REVIEW ARTICLE

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Migraine

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Migraine is a ubiquitous neurologic disorder that is estimated to affect approximately 1 billion people worldwide, predominantly females.[1] According to the Global Burden of Disease Study 2016, migraine is the second leading cause of disability and accounts for more disability than all other neurologic disorders combined.[2] The diagnosis is based on clinical criteria provided by the *International Classification of Headache Disorders, 3rd edition* (ICHD-3).[3] Broad clinical features suggestive of migraine are recurrent headache attacks of moderate-to-severe pain intensity, with a duration of 4 to 72 hours.[3] A diagnosis of migraine should be considered if a typical attack of head pain is unilateral, pulsating, and aggravated by physical activity.[3] Common accompanying symptoms are nausea, vomiting, photophobia, and phonophobia.[3] Some persons report that the migraine is preceded by an aura, which is characterized by reversible focal neurologic symptoms, typically comprising visual or hemisensory disturbances.[3]

Although the pathogenesis of migraine is incompletely understood, it is considered to involve the trigeminal nerve and its axonal projections to the intracranial vasculature (termed the trigeminovascular system).[4] Nociceptive signals from the trigeminovascular system are relayed to areas in the brain that yield the perception of migraine pain.[4] Further progress in understanding the pathogenesis has been made with the identification of signaling molecules that are involved in the genesis of a migraine attack. This advance has facilitated the development of mechanism-based therapies for migraine.[5] This review describes the current understanding of the pathogenesis of migraine, which is based predominantly on clinical data published within the past 10 years, and outlines recommended practices for the treatment of acute migraine and for preventive treatment of migraine, emphasizing medications that have recently been approved.

EPIDEMIOLOGY

Migraine is the second most prevalent neurologic disorder (after tension-type headache), with a female-to-male ratio of 3:1 and an estimated 1-year prevalence of approximately 15% in the general population.[1] The prevalence peaks between the ages of 35 and 39 years, and about 75% of affected persons report the onset of migraine before the age of 35 years.[1,6] Migraine also affects a considerable proportion of children, with one population-based study showing a 1-year prevalence of about 7% among school-age children.[7] Since the disorder tends to remit with older age, an onset of migraine after the age of 50 years should arouse suspicion of a secondary headache disorder.[1,8]

DIAGNOSIS

The ICHD-3 provides diagnostic criteria for the three main categories of migraine: migraine without aura, migraine with aura, and chronic migraine (Table 1).[3] Migraine aura typically involves visual scintillations and scotoma and, less often,

spreading hemisensory symptoms or speech dysfunction; these reversible focal neurologic symptoms develop gradually over a period of 5 to 60 minutes.[3] The aura phase of migraine is usually followed by the headache within 60 minutes, although aura symptoms may occur during or in the absence of a subsequent headache.[3] The diagnostic workup should include a physical examination, although there are usually no abnormal findings. The differential diagnosis of migraine includes other primary headache disorders, mainly tension-type headache, and some secondary headache disorders, such as post-traumatic headache.[3] Features suggestive of a secondary headache disorder include recent head trauma, progressively worsening headache, and thunderclap headache (the sudden onset of an extremely severe headache). Red flags on physical examination that require consideration of diagnoses other than migraine are fever, neck stiffness, and weight loss.[8]

GENETIC FEATURES

A family history of migraine is common, with the heritability estimated to be approximately 42%.[9] In a genomewide association meta-analysis, 38 susceptibility loci were identified for migraine, and migraine risk variants were enriched in genes related to vascular and visceral smooth muscle.[10] These findings are intriguing because vascular involvement in the pathogenesis of migraine has been debated through the years.[11] In another analysis, the findings were also suggestive of neuronal enrichment of genetic markers.[12] In summary, genetic studies have shown that the risk of migraine is polygenic, with rare exceptions of migraine-related monogenic syndromes such as familial hemiplegic migraine.[3]

PATHOGENESIS

The trigeminovascular system is considered to be the anatomical and physiological substrate from which nociceptive transmission originates and yields the perception of migraine pain (Fig. 1A).[4] In 1984, Moskowitz proposed that migraine initiation depends on activation and sensitization of first-order trigeminovascular neurons. The afferent fibers of these neurons innervate the meninges and its vessels and also project to structures in the central nervous system.[21] Activation of these neurons releases vasoactive peptides and induces local inflammatory reactions.[21] This process, in turn, sensitizes and discharges second-order neurons in the brain stem and then third-order neurons in the thalamus,[4] until ultimately nociceptive impulses reach the somatosensory and other cortical areas that are involved in pain perception.[4]

Table 1. Diagnostic Criteria for Migraine without Aura, Migraine with Aura, and Chronic Migraine.*

