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Emerging Target-Based Paradigms to Prevent and Treat Migraine

SD Silberstein[1]

Migraine is a primary brain disorder resulting from altered modulation of normal sensory stimuli and trigeminal nerve dysfunction. The second edition of the International Classification of Headache Disorders (ICHD-2) defines seven subtypes of migraine. Migraine treatment can be acute or preventive. New targeted therapies include 5-HT$_{1F}$ receptor agonists, calcitonin gene-related peptide (CGRP) antagonists, nitric oxide synthetase inhibitors, and ion channel antagonists. A recent development is the creation of antibodies to CGRP and its receptor for migraine prevention.

THE MIGRAINE ATTACK

The migraine attack can have four phases: premonitory, aura, headache, and resolution. Premonitory symptoms, which precede the aura and the headache, consist of depression, cognitive dysfunction, and bouts of food cravings.[1] Focal neurologic symptoms—visual, sensory, or motor (the aura)—can precede, accompany, or even follow an attack.[2,3] The most common of these is visual.[4] Auras develop slowly and last less than 60 min.[2,3] Headache usually starts during or following the aura.[4] The average attack frequency is 1–2 per month.[3] The headache is often unilateral (60%), of gradual onset, throbbing,[5] moderate to severe in intensity, and aggravated by movement. By definition, the headache lasts 4–72 h in adults and 2–48 h in children.[2,3]

Anorexia is common. Nausea occurs in almost 90% of patients, and vomiting occurs in about one-third.[6] Sensory hypersensitivity results in patients seeking a dark, quiet room.[1,6] Blurry vision, nasal stuffiness, anorexia, hunger, tenesmus, diarrhea, abdominal cramps, polyuria, facial pallor, sensations of heat or cold, and sweating may occur. Depression, fatigue, anxiety, nervousness, irritability, and impairment of concentration are common. Symptom complexes may be generated by linked neuronal modules.[7]

DIAGNOSTIC CRITERIA

The ICHD divides migraine on the basis of the absence (**Table 1**) or presence (**Table 2**) of aura.[2] A diagnosis of migraine without aura requires five attacks. A migraine headache that lasts longer than 3 days is "status migrainosus."[2] Migraine that occurs 15 or more days per month is called chronic migraine by the ICHD-2 (**Table 3**).[8]

PATHOPHYSIOLOGY

Migraine is a brain disorder that is due to altered modulation of normal sensory stimuli (e.g., light) and dysfunction of the trigeminal nerve and its central connections. The following components are involved: (i) intracranial blood vessels and meninges, (ii) intracranial trigeminal peripheral terminals, (iii) brainstem trigeminal connections in the trigeminal nucleus caudalis and to the cranial parasympathetic pathways, and (iv) local and descending pain modulation. The major pain pathways are the afferent peripheral and ascending central trigeminal sensory pathways. Brain imaging studies suggest that important modulation of the trigeminal sensory transmission involves the dorsal raphe nucleus, the locus ceruleus, and the nucleus raphe magnus.[9]

The migraine aura is most likely due to cortical spreading depression (CSD), described by Leao.[10] CSD is an intense depolarization of neuronal and glial membranes accompanied by a massive disruption of ionic gradients and loss of membrane resistance. It is characterized by cessation of spontaneous or evoked synaptic activity[11] and shifts in cortical steady-state potential. Headache probably results from the activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. Headache and its associated neurovascular changes are subserved by the trigeminal system. Trigeminal nerve stimulation results in the release of substance P (SP) and calcitonin gene-related peptide (CGRP) from sensory C-fiber terminals and neurogenic inflammation with plasma protein extravasation (PPE).[12] Triptans and ergots block neuropeptide release and prevent PPE. Neurogenic inflammation sensitizes nerve fibers (peripheral sensitization), which now respond to previously innocuous stimuli, such as cerebrospinal fluid or, perhaps, blood vessel pulsations, contributing to the pain of migraine (**Figure 1**).

[1]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA. Correspondence: SD Silberstein (stephen.silberstein@jefferson.edu)

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Table 1 Migraine without aura

Diagnostic criteria
A. At least five attacks fulfilling B–D
B. Headache attacks lasting 4–72 h and occurring <15 days/month (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity
4. Aggravation by or causing avoidance of routine physical activity (i.e., walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder

From ref. 2.

