=	=	= or −	=
25 mg	=	−	= or −	−	+
Zolmitriptan					
2.5 mg	+	=	=	=	=
5 mg	+	=	=	=	=
Naratriptan, 2.5 mg	+	−	−	−	++
Rizatriptan					
5 mg	+	=	=	=	=
10 mg	+	+	+	++	=
Eletriptan					
20 mg	+	−	−	−	=
40 mg	+	= or +	= or +	=	=
80 mg	+	+ (+)	+	=	−
Almotriptan, 12.5 mg	+	=	+	+	++

*An equals sign indicates a similar value to that associated with 100 mg of sumatriptan; a plus sign indicates superiority to 100 mg of sumatriptan (and a double plus sign indicates considerable superiority); a minus sign indicates inferiority to 100 mg of sumatriptan.

†The pharmacokinetic profile includes bioavailability and the time to maximal concentration during attacks.

‡The unusual design of the study involving rizatriptan makes it difficult to compare the consistency of its effect with the consistency of the effects of the other drugs.

ated symptoms, the preference of the patient, and the history of treatment. In patients with little headache-related disability, it is usually appropriate to initiate treatment with one or more analgesic drugs and to escalate treatment as needed. In a recent clinical trial, the probability of successful treatment with aspirin and metoclopramide decreased as the severity of headache-related disability increased. Among the most disabled 25 percent of patients (MIDAS grade IV[126]), the attacks were controlled successfully with a combination of aspirin and metoclopramide in only 26 percent of the patients.[127] It is critical to establish realistic expectations and to advise patients to seek follow-up care if treatment fails. In patients with substantial disability, it is appropriate to prescribe a triptan early in the course of treatment, in keeping with a stratified approach to care.[127]

THE FUTURE OF MIGRAINE TREATMENT

Although the triptans represent an important advance, they are ineffective in some patients. A crucial improvement would be a treatment for acute attacks that had no vascular effects — in other words, an antimigraine treatment with exclusively neural action.

If the hypothesis that neurogenic inflammation caused the pain was correct, selective neuronally active compounds with peripheral action should be effective.[128] Unfortunately, antagonists of neurokinin-1 receptors (which mediate the biologic actions of substance P),[129-133] an endothelin antagonist,[134] a neurosteroid,[135] and two specific inhibitors of the extravasation of plasma protein (CP122,288[136] and 4991W93[137]) have proved ineffective in clinical trials. The selective 5-HT_{1F}–receptor agonist LY334370[98] was effective, but it may act on both peripheral and central trigeminal targets.[102] However, purely neural compounds do work. The α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid–kainate antagonist LY293558[138] and GR79236, a selective adenosine-A_1–receptor agonist,[139,140] have proved effective in acute attacks of migraine. Another nonvascular approach would be to block the effects of calcitonin-gene–related peptide,[47] and suitable compounds that do so are now available.[141] Another approach is blockade of nitric oxide synthesis, which has proved effective in one preliminary study.[142]

There are novel clinical-trial designs and end points that are expected to reflect clinical practice more accurately. These end points include efficacy over the course of multiple attacks (intrapatient consistency), sustained freedom from pain over a 24-hour period, and the preference of the patient. Furthermore, so-called ASAP (as soon as possible) trials, in which patients are allowed to treat their attacks as soon as they are sure migraine is developing, will better reflect the nature of migraine treatment in real life.[143]

Finally, patients prefer not to have attacks at all. Current prophylactic therapies for migraine are relatively nonspecific, their efficacy is moderate, and they have substantial side effects.[52] Studying the mechanisms involved in the onset of migraine[23,24] and the predisposition to attacks[144] is likely to lead to more specific, more efficacious, and better-tolerated prophylactic drugs. We are very optimistic about the future for persons with migraine.