Type of Migraine	Diagnostic Criteria
Migraine without aura	At least five attacks that meet the following four criteria:
	Headache lasting 4–72 hours (when untreated or unsuccessfully treated)
	Headache with at least two of the following four characteristics: Unilateral location Pulsating quality Moderate or severe pain intensity Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
	Headache accompanied by at least one of the following symptoms: Nausea, vomiting, or both Photophobia and phonophobia
	Not better accounted for by another ICHD-3 diagnosis
Migraine with aura	At least two attacks that meet the following three criteria:
	One or more of the following fully reversible aura symptoms: Visual Sensory Speech, language, or both Motor Brain stem Retinal
	At least three of the following six characteristics: At least one aura symptom spreading gradually over a period ≥5 minutes Two or more aura symptoms occurring in succession Each aura symptom lasting 5–60 minutes At least one unilateral aura symptom At least one positive aura symptom Headache accompanying the aura or following the aura within 60 minutes
	Not better accounted for by another ICHD-3 diagnosis
Chronic migraine	Headaches (suggestive of migraine or tension headaches) on ≥15 days/month for >3 months that fulfill the following criteria:
	Occurring in a patient who has had at least five attacks meeting the criteria for migraine without aura or the criteria for migraine with aura or both On ≥8 days/month for >3 months, features of migraine without aura or of migraine with aura or believed by the patient to be migraine at onset that is relieved by a triptan or ergot derivative Not better accounted for by another ICHD-3 diagnosis

* Diagnostic criteria are from the *International Classification of Headache Disorders, 3rd edition* (ICHD-3).[3]

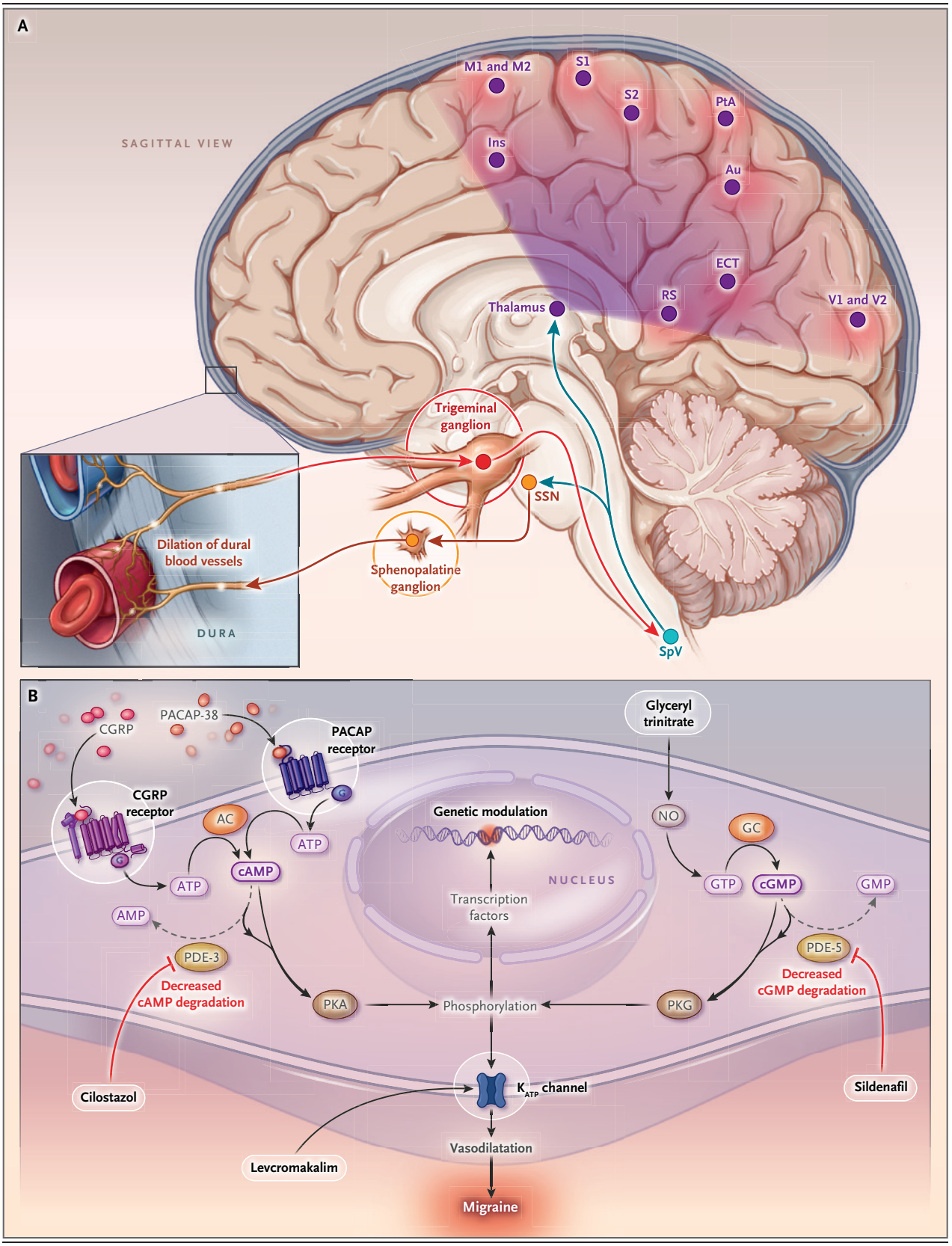

A
SAGITTAL VIEW
M1 and M2
S1
S2
PtA
Ins
Au
ECT
RS
V1 and V2
Thalamus
Trigeminal ganglion
SSN
Sphenopalatine ganglion
Dilation of dural blood vessels
DURA
SpV
B
CGRP
PACAP-38
PACAP receptor
CGRP receptor
AC
ATP
cAMP
ATP
AMP
PDE-3
Decreased cAMP degradation
Cilostazol
Genetic modulation
NUCLEUS
Transcription factors
PKA
Phosphorylation
PKG
Glyceryl trinitrate
NO
GC
GTP
cGMP
GMP
PDE-5
Decreased cGMP degradation
Sildenafil
K ATP channel
Levcromakalim
Vasodilatation
Migraine