Table 2 Migraine with aura

Typical aura with migraine headache
Diagnostic criteria
A. At least two attacks fulfilling B–E
B. Fully reversible visual and/or sensory and/or speech symptoms but no motor weakness
C. Homonymous or bilateral visual symptoms including positive features (i.e., flickering lights, spots, lines) or negative features (e.g., loss of vision) and/or unilateral sensory symptoms including positive features (e.g., visual loss, pins, and needles) and/or negative features (e.g., numbness)
D. At least one of the following two:
1. At least one symptom develops gradually over ≥5 min and/or different symptoms occur in succession
2. Each symptom lasts ≥5 min and ≤60 min
E. Headache that meets criteria B–D for migraine without aura (1.1 in **Table 3**) begins during the aura or follows aura within 60 min
F. Not attributed to another disorder

From ref. 2.

Table 3 Migraine classification according to the International Classification of Headache Disorders (second edition)

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Typical aura with migraine headache
1.2.2 Typical aura with nonmigraine headache
1.2.3 Typical aura without headache
1.2.4 Familial hemiplegic migraine
1.2.5 Sporadic hemiplegic migraine
1.2.6 Basilar-type migraine
1.3 Childhood periodic syndromes that are commonly precursors of migraine
1.3.1 Cyclical vomiting
1.3.2 Abdominal migraine
1.3.3 Benign paroxysmal vertigo of childhood
1.4 Retinal migraine
1.5 Complications of migraine
1.5.1 Chronic migraine
1.5.2 Status migrainosus
1.5.3 Persistent aura without infarction
1.5.4 Migrainous infarction
1.5.5 Migraine-triggered seizures
1.6 Probable migraine
1.6.1 Probable migraine without aura
1.6.2 Probable migraine with aura

From ref. 2.

Central sensitization of trigeminal nucleus caudalis neurons can also occur and may play a role in headache continuation. Brainstem activation occurs in migraine without aura, due to increased activity of the endogenous antinociceptive system. The migraine aura can trigger headache; CSD activates trigeminovascular afferents. Stress can also activate meningeal plasma cells via a parasympathetic mechanism, leading to nociceptor activation.[13]

Migraine may be a result of a change in pain processing and sensory input. The aura is triggered in the hyperexcitable cortex (CSD). Headache is generated by central pain facilitation and neurogenic inflammation. Central sensitization can occur, in part mediated by supraspinal facilitation. Decreased antinociceptive system activity and increased peripheral input may be present.

TREATMENT

Migraine varies widely in its frequency, severity, and impact on patients' quality of life. A treatment plan should consider not only the patient's diagnosis, symptoms, and coexistent or comorbid conditions but also his or her expectations, needs, and goals.[14] Migraine treatment begins with making the diagnosis,[1] explaining it to the patient, and developing a treatment plan that considers coincidental or comorbid conditions.[15] Comorbidity implies that two disorders occur together more than expected by chance. Conditions comorbid with migraine include stroke, myocardial infarction, angina, patent foramen ovale (aura), epilepsy, Raynaud's syndrome, depression, mania, anxiety, panic disorder, and possibly essential tremor, mitral valve prolapse, and irritable bowel syndrome.

Migraine treatment can be acute or preventive, and some patients require both modalities. Acute treatment is used to relieve the pain and migraine-associated symptoms. It is appropriate for most attacks and should be used no more than 2–3 days a week. Preventive treatment is used mainly to reduce attack frequency. It may also decrease attack duration or severity and often enhances the benefit of acute treatment.

ACUTE MIGRAINE TREATMENT

Acute treatment can be specific (ergots and triptans) or nonspecific (analgesics and opioids). Nonspecific acute treatment can be used to treat all types of pain, whereas specific acute treatments are effective in migraine and certain other headache types but are not useful for other pain disorders.[16] Attack severity, frequency, associated symptoms, and coexistent disorders suggest drug