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REFERENCES

1. Lance JW, Goadsby PJ. Mechanism and management of headache. 6th ed. Boston: Butterworth–Heinemann, 1998.
2. Silberstein SD, Lipton RB, Goadsby PJ. Headache in clinical practice. Oxford, England: Isis Medical Media, 1998.
3. Goadsby PJ, Silberstein SD, eds. Headache. Vol. 17 of Blue books of practical neurology. Boston: Butterworth–Heinemann, 1997.
4. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. Headache 2001;41:638-45.
5. Olesen J, Tfelt-Hansen P, Welch KMA. The headaches. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000.
6. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1998;8:Suppl 7:1-96.
7. Goadsby PJ, Olesen J. Diagnosis and management of migraine. BMJ 1996;312:1279-83.
8. Lance JW. Headache and face pain. Med J Aust 2000;172:450-5.
9. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992;12:221-8.
10. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-42.
11. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the Migraine Disability Assessment score in a population-based sample of headache sufferers. Cephalalgia 1999;19:107-14.
12. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race and other sociodemographic factors. JAMA 1992;267:64-9.
13. Rasmussen BK, Olesen J. Symptomatic and nonsymptomatic headaches in a general population. Neurology 1992;42:1225-31.
14. Steiner TJ, Stewart WF, Kolodner K, Liberman J, Lipton RB. Epidemiology of migraine in England. Cephalalgia 1999;19:305-6. abstract.
15. Lipton RB, Stewart WF, von Korff M. Burden of migraine: societal costs and therapeutic opportunities. Neurology 1997;48:Suppl 3:S4-S9.
16. Menken M, Munsat TL, Toole JF. The Global Burden of Disease Study: implications for neurology. Arch Neurol 2000;57:418-20.
17. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. Wolff's headache and other head pain. 7th ed. Oxford, England: Oxford University Press, 2001:57-72.
18. May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab 1999;19:115-27.
19. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4. Cell 1996;87:543-52.
20. Terwindt GM, Ophoff RA, van Eijk R, et al. Involvement of the