Figure 1 (facing page). Anatomy and Pathogenesis of Migraine.

The trigeminovascular system (Panel A) is the anatomical and physiological substrate of migraine. Nociceptive transmission originates from activation and sensitization of first-order trigeminovascular neurons. Their cell bodies are in the trigeminal ganglion, and their afferent fibers innervate the meninges and its vessels.[4] Ascending nociceptive transmission from the trigeminal ganglion is projected to the brain stem, activating and sensitizing second-order trigeminovascular neurons, including those in the spinal trigeminal nucleus.[4] This, in turn, activates and sensitizes third-order trigeminovascular neurons in the thalamus, which subsequently relay the nociceptive transmission to the somatosensory cortex and other cortical areas, ultimately resulting in the perception of migraine pain.[4] Preclinical data suggest that activation of the trigeminovascular system results in parasympathetic outflow to the intracranial arteries (including the dural arteries) through the superior salivatory nucleus (SSN) and the sphenopalatine ganglion. This outflow, in turn, leads to dilation of intracranial arteries due to release of signaling molecules such as pituitary adenylate cyclase–activating peptide (PACAP) and vasoactive intestinal polypeptide. Furthermore, ample preclinical data have shown that activation of the trigeminovascular system results in antidromic release of vasoactive signaling molecules such as calcitonin gene–related peptide (CGRP). These molecules, in turn, also contribute to dilation of intracranial arteries. Although the biologic underpinnings of migraine are incompletely understood, signaling pathways have been identified that are putatively responsible for the genesis of a migraine attack (Panel B).[4,5] Provocation models of migraine have been used to test whether administration of endogenous signaling molecules and other putative trigger molecules induce migraine attacks.[5] These studies have implicated cyclic adenosine monophosphate (cAMP)–mediated and cyclic guanosine monophosphate (cGMP)–mediated pathways in the pathogenesis of migraine attacks and suggest that a possible unifying mechanism results in the opening of ATP-sensitive potassium (K_{ATP}) channels.[13-20] The site of action of these trigger molecules is probably within the vascular smooth-muscle cells of the intracranial arteries but may also include other cells, such as perivascular trigeminal primary afferents.[4,5,20] AC denotes adenylate cyclase, Au auditory cortex, Ins insular cortex, ECT ectorhinal cortex, GC guanylate cyclase, GTP guanosine triphosphate, M1 and M2 primary and secondary motor cortexes (respectively), PDE-3 phosphodiesterase type 3, PKA protein kinase A, PKG protein kinase G, PtA parietal association cortex, RS retrosplenial cortex, S1 and S2 primary and secondary somatosensory cortexes (respectively), SpV spinal trigeminal nucleus, and V1 and V2 primary and secondary visual cortexes (respectively).

The mechanisms that initiate a migraine attack are unclear. Some evidence favors a peripheral origin at the level of perivascular trigeminal afferents,[4,11] whereas other data suggest that the genesis is more likely within the central nervous system, involving dysfunction of neurons in the brain stem and diencephalon.[4,11] These possible peripheral and central sites of the origin of migraine attacks are shown in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

An inherent trait of migraine is its recurrent nature. Patients often describe factors that they perceive as triggering their migraine attacks (e.g., stress, sleep disturbance, particular foods, and not eating).[22] However, retrospective assessments are limited by recall bias and false attribution.[23] The high frequency of misattribution of migraine triggers is supported by a study that aimed to induce migraine attacks by exposing patients who had a history of migraine with aura to self-perceived triggers.[24] Only 3 of 27 patients had migraine attacks after exposure to their personal triggers, suggesting, contrary to popular belief, that the role of these triggers is limited.