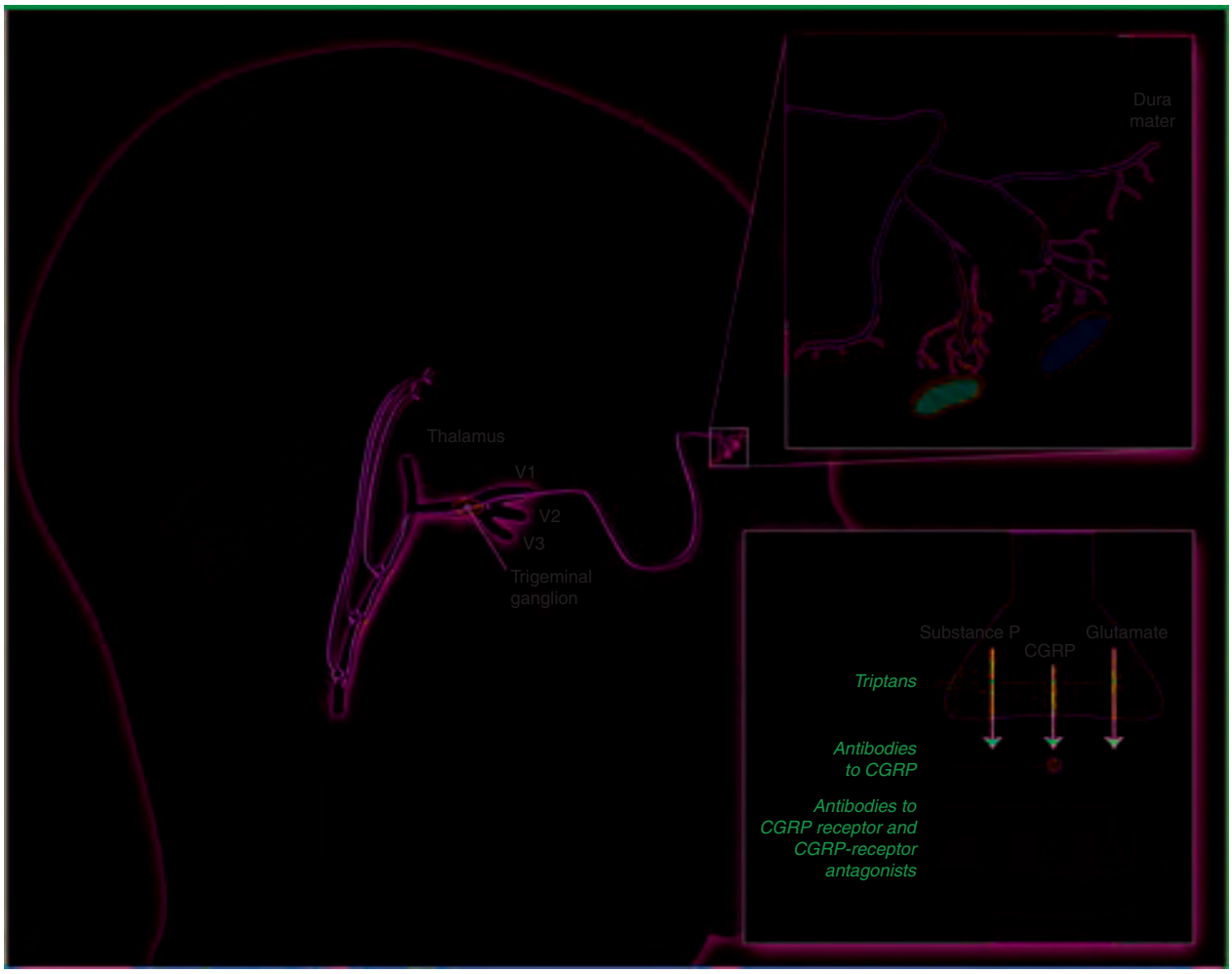

Figure 1 Central and peripheral connections of the trigeminal nerve and sites of action of triptans, antibodies to CGRP, and antibodies to CGRP receptor and CGRP-receptor antagonists. CGRP, calcitonin gene–related peptide.

choice, as do the drug's efficacy and adverse events (AEs). With severe nausea or vomiting, a parenteral route of administration and an antiemetic are used.[17] Headaches can be stratified by severity and disability. Analgesics are effective for mild to moderate but not severe headaches.[17] Triptans or dihydroergotamine are more effective for severe attacks and can be used for less severe attacks that respond inadequately to nonspecific treatment.[17]

Specific medications

Ergots and triptans are indicated for acute migraine treatment. Patients with sepsis, renal or hepatic failure, and cerebral or peripheral vascular disease should avoid ergots. There is little consensus as to how many risk factors preclude triptan use and what constitutes an appropriate evaluation.[18] Contraindications include documented or suspected ischemic heart disease, Prinzmetal angina, uncontrolled hypertension, basilar or hemiplegic migraine, and pregnancy.