CACNA1A gene containing region on 19p13 in migraine with and without aura. Neurology 2001;56:1028-32.
21. Gowers WR. A manual of diseases of the nervous system. Philadelphia: P. Blakiston, 1888.
22. Goadsby PJ. Migraine, aura, and cortical spreading depression: why are we still talking about it? Ann Neurol 2001;49:4-6.
23. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. Nat Med 1995;1:658-60.
24. Bahra A, Matharu MS, Buchel C, Frackowiak RSJ, Goadsby PJ. Brainstem activation specific to migraine headache. Lancet 2001;357:1016-7.
25. Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944;7:359-90.
26. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344-52.
27. Woods RP, Iacoboni M, Mazziotta JC. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med 1994; 331:1689-92.
28. Sanchez del Rio M, Bakker D, Wu O, et al. Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia 1999;19:701-7.
29. Cutrer FM, Sorensen AG, Weisskoff RM, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol 1998;43: 25-31.
30. Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain 1994;117:199-210.
31. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 2001;98:4687-92.
32. Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 1990;28:791-8.
33. Cao Y, Welch KMA, Aurora S, Vikingstad EM. Functional MRI-BOLD of visually triggered headache in patients with migraine. Arch Neurol 1999;56:548-54.
34. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol 2000;47: 614-24.
35. McNaughton FL, Feindel WH. Innervation of intracranial structures: a reappraisal. In: Rose FC, ed. Physiological aspects of clinical neurology. Oxford, England: Blackwell Scientific, 1977:279-93.
36. Martins IP, Baeta E, Paiva T, Campos J, Gomes L. Headaches during intracranial endovascular procedures: a possible model of vascular headache. Headache 1993;33:227-33.
37. Nichols FT III, Mawad M, Mohr JP, Hilal S, Adams RJ. Focal headache during balloon inflation in the vertebral and basilar arteries. Headache 1993;33:87-9.
38. Cushing H. The sensory distribution of the fifth cranial nerve. Bull Johns Hopkins Hosp 1904;15:213-32.
39. Penfield W, McNaughton F. Dural headache and innervation of the dura mater. Arch Neurol Psychiatry 1940;44:43-75.
40. Feindel W, Penfield W, McNaughton F. The tentorial nerves and localization of intracranial pain in man. Neurology 1960;10:555-63.
41. Arbab MA-R, Wiklund L, Svendgaard NA. Origin and distribution of cerebral vascular innervation from superior cervical, trigeminal and spinal ganglia investigated with retrograde and anterograde WGA-HRP tracing in the rat. Neuroscience 1986;19:695-708.
42. Hoskin KL, Zagami A, Goadsby PJ. Stimulation of the middle meningeal artery leads to bilateral Fos expression in the trigeminocervical nucleus: a comparative study of monkey and cat. J Anat 1999;194:579-88.
43. Goadsby PJ, Hoskin KL. The distribution of trigeminovascular afferents in the nonhuman primate brain *Macaca nemestrina*: a c-fos immunocytochemical study. J Anat 1997;190:367-75.
44. Kerr FWL. A mechanism to account for frontal headache in cases of posterior-fossa tumors. J Neurosurg 1961;18:605-9.
45. Goadsby PJ, Knight YE, Hoskin KL. Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. Pain 1997;73:23-8.
46. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve (GON) enhances responses of dural responsive convergent neurons in the trigemino-cervical complex in the rat. Cephalalgia 2001;21:401-2. abstract.
47. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 1990;28:183-7.
48. Moskowitz MA, Cutrer FM. Sumatriptan: a receptor-targeted treatment for migraine. Annu Rev Med 1993;44:145-54.
49. May A, Shepheard S, Wessing A, Hargreaves RJ, Goadsby PJ, Diener HC. Retinal plasma extravasation in animals but not in humans: implications for the pathophysiology of migraine. Brain 1998;121:1231-7.
50. May A, Buchel C, Turner R, Goadsby PJ. Magnetic resonance angiography in facial and other pain: neurovascular mechanisms of trigeminal sensation. J Cereb Blood Flow Metab 2001;21:1171-6.
51. Silberstein SD, Rosenberg J. Multispecialty consensus on diagnosis and treatment of headache. Neurology 2000;54:1553.
52. Welch KMA. Drug therapy of migraine. N Engl J Med 1993;329: 1476-83.
53. Lipton RB, Stewart WF, Cady R, et al. 2000 Wolfe Award: sumatriptan for the range of headaches in migraine sufferers: results of the Spectrum Study. Headache 2000;40:783-91.
54. Harrison SD, Balawi SA, Feinmann C, Harris M. Atypical facial pain: a double-blind placebo-controlled crossover pilot study of subcutaneous sumatriptan. Eur Neuropsychopharmacol 1997;7:83-8.
55. Jhee SS, Salazar DE, Ford NF, Fulmor IE, Sramek JJ, Cutler NR. Monitoring of acute migraine attacks: placebo response and safety data. Headache 1998;38:35-8.
56. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001;41:119-28.
57. Potter DL, Hart DE, Calder CS, Storey JR. A double-blind, randomized, placebo-controlled, parallel study to determine the efficacy of topiramate in the prophylactic treatment of migraine. Neurology 2000;54:Suppl 3:A15. abstract.
58. Graham JR, Suby HI, LeCompte PR, Sadowsky NL. Fibrotic disorders associated with methysergide therapy for headache. N Engl J Med 1966;274:359-68.
59. Graham JR. Cardiac and pulmonary fibrosis during methysergide therapy for headache. Am J Med Sci 1967;254:1-12.
60. Silberstein SD. Divalproex sodium in headache: literature review and clinical guidelines. Headache 1996;36:547-55.
61. Cady RK, Sheftell F, Lipton RB, et al. Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. Clin Ther 2000;22:1035-48.
62. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet 1995;346:923-6.
63. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. Cephalalgia 1984;4:107-11.
64. Lipton RB, Baggish JE, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the nonprescription treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. Arch Intern Med 2000;160:3486-92.
65. Welch KMA. Naproxen sodium in the treatment of migraine. Cephalalgia 1986;6:Suppl 4:85-92.
66. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. Cephalalgia 2000;20:233-43.
67. Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. Arch Neurol 1998;55:210-7.
68. Goldstein J, Hoffman HD, Armellino JJ, et al. Treatment of severe, disabling migraine attacks in an over-the-counter population of migraine sufferers: results from three randomized, placebo-controlled studies of the combination of acetaminophen, aspirin, and caffeine. Cephalalgia 1999;19:684-91.
69. Volans GN. Absorption of effervescent aspirin during migraine. Br Med J 1974;4:265-8.
70. Cottrell J, Mann SG, Hole J. A combination of ibuprofen lysine (IBL) and domperidone maleate (DOM) in the acute treatment of migraine: a double-blind study. Cephalalgia 2000;20:269. abstract.
71. Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus (summary statement): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995;45:585-7.
72. Tfelt-Hansen P, Saxena PR, Dahlof C, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. Brain 2000;123: 9-18.
73. Plosker GL, McTavish D. Sumatriptan: a reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs 1994;47:622-51.
74. Cabarrocas X, Salvà M. Pharmacokinetic and metabolic data on almotriptan, a new antimigraine drug. Cephalalgia 1997;17:421. abstract.