CLINICAL MODELS OF MIGRAINE

Signaling molecules involved in the genesis of a migraine attack have been identified in clinical models of migraine (Fig. 1B).[5] These molecules, which are potent vasodilators and are widely distributed in the trigeminovascular system, include calcitonin gene–related peptide (CGRP), pituitary adenylate cyclase–activating peptide 38 (PACAP-38), and nitric oxide.[5] To determine whether these and other molecules have a role in the pathogenesis of migraine, my colleagues and I administered them to patients with migraine and to healthy volunteers.[5] Three decades of studies using this model have established that migraine attacks develop in patients with migraine when they are exposed to these molecules, whereas healthy persons report mild or no headache.[5] For example, intravenous infusion of the nitric oxide donor glyceryl trinitrate (GTN) induced migraine attacks in 80% of patients with migraine, CGRP infusion in 57%, and PACAP-38 infusion in 58%.[13-15] Furthermore, drugs that block the degradation of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) induced migraine attacks in more than 80% of patients with migraine.[16,17] The observation that GTN causes increased intracellular cGMP and that CGRP and PACAP-38 cause increased intracellular cAMP[5] has led to speculation that

these are unifying neurochemical mechanisms inciting migraine. There is preclinical evidence that activation of cAMP- and cGMP-mediated pathways results in the opening of ATP-sensitive potassium (K_{ATP}) channels.[18,19] These findings have led to the hypothesis that modulation of nociceptive transmission by ion channels, mainly potassium channels, may be a final common pathway in the genesis of a migraine attack.[20] This hypothesis has been supported by the observation that migraine attacks developed in all patients with migraine after intravenous infusion of the K_{ATP} channel opener levcromakalim.[20]

Explaining the findings from clinical models of migraine within the framework of the trigeminovascular system has been a challenge (Fig. S2).[21] It is plausible that during a migraine attack, K_{ATP} channels are opened on vascular smooth-muscle cells in the walls of the intracranial arteries,[25] causing vasodilatation.[26,27] This, in turn, activates the perivascular trigeminal primary afferents, generating nociceptive impulses that are transmitted to cortical and subcortical brain regions through ascending trigeminal pain pathways and ultimately resulting in the perception of migraine pain.[4] This line of reasoning emphasizes that elevations in extracellular levels of positively charged ions, perhaps not exclusively potassium, may activate and sensitize perivascular trigeminal primary afferents (Fig. S2). Modulatory activity by ion channels has been described in other paroxysmal pain disorders, such as familial episodic pain syndrome.[28,29]

Insights from clinical models of migraine and supportive preclinical data have also provided a basis for the development of targeted therapies. Not all have proved effective for the treatment of migraine, and some provide only modest therapeutic benefits, findings that underscore the complex biologic underpinnings of the disorder. For example, initial evidence from a small, randomized clinical trial showed that targeting nitric oxide signaling through nonselective inhibition of nitric oxide synthase (NOS) was promising as a treatment for migraine.[30] However, selective inhibition of inducible NOS (one of three isoforms) was not beneficial in larger trials.[31,32] It remains unknown whether other isoforms of NOS (endothelial NOS and neuronal NOS) could be effective for initial or preventive treatment.

Figure 2 (facing page). Freedom from Pain at 2 Hours in Randomized Clinical Trials of Treatments for Migraine.

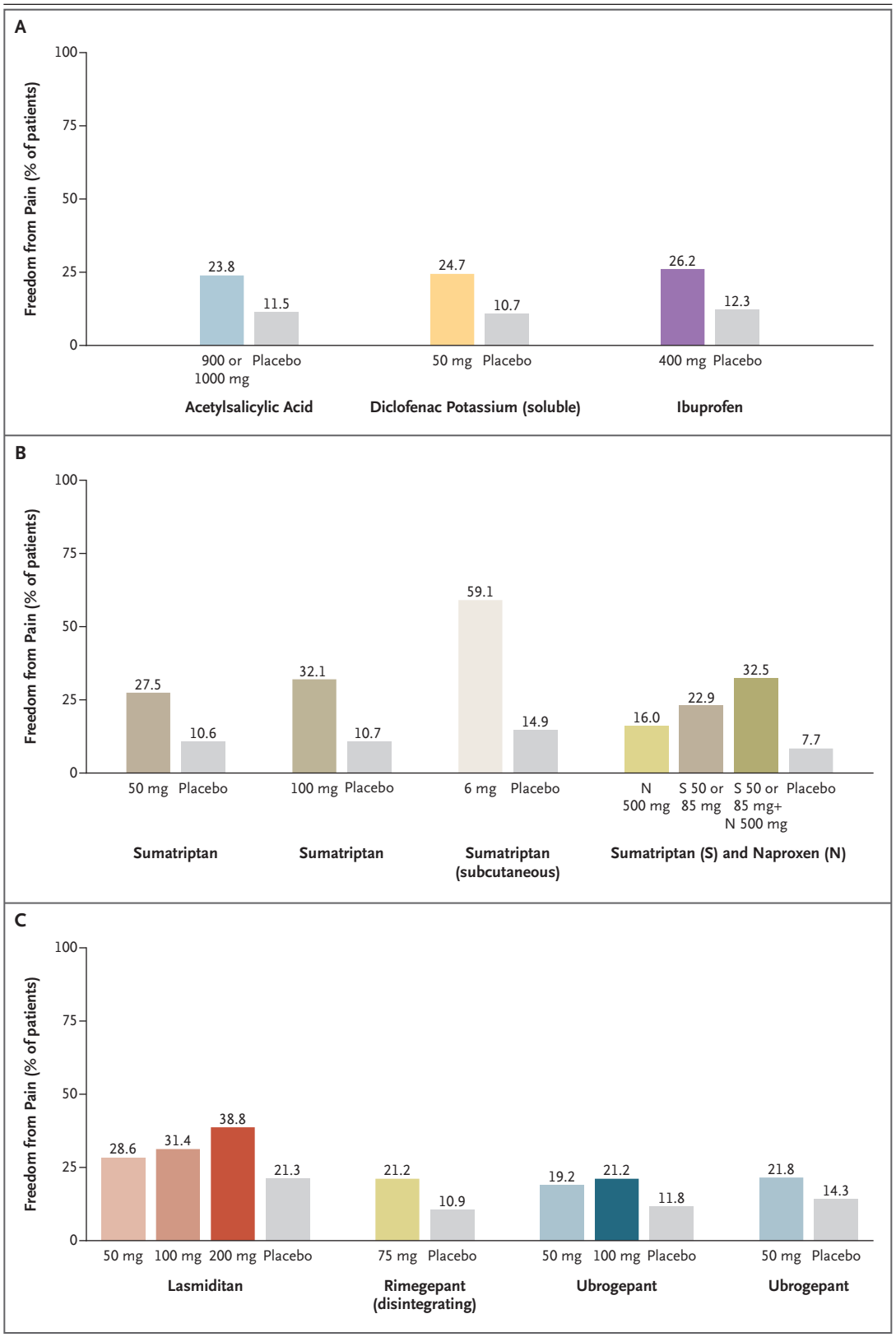
Freedom from pain 2 hours after treatment and before the use of rescue medication is the primary measure of efficacy that has been used in controlled trials of treatments for migraine attacks in adults. Panel A shows the proportion of patients who were free of pain 2 hours after treatment with oral acetylsalicylic acid, oral diclofenac, or oral ibuprofen, as determined in meta-analyses by the Cochrane Collaboration.[46-48] Panel B shows the proportion of patients who were free of pain 2 hours after treatment with oral sumatriptan, subcutaneous sumatriptan, or the combination of oral sumatriptan and naproxen sodium, as determined in meta-analyses by the Cochrane Collaboration.[49,50] Panel C shows the proportion of patients who were free of pain 2 hours after treatment with doses of lasmiditan, rimegepant, or ubrogepant approved by the Food and Drug Administration, as determined in phase 3 trials.[51-54]