Serotonin (5-HT) receptors

Seven 5-HT receptors exist: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 (ref. 19). Five 5-HT_1 receptor subtypes occur in humans: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} (ref. 20). 5-HT_{1B} receptors are located on intracranial blood vessels and central nervous system neurons. 5-HT_{1D} receptors are located on central nervous system neurons and trigeminal nerve endings. 5-HT_{1F} receptors are located on trigeminal nerve endings.[21] Triptans and ergots block the release of CGRP and SP by acting at presynaptic 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors in the periphery, blocking neurogenic inflammation and PPE, and in the dorsal horn, blocking synaptic transmission between axon terminals of the peripheral trigeminovascular neurons and the cell bodies of their central counterparts.[22] Migraine-specific drugs also constrict meningeal, dural, cerebral, and pial vessels by stimulating vascular 5-HT_{1B} receptors.[21,23,24] Ergots have greater receptor affinity at 5-HT_{1A}, 5-HT_2, adrenergic, and dopaminergic receptors than do triptans, accounting for their frequent AEs.

The first triptan was sumatriptan, followed by zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan, all of which are more centrally penetrant than sumatriptan. All are effective, even if taken after the onset of migraine, and may be more effective when pain is mild.[25] They relieve head pain and nausea and vomiting. Efficacy is

measured by 2-h response rates and therapeutic gain (the difference between active drug and placebo) (Table 4). Other measures include 2-h pain-free and recurrence rates. Common AEs include subcutaneous injection site pain, tingling, flushing, burning, warm or hot sensations, dizziness, paresthesias, somnolence, fatigue, heaviness, neck pain, and dysphoria.[26]

Headache severity, rapidity of onset, and duration are important factors when deciding which triptan should be used. When the headache intensifies rapidly (<30 min), or nausea and emesis occur early and severe associated symptoms are present, nonoral formulations should be used. Subcutaneous sumatriptan is the most effective triptan. Triptans given by nasal spray may have a slightly faster onset of action than oral triptans but may be associated with a disagreeable taste. Triptans, if given early, can prevent central sensitization (manifested by cutaneous allodynia), and established central sensitization impairs their effectiveness.[27] At least two attacks must be unsuccessfully treated before the drug is deemed ineffective. If the drug does fail, one can change the dose, formulation, and route of administration and treat earlier in an attack. If all of this fails, or AEs are especially bothersome, a medication change may be needed. Limit the use of acute treatment to 2–3 days a week to prevent medication overuse.[28] Because all treatments occasionally fail, rescue treatments (opioids, neuroleptics, and corticosteroids) are needed; however, these medications often limit function as a result of sedation or other AEs.

NEW ACUTE THERAPIES

Triptans are not the ideal treatment of migraine attacks, despite their relatively high efficacy score. Recurrence, AEs, and cardiovascular safety are the major issues. There is a need for drugs with greater efficiency and better tolerance.

5-HT $_{1F}$ RECEPTOR AGONISTS

The presence of 5-HT$_{1F}$ receptor mRNA in trigeminal ganglia neurons led to the suggestion that 5-HT$_{1F}$ receptors could be a therapeutic target for migraine.[29] Lasmiditan (COL-144) is a new, highly selective, centrally acting 5-HT$_{1F}$ agonist. Lasmiditan inhibits dural PPE and decreases trigeminal nucleus caudalis c-Fos expression following trigeminal ganglion stimulation; unlike triptans, it did not constrict the rabbit saphenous vein.[30] An intravenous formulation was effective in a proof-of-concept migraine study. Färkkilä *et al.*[31] reported on the efficacy and safety of oral lasmiditan (50, 100, 200, and 400 mg) in acute migraine treatment in a multicenter, double-blind, parallel-group, dose-ranging study. A linear association between headache response rate at 2 h and the dose of lasmiditan was shown to exist. All doses were superior to placebo. Treatment-emergent AEs were dose-dependent and mild or moderate in intensity. The most common AEs were vertigo, dizziness, fatigue, paresthesia, and somnolence. Vestibular AEs could be due to activation of 5-HT$_{1F}$ receptors in the lateral vestibular nucleus, temporoparietal cortex, and cerebellum. Further studies are needed.