75. Cabarrocas X, Jansat JM, Ferrer P, Luria X. Pharmacokinetics of oral almotriptan during and outside a migraine attack. Cephalalgia 2000;20: 417-8. abstract.
76. Milton KA, Allen MJ, Abel S, et al. The safety, tolerability, pharmacokinetics and pharmacodynamics of oral and intravenous eletriptan, a potent and selective "$5HT_{1D}$-like" receptor partial agonist. Cephalalgia 1997; 17:414. abstract.
77. Morgan P, Rance D, James G, Mitchell R, Milton A. Comparative absorption and elimination of eletriptan in rat, dog and human. Cephalalgia 1997;17:414. abstract.
78. Buchan P, Ward C, Zeig S. Frovatriptan pharmacokinetics are unaffected during a migraine attack. Cephalalgia 1999;19:365. abstract.
79. Buchan P, Keywood C, Ward C. Pharmacokinetics of frovatriptan (VML251/SB 209509) in healthy young and elderly male and female subjects. Cephalalgia 1998;18:410. abstract.
80. Kempsford RD, Baille P, Fuseau E. Oral naratriptan tablets (2.5–10 mg) exhibit dose-proportional pharmacokinetics. Cephalalgia 1997;17: 408. abstract.
81. Fuseau E, Baille P, Kempsford RD. A study to determine the absolute oral bioavailability of naratriptan. Cephalalgia 1997;17:417. abstract.
82. Sciberras DG, Polvino WJ, Gertz BJ, et al. Initial human experience with MK-462 (rizatriptan): a novel 5-HT_{1D} agonist. Br J Clin Pharmacol 1997;43:49-54. [Erratum, Br J Clin Pharmacol 1997;43:450.]
83. Lee Y, Conroy JA, Stepanavage ME, et al. Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. Br J Clin Pharmacol 1999;47:373-8.
84. Seaber E, On N, Phillips S, Churchus R, Posner J, Rolan P. The tolerability and pharmacokinetics of the novel antimigraine compound 311C90 in healthy male volunteers. Br J Clin Pharmacol 1996;41:141-7.
85. Thomsen LL, Dixon R, Lassen LH, et al. 311C90 (zolmitriptan), a novel centrally and peripheral acting oral 5-hydroxytryptamine-1D agonist: a comparison of its absorption during a migraine attack and in a migraine-free period. Cephalalgia 1996;16:270-5.
86. Palmer KJ, Spencer CM. Zolmitriptan. CNS Drugs 1997;7:468-78.
87. Welch KMA, Mathew NT, Stone P, Rosamond W, Saiers J, Gutterman D. Tolerability of sumatriptan: clinical trials and post-marketing experience. Cephalalgia 2000;20:687-95. [Erratum, Cephalalgia 2001;21:164-5.]
88. Humphrey PPA, Feniuk W, Perren MJ, Beresford IJM, Skingle M, Whalley ET. Serotonin and migraine. Ann N Y Acad Sci 1990;600:587-98.
89. Sicuteri F, Testi A, Anselmi B. Biochemical investigations in headache: increase in hydroxyindoleacetic acid excretion during migraine attacks. Int Arch Allergy Appl Immunol 1961;19:55-8.
90. Curran DA, Hinterberger H, Lance JW. Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. Brain 1965;88:997-1010.
91. Anthony M, Hinterberger H, Lance JW. Plasma serotonin in migraine and stress. Arch Neurol 1967;16:544-52.
92. Kimball RW, Friedman AP, Vallejo E. Effect of serotonin in migraine patients. Neurology 1960;10:107-11.
93. Lance JW, Anthony M, Hinterberger H. The control of cranial arteries by humoral mechanisms and its relation to the migraine syndrome. Headache 1967;7:93-102.
94. Johnston BM, Saxena PR. The effect of ergotamine on tissue blood flow and the arteriovenous shunting of radioactive microspheres in the head. Br J Pharmacol 1978;63:541-9.
95. Feniuk W, Humphrey PPA, Perren MJ. The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetized dogs. Br J Pharmacol 1989;96:83-90.
96. Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 1994;46:157-203.
97. Hartig PR, Hoyer D, Humphrey PPA, Martin GR. Alignment of receptor nomenclature with the human genome: classification of 5-HT1B and 5-HT1D receptor subtypes. Trends Pharmacol Sci 1996;17:103-5.
98. Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT_{1F}) receptor agonist LY334370 for acute migraine: a randomised controlled trial. Lancet 2001;358:1230-4.
99. Pregenzer JF, Alberts GL, Im WB, et al. Differential pharmacology between the guinea-pig and the gorilla 5-HT_{1D} receptor as probed with isochromans (5-HT_{1D}-selective ligands). Br J Pharmacol 1999;127:468-72.
100. Gomez-Mancilla B, Cutler NR, Leibowitz MT, et al. Safety and efficacy of PNU-142633, a selective 5-HT_{1D} agonist, in patients with acute migraine. Cephalalgia 2001;21:727-32.