Clinical models of migraine have also spawned the development of drugs targeting CGRP or its receptor.[4] Three small receptor antagonists have proved beneficial for the initial treatment of migraine, and four monoclonal antibodies targeting CGRP or its receptor have proved effective for the prevention of migraine. These drugs and their integration in the clinical management of migraine are described below. Drugs targeting PACAP-38 or the pituitary adenylate cyclase–activating polypeptide type I (PAC1) receptor have also been developed for migraine prevention.[33,34] A monoclonal PAC1 receptor antibody failed in a proof-of-concept study,[33] whereas another monoclonal antibody, designed to target PACAP, is in the early stage of development.[34]

AURA PHASE OF MIGRAINE

The physiological basis of the aura phase of migraine is thought to be cortical spreading depression, a self-propagating wave of depolarization across the cerebral cortex that disrupts ionic gradients and is followed by cerebral hypoperfusion.[35] Hemodynamic changes accompanying cortical spreading depression have been documented on neuroimaging in patients who have migraine with aura, whereas no changes have been found in patients who have migraine without aura.[36]

A fundamental question regarding the pathogenesis of migraine concerns the mechanisms underlying activation of the trigeminovascular system through cortical spreading depression,


A
Freedom from Pain (% of patients)
100
75
50
25
0
23.8
11.5
24.7
10.7
26.2
12.3
900 or 1000 mg
Placebo
50 mg
Placebo
400 mg
Placebo
Acetylsalicylic Acid
Diclofenac Potassium (soluble)
Ibuprofen
B
Freedom from Pain (% of patients)
27.5
10.6
32.1
10.7
59.1
14.9
16.0
22.9
32.5
7.7
50 mg
Placebo
100 mg
Placebo
6 mg
Placebo
N 500 mg
S 50 or 85 mg
S 50 or 85 mg+ N 500 mg
Placebo
Sumatriptan
Sumatriptan
Sumatriptan (subcutaneous)
Sumatriptan (S) and Naproxen (N)
C
Freedom from Pain (% of patients)
28.6
31.4
38.8
21.3
21.2
10.9
19.2
21.2
11.8
21.8
14.3
50 mg
100 mg
200 mg
Placebo
75 mg
Placebo
50 mg
100 mg
Placebo
50 mg
Placebo
Lasmiditan
Rimegepant (disintegrating)
Ubrogepant
Ubrogepant

leading to the headache phase of migraine with aura.[4,35] In a possible cascade of events, spreading depression transiently opens neuronal pannexin-1 channels,[37] which results in the release of inflammatory mediators (e.g., nitric oxide and prostanoids) that are dilators of intracranial arteries.[5] These processes are hypothesized to activate and sensitize trigeminal primary afferents that terminate in the perivascular space of intracranial arteries.[38] In this way, spreading depression activates and sensitizes perivascular trigeminal primary afferents that are responsible for transmission of nociceptive impulses, which are subsequently processed in cortical areas, yielding the perception of migraine pain.[4]