Table 4 Triptans

	Headache response (2 h)[a]	Therapeutic gain (2 h)[a]	Pain-free frequency (2 h)[a]	Pain-free therapeutic gain (2 h)[a]	Recurrence rate
Almotriptan					
12.5 mg	61% (57–65)	25% (14–36)	36% (32–40)	21% (17–25)	26% (22–30)[b]
Eletriptan					
40 mg	60% (58–64)	35% (27–41)	27% (25–29)	22% (18–26)	21% (18–24)[b]
80 mg	66% (62–70)	42% (36–48)	33% (28–38)	28% (23–33)	20% (1–28)[b]
Frovatriptan	42% (40–44)	17% (27–44)			
2.5 mg					
Naratriptan					21% (13–28)[b]
2.5 mg	49% (46–92)	22% (17–27)	22% (20–24)	14% (11–17)	24% (21–27)[c]
Rizatriptan					
5 mg	62% (60–64)	28% (23–33)	30% (28–32)	22% (20–24)	39% (36–42)[b]
10 mg	69% (67–71)	35% (30–40)	40% (38–42)	30% (27–33)	37% (35–39)[b]
Zolmitriptan					
2.5 mg	64% (59–69)	34% (27–41)	25% (21–29)	19% (14–24)	30% (26–34)[b]
5 mg	66% (62–70)	37% (30–44)	34% (30–38)	28% (23–33)	34% (25–43)[b]
5 mg (IN)	69% (62–75)	38% (30–47)	36% (29–42)	29% (22–36)	27% (20–34)[b]
Sumatriptan					
50 mg	63% (60–64)	31% (24–38)	28% (26–30)	18% (12–24)	28% (29–31)[b]
100 mg	59% (57–61)	29% (25–33)	29% (27–31)	20% (18–22)	
20 mg (IN)	61% (55–78)	31% (28–43)	27–37%	11–28%	30% (27–33)[b]
6 mg (SC)[a]	69% (70–88)	50% (38–77)	48–49%	46–43%	

All oral except for IN and SC.

IN, intranasal; SC, subcutaneous.

[a]All 2 h except for sumatriptan SC = 1 h. [b]2–24 h. [c]4–24 h.

Adapted from refs. 76–79.

NEUROPEPTIDE ANTAGONISTS

Trigeminal ganglion stimulation results in elevation of CGRP and SP,[32] but only external jugular vein CGRP was found to be elevated during an acute migraine attack.[33,34] On the basis of the fact that triptans and ergots block the release of CGRP and SP, antagonists to their receptors were developed. The first to be studied were the neurokinin (NK) (SP) antagonists.

SP ANTAGONISTS

Lanepitant is a high-affinity selective NK-1 receptor antagonist. It inhibited neurogenic inflammation (with PPE) in the dura, a model of migraine. However, lanepitant 30, 80, and 240 mg given orally was no more effective than placebo in a controlled, double-blind, crossover trial. Some suggested that the negative result could have been due to inadequate plasma concentration of the drug.[35] Another NK-1 receptor antagonist, RPR100893-201, was also not effective in acute migraine treatment at a 20 mg oral dose. Again, sufficient plasma concentration may not have been achieved.[36] However, a third NK-1-proven centrally penetrant antagonist, aprepitant (L-754030), also failed to show efficacy for the acute treatment of migraine. It is currently marketed as an antiemetic.[37] This suggests that SP is not primarily involved in the pathogenesis of migraine and is consistent with the observation that SP is not elevated in external jugular venous blood during migraine.[34]