101. Fleishaker JC, Pearson LK, Knuth DW, et al. Pharmacokinetics and tolerability of a novel 5-HT1D agonist, PNU-142633F. Int J Clin Pharmacol Ther 1999;37:487-92.
102. Goadsby PJ. The pharmacology of headache. Prog Neurobiol 2000; 62:509-25.
103. Humphrey PPA, Goadsby PJ. The mode of action of sumatriptan is vascular? A debate. Cephalalgia 1994;14:401-10.
104. John GW, Perez M, Pawels PJ, Le Grand B, Verscheure Y, Colpaert FC. Donitriptan, a unique high efficacy 5-$HT_{1B/1D}$ agonist: key features and acute antimigraine potential. CNS Drug Rev 2000;6:278-89.
105. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache 1999;39: Suppl 2:S20-S26.
106. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. N Engl J Med 1991;325:316-21.
107. Tepper SJ, Cochran A, Hobbs S, Woessner M. Sumatriptan suppositories for the acute treatment of migraine. Int J Clin Pract 1998;52:31-5.
108. Dahlof C. Sumatriptan nasal spray in the acute treatment of migraine: a review of clinical studies. Cephalalgia 1999;19:769-78.
109. Maassen VanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation 1998;98:25-30.
110. Smith D, Shaw D, Hopkins R, et al. Development and characterisation of human 5-HT1B- or 5HT1D-receptor specific antibodies as unique research tools. J Neurosci Methods 1998;80:155-61.
111. Longmore J, Shaw D, Smith D, et al. Differential distribution of 5HT1D- and 5HT1B-immunoreactivity within the human trigemino-cerebrovascular system: implications for the discovery of new antimigraine drugs. Cephalalgia 1997;17:833-42.
112. Pilgrim AJ. Methodology of clinical trials of sumatriptan in migraine and cluster headache. Eur Neurol 1991;31:295-9.
113. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Triptans (serotonin, 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-75.
114. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-$HT_{1B/1D}$ agonists) in migraine: methods and detailed results of a meta-analysis of 53 trials. Cephalalgia (in press).
115. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997;126:712-20.
116. Tfelt-Hansen P, Block G, Dahlof C, et al. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765-86.
117. Kramer MS, Matzura-Wolfe D, Polis A, et al. A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks. Neurology 1998;51:773-81.
118. Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner RJN, Baber NS. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. Eur Neurol 1991;31:291-4.
119. Visser WH, Vriend RH, Jaspers MW, Ferrari MD. Sumatriptan in clinical practice: a 2-year review of 453 migraine patients. Neurology 1996; 47:46-51.
120. Visser WH, Ferrari MD, Bayliss EM, Ludlow S, Pilgrim AJ, Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with subcutaneous sumatriptan: first placebo-controlled study. Cephalalgia 1992;12:308-13.
121. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. N Engl J Med 1991;325:322-6.
122. Ueberall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 1999;52:1507-10.
123. Winner P, Saper JR, Nett R, Asgharnejad M, Laurenza A, Peykamian M. Sumatriptan nasal spray in the acute treatment of migraine in adolescent migraineurs. Pediatrics 1999;104:Suppl:694-5. abstract.
124. Korsgaard AG. The tolerability, safety and efficacy of oral sumatriptan 50mmg and 100mg for the acute treatment of migraine in adolescents. Cephalalgia 1995;16:98.
125. Rothner A, Edwards K, Kerr L, DeBussey S, Asgharnejad M. Efficacy and safety of naratriptan tablets in adolescent migraine. J Neurol Sci 1997;150:Suppl:S106. abstract.
126. Lipton RB, Stewart WF, Edmeads J, Sawyer J. Clinical utility of a new instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) score. Headache 1998;38:390-1. abstract.
127. Lipton RB, Stewart WF, Stone AM, Lainez MJA, Sawyer JPC, Disability in Strategies of Care Study Group. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. JAMA 2000;284:2599-605.
128. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. Trends Pharmacol Sci 1992; 13:307-11.
129. Diener HC. Substance-P antagonist RPR 100893-201 is not effective in human migraine attacks. In: Olesen J, Tfelt-Hansen P, eds. Proceedings