TREATMENT

Clinical management of migraine should ideally be initiated and maintained by primary care practitioners, with referral to specialists for cases that are diagnostically challenging or do not respond to treatment.[8] Pharmacologic therapy, the mainstay of treatment, includes initial and preventive medications, with nonpharmacologic therapies used as adjuncts to medication.[8] Nonpharmacologic therapies may be used as stand-alone preventive treatment in the case of patients for whom medications are best avoided — for example, in pregnant women.[8,39] Modest evidence exists for the benefit of noninvasive neuromodulatory devices, biobehavioral therapies, and acupuncture,[40-42] whereas there is little or no evidence in support of physical therapy, chiropractic manipulation, or dietary approaches for the treatment of migraine in adults.[43-45]

EARLY TREATMENT

As a general principle, medications used in clinical practice to alleviate or remove the pain of migraine should be administered early in the headache phase of an attack (i.e., when the headache is still mild).[8] The most widely used initial medications for migraine are nonsteroidal antiinflammatory drugs (NSAIDs),[45] which are low-cost, over-the-counter analgesic agents. Effectiveness has been best documented for acetylsalicylic acid, ibuprofen, and diclofenac[46-48] (Fig. 2A). Triptans are considered second-line medications (Fig. 2B), and in patients for whom one oral triptan is ineffective, others in the drug class may provide adequate pain relief.[55] At present, seven oral triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are available for clinical use. Patients are advised to switch from one oral triptan to another if three migraine attacks have been treated without success.[8] If treatment with an oral triptan provides some but inadequate pain relief, clinicians may recommend the combination of an oral triptan with a fast-acting NSAID (e.g., sumatriptan and naproxen sodium) (Fig. 2B).[49] Subcutaneous sumatriptan is the most effective dosing method on the basis of the proportion of patients who report freedom from pain at 2 hours after treatment (Fig. 2B), but its use is limited because it costs more and is less widely available than oral triptans. Subcutaneous sumatriptan is therefore first offered when a patient has had inadequate pain relief from oral triptans.[50] An exception can be made for patients who cannot ingest oral triptans because of vomiting or a rapidly peaking headache. Clinicians should be aware of the risk of medication-overuse headache, which is the condition of daily headache or increasing headache frequency resulting from regular overuse of medications for migraine by patients who have at least 15 days per month with headache.[3,56] Withdrawal of the overused medication and initiation of preventive treatment are considered the necessary remedy in such instances.[56]

There has been cautious enthusiasm for the small-molecule CGRP receptor antagonists, called gepants, and the 5-hydroxytryptamine type 1F (5-HT_{1F}) receptor agonists, called ditans, in the treatment of acute migraine.[51-54] The Food and Drug Administration has approved the following oral gepants and ditans for the treatment of acute migraine: ubrogepant, rimegepant, and lasmiditan (Fig. 2C). At present, the high costs and restricted availability of gepants and ditans probably limit their use to patients for whom NSAIDs and triptans are ineffective, have unacceptable side-effect profiles, or are contraindicated. Lasmiditan is associated with impaired driving and an inability to assess one's driving competence.[57] Consequently, because patients are advised not to drive a motor vehicle or operate machinery for at least 8 hours after ingestion,[57] broad use of lasmiditan may be limited. Consensus guidelines advise against the use of opioids and barbiturates in the treatment of migraine because of adverse effects and the risk of dependency.[8,58]

PREVENTIVE TREATMENT

Migraine is a recurrent disorder, and long-term management may require preventive treatment. The aim is to reduce the frequency, duration, or severity of migraine attacks rather than to cure the migraine.[8] Clinicians may relay such information to patients in order to reach an agreement about realistic treatment goals. Advice regarding when preventive treatment should be initiated in the course of an individual patient's migraine trajectory varies among countries, but such treatment is generally recommended for patients who have at least two migraine days per month and whose lives are adversely affected despite therapy.[8] Off-label use of therapies has become common because of the limited number of approved preventive medications.[59] The most widely used drug classes are antihypertensive agents (e.g., beta-blockers and candesartan), antidepressant agents (e.g., amitriptyline), anticonvulsant agents (e.g., topiramate and sodium valproate), and calcium-channel blockers (flunarizine).[45] For chronic migraine, the evidence-based effectiveness of topiramate and onabotulinumtoxinA (Botox) has been documented.[60,61]

New mechanism-based preventive therapies have recently been introduced. These include four injectable monoclonal antibodies targeting CGRP or its receptor (eptinezumab, erenumab, fremanezumab, and galcanezumab), which all have documented effectiveness in randomized trials for the preventive treatment of episodic and chronic migraine.[62-71] A summary of results from trials in migraine prevention is shown in Figure 3 and Figure S3. These drugs have a rapid onset of effect and result in few adverse events, the most common being injection-site reactions, such as erythema and pain.[62] Erenumab, fremanezumab, and galcanezumab have also proved beneficial in patients who do not have a response to other classes of preventive medications.[62] In a 5-year, open-label extension study, erenumab continued to be safe in patients with episodic migraine,[63] although more data are needed to confirm these findings and assess the long-term safety of all agents in this class. The agents have not been compared with the commonly used oral preventive medications listed above, which are less expensive and more accessible. Clinical experience suggests that the treatment response can be assessed and substitution of another medication can be considered after about 2 to 3 months for oral preventive