CGRP ANTAGONISTS

In humans, CGRP exists in two forms: α-CGRP and β-CGRP. α-CGRP and its receptors are relevant to migraine. The 37-amino-acid neuropeptide α-CGRP, which is produced by alternative RNA splicing of the calcitonin gene, is the main form expressed in trigeminal ganglia neurons.[38] Functional CGRP receptors are composed of a G protein–coupled receptor known as the calcitonin-like receptor, a single transmembrane domain protein called receptor activity–modifying protein type 1, and a receptor component protein that defines the G-protein to which the receptor couples.[39] CGRP receptors are found on meningeal blood vessels, trigeminal ganglion, and afferents, and in the periaqueductal gray and other areas of the brain associated with migraine.[40] CGRP is elevated in external jugular venous blood during a migraine attack.[34] Selective CGRP receptor antagonists (gepants) have no vasoconstrictor properties and few AEs. Four chemically unrelated CGRP receptor antagonists (olcegepant, telcagepant, MK-3207, and BI 44370 TA) are effective in acute migraine treatment. The first gepant, olcegepant (BIBN4096BS), was effective in migraine, but because it could only be administered intravenously it was abandoned after phase II.[41] Intravenous administration of 2.5 mg of olcegepant produced a response rate of 66%, as compared with 27% for placebo.

A second gepant, telcagepant, was orally available, and six positive phase III trials have been reported.[42–44] The AE profile of telcagepant was similar to that of placebo. However, the pooled results of four randomized controlled trials with telcagepant (300 mg orally)[45] showed that it acted less rapidly than triptans: 26% of patients were pain free at 2 h (11% with placebo, number needed to treat 6.7) as compared with 41% in rizatriptan (10 mg) and 35% in almotriptan (12.5 mg) trials. Telcagepant development has been stopped. In a phase IIa exploratory study, a small number of patients taking telcagepant twice daily for 3 months for migraine prevention showed elevations in liver transaminase levels. Similar elevations in liver transaminase were found in a short-term study of menstrual migraine. The development of MK-3207 was also terminated following review of phase I and II clinical trial results that showed the presence of asymptomatic liver test abnormalities. A backup compound is now in clinical trials.[46] Boehringer Ingelheim completed a phase II trial that treated 341 patients who experience migraines with the oral CGRP receptor antagonist BI 44370 TA. It compared 50, 200, and 400 mg of BI 44370 TA with the active comparator eletriptan (40 mg) and placebo. The number of patients reaching the primary end point—pain freedom after 2 h—was significant exclusively in the 400-mg group (27.4 %) and the eletriptan group (34.8 %) as compared with placebo.[47]

A potent, orally active CGRP receptor antagonist was synthesized with limited aqueous solubility (BMS-846372).[48] A derivative was then created (BMS-927711) by adding a primary amine to the cycloheptane ring of BMS-846372 to increase solubility. Clinical trials are now under way (BMS-927711 | The Haystack http://cenblog.org/the-haystack/tag/bms-927711/).

NITRIC OXIDE SYNTHETASE INHIBITORS

Nitric oxide (NO), a highly reactive free-radical gas, was initially discovered in macrophages and endothelial cells. It is released in response to acetylcholine and acts as a vascular relaxing factor. It is synthesized by the enzyme NO synthetase (NOS). NO activates soluble guanyl cyclase, which results in increased cyclic guanosine monophosphate. NOS is present throughout the brain and spinal cord in neurons. Activation of postsynaptic neuronal *N*-methyl-D-aspartate receptors results in NO production. It can act as an intercellular messenger, inducing changes in synaptic contact and resulting in the release of CGRP. Nitroglycerin, a NO prodrug, is metabolized to NO, producing vasodilation and headache. Olesen *et al.*[49] infused nitroglycerin in volunteers; it triggered an immediate headache in all, but a delayed migraine headache in migraineurs. NO may also link neuronal activity and cerebral blood flow.[50–52] This finding led to a double-blind, placebo-controlled trial of the nonselective NOS inhibitor, L-NGmethylarginine hydrochloride (546 C88) in acute migraine. The 2-h response was 67% for the L-NGmethylarginine hydrochloride group ($n = 15$) and 14% for the placebo group ($n = 14$).[53] GlaxoSmithKline developed a highly selective inhibitor of the inducible isoform of NOS (GW274150),[54,55] but this was no more effective than placebo for the acute[56] and preventive[57,58] treatment of migraine. No significant differences were found in the primary end point (pain-free after 2 h) or on any migraine-associated symptom.[56] Therefore, the inducible isoform of NOS is not a suitable target for migraine treatment.