of the VIth International Headache Seminar. Philadelphia: Lippincott-Raven, 1996.
130. Goldstein DJ, Wang O, Saper JR, Stoltz R, Silberstein SD, Mathew NT. Ineffectiveness of neurokinin-1 antagonist in acute migraine: a crossover study. Cephalalgia 1997;17:785-90.
131. Goldstein DJ, Offen WW, Klein EG, et al. Lanepitant, an NK-1 antagonist, in migraine prevention. Cephalalgia 2001;21:102-6.
132. Norman B, Panebianco D, Block GA. A placebo-controlled, in-clinic study to explore the preliminary safety and efficacy of intravenous L-758,298 (a prodrug of the NK1 receptor antagonist L-754,030) in the acute treatment of migraine. Cephalalgia 1998;18:407. abstract.
133. Connor HE, Bertin L, Gillies S, Beattie DT, Ward P, GR205171 Clinical Study Group. Clinical evaluation of a novel, potent, CNS penetrating NK_1 receptor antagonist in the acute treatment of migraine. Cephalalgia 1998;18:392. abstract.
134. May A, Gijsman HJ, Wallnofer A, Jones R, Diener HC, Ferrari MD. Endothelin antagonist bosentan blocks neurogenic inflammation, but is not effective in aborting migraine attacks. Pain 1996;67:375-8.
135. Data J, Britch K, Westergaard N, et al. A double-blind study of ganaxolone in the acute treatment of migraine headaches with or without an aura in premenopausal females. Headache 1998;38:380. abstract.
136. Roon KI, Olesen J, Diener HC, et al. No acute antimigraine efficacy of CP-122,288, a highly potent inhibitor of neurogenic inflammation: results of two randomized, double-blind, placebo-controlled clinical trials. Ann Neurol 2000;47:238-41.
137. Earl NL, McDonald SA, Lowy MT. Efficacy and tolerability of the neurogenic inflammation inhibitor, 4991W93, in the acute treatment of migraine. Cephalalgia 1999;19:357. abstract.
138. Ramadan N, Sang C, Chappell A, et al. IV LY293558, an AMPA/KA receptor antagonist, is effective in migraine. Cephalalgia 2001; 21:267-8. abstract.
139. Goadsby PJ, Hoskin KL, Storer RJ, Edvinsson L, Connor HE. Inhibitory effects of adenosine A1 agonists on the cat trigeminovascular system: a new target for anti-migraine drugs? Cephalalgia 2001;21:352. abstract.
140. Humphrey PP, Bland-Ward PA, Carruthers AM, et al. Inhibition of trigeminal nociceptive afferents by adenosine A_1 receptor activation: a novel approach towards the design of new anti-migraine compounds. Cephalalgia 2001;21:268-9. abstract.
141. Doods H, Hallermayer G, Wu D, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol 2000;129:420-3.
142. Lassen LH, Ashina M, Christiansen I, Ulrich V, Olesen J. Nitric oxide synthase inhibition in migraine. Lancet 1997;349:401-2.
143. Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: results of the Spectrum Study. Headache 2000;40:792-7.
144. Ophoff RA, Terwindt GM, Frants RR, Ferrari MD. P/Q-type Ca^{2+} channel defects in migraine, ataxia and epilepsy. Trends Pharmacol Sci 1998;19:121-7.

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