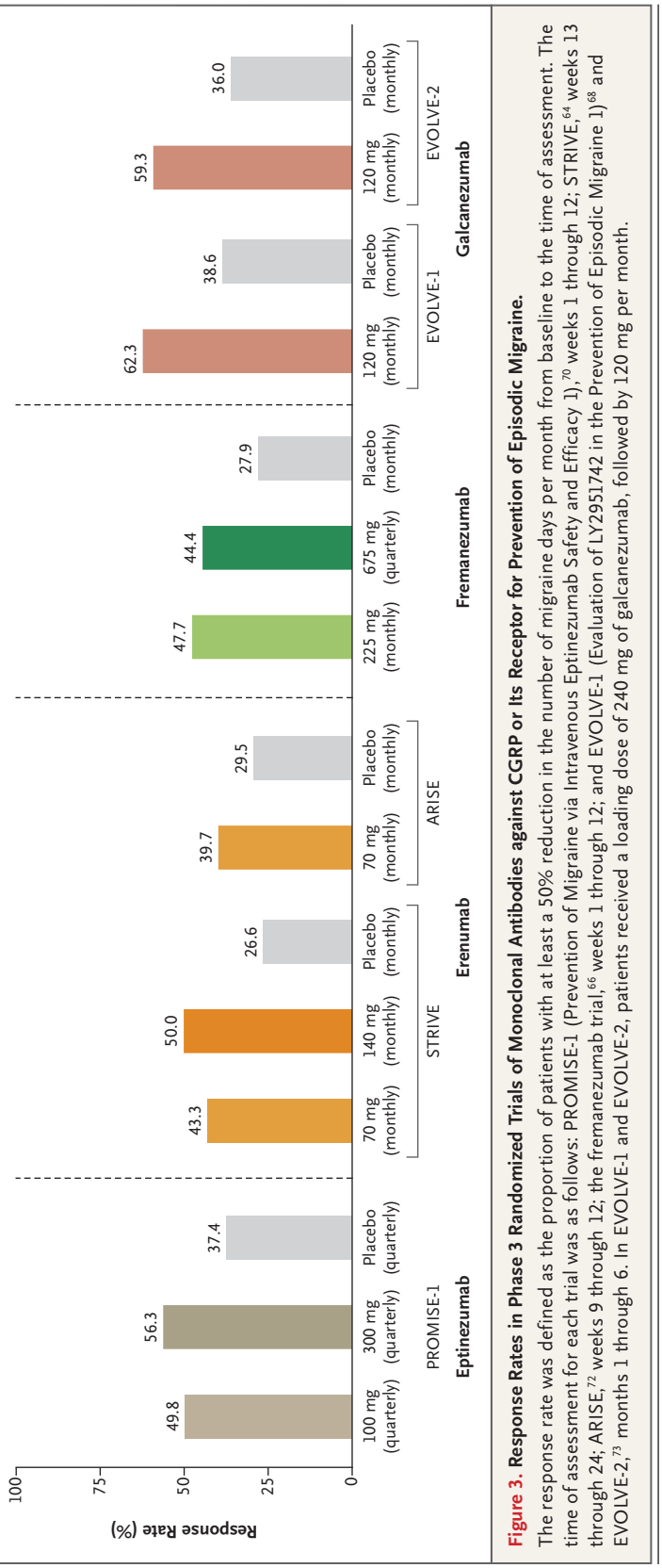


Figure 3. Response Rates in Phase 3 Randomized Trials of Monoclonal Antibodies against CGRP or Its Receptor for Prevention of Episodic Migraine.

The response rate was defined as the proportion of patients with at least a 50% reduction in the number of migraine days per month from baseline to the time of assessment. The time of assessment for each trial was as follows: PROMISE-1 (Prevention of Migraine via Intravenous Eptinezumab Safety and Efficacy 1),[70] weeks 1 through 12; STRIVE,[64] weeks 13 through 24; ARISE,[72] weeks 9 through 12; the fremanezumab trial,[66] weeks 1 through 12; and EVOLVE-1 (Evaluation of LY2951742 in the Prevention of Episodic Migraine 1)[68] and EVOLVE-2,[73] months 1 through 6. In EVOLVE-1 and EVOLVE-2, patients received a loading dose of 240 mg of galcanezumab, followed by 120 mg per month.