ION CHANNEL ANTAGONISM

The three genes known to cause familial hemiplegic migraine are all involved in ion homeostasis across the neuronal cell membrane. ATP-sensitive potassium channel openers have induced headache in clinical trials.[59] TRESK is a two-pore

domain (K2P) potassium channel, encoded by *KCNK18*.[60] K2P channels control neuronal resting membrane potential and neuronal excitability.[61] K2P channels are a site of action for many volatile anesthetics such as halothane[62] (which inhibit CSD) and neuroprotective agents. The TRESK K2P channel modulates cellular excitability. It is activated by calcineurin after $G_q\alpha$ receptor stimulation and a subsequent rise in intracellular calcium.[63,64] This may explain the calcineurin inhibitor–induced pain syndrome.[64,65]

Lafrenière *et al.*[66] looked at TRESK mutations in migraine with aura. They screened the *KCNK18* gene in migraineurs and found a frameshift mutation, F139WfsX24, that segregates perfectly with typical migraine with aura. TRESK was found to be expressed in the trigeminal ganglion. This mutation causes a complete loss of TRESK function and suppresses normal channel function through a dominant negative effect. This explains its dominant effect. These studies support a role for TRESK in the pathogenesis of typical migraine with aura and further support the role of this channel as a potential therapeutic target.[66]

PREVENTIVE TREATMENT

Preventive treatment is used mainly to reduce attack frequency. It may also decrease attack duration or severity and often enhances the benefit of acute treatment.[1,67] Preventive treatment can result in the reduction of health-care costs. Silberstein *et al.*[68] found that adding a migraine preventive drug to an acute-medication-only regimen reduced resource consumption. Outpatient visits for migraine decreased by 51.1%, emergency department visits decreased by 81.8%, computed tomography scans decreased by 75.0%, magnetic resonance imaging decreased by 88.2%, and other migraine drug use decreased by14.1%.

Indications for preventive treatment include:[69,70]

- Recurring migraine that significantly interferes with the patient's quality of life and daily routine despite acute treatment
- Failure of, contraindication to, or troublesome AEs from acute medications
- Acute medication overuse
- Very frequent headaches (more than one a week) (risk of chronic migraine or medication overuse)
- Patient preference
- Special circumstances, such as hemiplegic migraine, frequent, very long, or uncomfortable auras, or attacks with a risk of permanent neurologic injury

Preventive medication groups include β-adrenergic blockers, antidepressants, calcium channel antagonists, serotonin antagonists, anticonvulsants, and nonsteroidal anti-inflammatory drugs. A drug is chosen based on its efficacy, AEs, and the presence of any coexistent disorder. Preventive drugs with the best proven efficacy are the β-blockers, divalproex, and topiramate. The chosen drug should have the best risk-to-benefit ratio for the individual patient and take advantage of the drug's side effect profile. An underweight patient would be a candidate for one of the medications that commonly produce weight gain, such as a tricyclic antidepressant; by contrast, one would try to avoid these drugs and consider topiramate when a patient is overweight. Tertiary tricyclic antidepressants that have a sedating effect would be useful at bedtime for patients with insomnia. Older patients with cardiac disease or patients with significant hypotension may not be able to use tricyclic antidepressants or calcium channel or β-blockers but could use divalproex or topiramate. The athletic patient should use β-blockers with caution. Medication that can impair cognitive functioning should be avoided when patients are dependent on their wits.

The drug must be started at a low dose and increased slowly. This may take 2–3 months because it takes time to develop the therapeutic effect. Dose reduction may provide a better risk-to-benefit ratio. Preventive treatment is often recommended for only 6–9 months, but until now no randomized, placebo-controlled trials have been performed to investigate migraine frequency after discontinuation of preventive treatment. Diener *et al.*[71] assessed 818 migraine patients who were treated with topiramate for 6 months to observe the effects of topiramate discontinuation. Patients received topiramate in a 26-week open-label phase. They were then randomly assigned to continue this dose or switch to placebo for a 26-week, double-blind phase. The mean increase in number of migraine days was greater in the placebo group (1.19 days in 4 weeks, 95% confidence interval 0.71 to 1.66; $P < 0.0001$) than in the topiramate group (0.10, −0.36 to 0.56; $P = 0.5756$). Patients in the placebo group had more days on acute medication than did those in the topiramate group (mean difference between groups −0.95,−1.49 to −0.41; $P = 0.0007$). Sustained benefit was reported after topiramate was discontinued, although the number of migraine days did increase. These findings suggest that patients should be treated for 6 months, with the option to continue to 12 months. If headaches are well controlled, medication can be tapered and discontinued. Dose reduction may provide a better risk-to-benefit ratio.