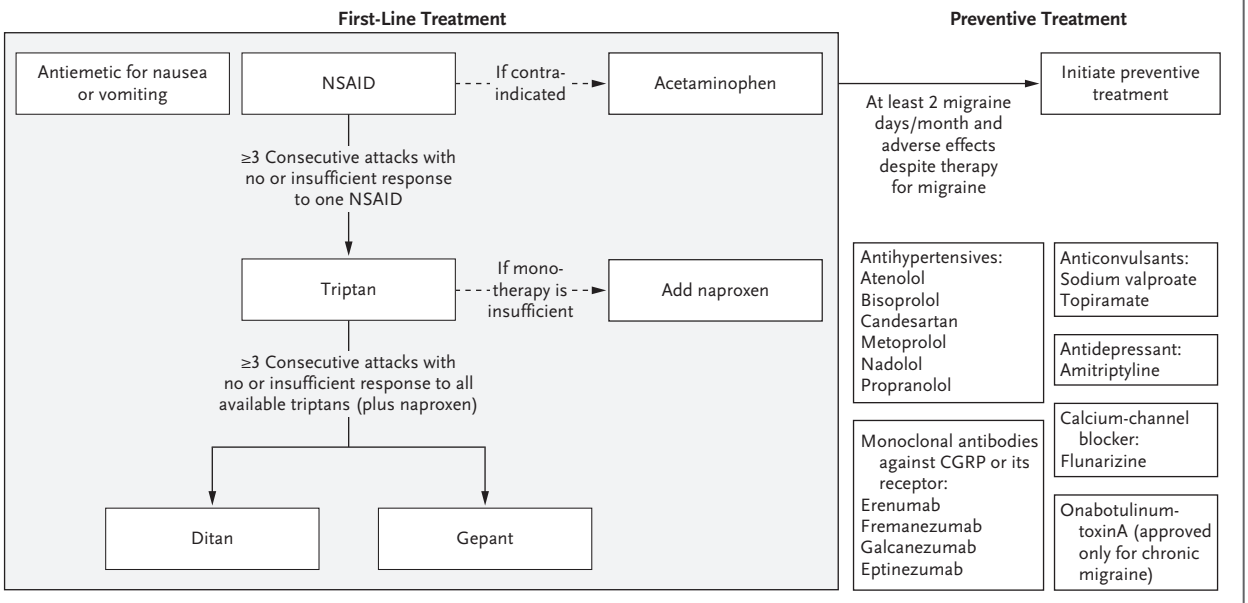


Figure 4. Proposed Treatment Algorithm for the Clinical Management of Migraine.

Nonsteroidal antiinflammatory drugs (NSAIDs) should be considered first-line medications for the treatment of migraine attacks. Patients in whom NSAIDs provide no or inadequate pain relief should be offered an oral triptan. If an oral triptan provides no pain relief, other triptans should be offered. Combination therapy with naproxen sodium should be offered to patients who have inadequate pain relief with triptan. Ideally, clinicians should first offer subcutaneous sumatriptan when a patient has had inadequate pain relief with all oral triptans. However, subcutaneous sumatriptan may be tried at an earlier stage if oral triptans cannot be ingested because of vomiting or if headache intensity peaks rapidly. Ditans and gepants may be considered for patients in whom NSAIDs and all available triptans are ineffective, have unacceptable side-effect profiles, or are contraindicated. The decision about when to substitute a triptan with a gepant or ditan may differ among countries and should be made in accordance with local practice guidelines. Antiemetic agents may be offered as adjunctive therapy in patients with attacks accompanied by nausea or vomiting. Initiation of preventive treatment depends on local practice guidelines but should, in general, be considered for patients who have at least 2 migraine days per month and are adversely affected despite therapy.

medications, after 3 to 6 months for monoclonal antibodies targeting CGRP or its receptor, and after 6 to 9 months for onabotulinumtoxinA.

TREATMENT ALGORITHM AND GUIDELINES

A proposed treatment algorithm for clinical management of migraine that may support clinical decision making is shown in Figure 4. Guidelines for clinical management of migraine have been published by professional organizations, including the American Headache Society and the European Headache Federation.[36,54,57]

MIGRAINE IN CHILDREN AND ADOLESCENTS

Clinical management strategies for migraine in children and adolescents differ somewhat from the management strategies for migraine in adults and may require the involvement of family members. When a clinician determines that medication is needed for migraine in a child, ibuprofen is considered the initial drug of choice.[74,75] If ibuprofen is ineffective, oral triptans and the combination of sumatriptan and naproxen sodium may be tried.[74,75] There is less evidence supporting the use of preventive medications, such as topiramate, amitriptyline, and propranolol in children and adolescents. In a placebo-controlled trial, topiramate and amitriptyline were not superior to placebo for the prevention of migraine in patients 8 to 17 years of age.[76] Children and adolescents may benefit from biobehavioral therapies, such as biofeedback, relaxation, and cognitive behavioral therapy.[74] A review of treatment strategies for children and adolescents has been published.[74]

CONCLUSIONS

Our understanding of the mechanisms underlying migraine has evolved during the past decade, with new insights into the pathogenesis of mi-

graine and the development of mechanism-based therapies, but uncertainties regarding mechanisms and medications remain. These uncertainties include the exact origin of migraine pain, the mechanism underlying the paroxysmal nature and features of migraine, and the exact site and mode of action of migraine-specific medications. An effort is needed to find new drug targets and develop biomarkers that can predict which patients will have a response to each targeted therapy.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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