NEW PREVENTIVE TREATMENTS

A recent development is the creation of antibodies to CGRP and its receptor.[66] Human monoclonal antibodies that specifically target the human CGRP receptor have been generated. They have minimum activity at the rat receptor and have >50-fold selectivity over other closely related receptors. The inhibition of capsaicin-induced increases in dermal blood flow has been used as an *in vivo* pharmacodynamic model in humans and in nonhuman primates during the development of CGRP receptor antagonists. Topically applied capsaicin stimulates dermal neurons to release CGRP that in turn results in a localized increase in dermal blood flow, measured by laser Doppler imaging. The CGRP receptor antagonist monoclonal antibody AA95 prevented capsaicin-induced increase in dermal blood flow in cynomolgus monkeys for up to 7 days.[72]

The immunochemical distribution of another antibody in the series, AA32, has been tested; this recognizes the functional calcitonin-like receptor/receptor activity modifying protein type 1 receptor complex but not its individual components. AA32-positive CGRP receptor complexes are expressed on multiple levels in the trigeminal vascular system of the cynomolgus monkey: (i) in the meningeal vasculature innervated

by CGRP-positive nerve fibers, (ii) in neurons and satellite cells in the trigeminal ganglion, and (iii) in neurons in the spinal trigeminal nucleus. The CGRP receptor localization is consistent with CGRP's role in trigeminal sensitization and suggests that interfering with CGRP receptor transmission may be beneficial for the treatment of migraines.[73]

Zeller *et al.*[74] took another approach, using monoclonal antibodies to previously identified rat α-CGRP received through a licensing agreement from the University of California, Los Angeles.[75] They investigated whether function-blocking CGRP antibodies would inhibit neurogenic vasodilation with a long duration of action. They used two rat blood-flow models that measure electrically stimulated vasodilation in the skin or the middle meningeal artery. These responses are largely dependent on the neurogenic release of CGRP from sensory afferents. Treatment with anti-CGRP antibodies inhibited skin vasodilation or the increase in middle meningeal artery diameter to a similar magnitude as treatment with CGRP receptor antagonists but with a slower onset of action. The inhibition was still evident 1 week after dosing. Chronic treatment with anti-CGRP antibodies had no detectable effects on heart rate or blood pressure. Anti-CGRP antibodies may be a suitable drug candidate for the preventive treatment of migraine. They are currently being developed by Pfizer.

Another humanized monoclonal antibody, LY2951742, has been shown to prevent capsaicin-induced increases in dermal blood flow in rats, nonhuman primates, and healthy human volunteers. It is administered by subcutaneous injection. The time to maximum serum concentration ranges from 7 to 13 days, with an elimination half-life of ~28 days. A phase II randomized, double-blind, placebo-controlled study of LY2951742 in patients with migraine is now under way. The study is composed of four trial periods: screening and washout; baseline for assessment of type, frequency, and severity of headaches (4 weeks); treatment (12 weeks); and follow-up (12 weeks). LY2951742 (150 mg) will be administered subcutaneously once every other week for 12 weeks. The primary outcome measure is the mean change from baseline in the number of migraine headache days in a 28-day period.

SUMMARY

Migraine is a disabling primary episodic headache disorder resulting from altered modulation of normal sensory stimuli and dysfunction of the trigeminal nerve and its central connections. It ranks among the world's most disabling medical illnesses. Diagnosis is based on the headache's characteristics and associated symptoms. The economic and societal impact of migraine is substantial. It impacts sufferers' quality of life and impairs work, social activities, and family life. There are many acute and preventive migraine treatments on the market. Acute treatment is either specific (triptans and ergots) or nonspecific (analgesics). Disabling migraine should be treated with triptans. Increased headache frequency is an indication for preventive treatment. Preventive treatment decreases migraine frequency and improves quality of life. More treatments are being developed, and this provides hope to the many sufferers who still experience uncontrolled migraine.

CONFLICT OF INTEREST

The author declared no conflict of interest.

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