CNS SPECTRUMS

CME Review Article

Current Management: Migraine Headache

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- Identify pathophysiologic targets of current and investigational therapies in migraine treatment and prevention

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REVIEW ARTICLE

Current management: migraine headache

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Migraine varies in its frequency, severity, and impact; treatment should consider these variations and the patient's needs and goals. Migraine pharmacologic treatment may be acute (abortive) or preventive (prophylactic), and patients often require both. New medication devices are available or in development, including an intracutaneous, microneedle system of zolmitriptan and sumatriptan, and breath-powered powder sumatriptan intranasal treatment. Lasmiditan, a 5-HT_{1F} receptor agonist, is in development for acute treatment, as are small molecule calcitonin gene-related peptide (CGRP) receptor antagonists (Gepants) for acute and preventive treatment. Antibodies to CGRP and its receptor are being developed for migraine prevention. All 4 treatments are effective and have, as of yet, no safety concerns.

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Key words: Acute treatment, headache, migraine, monoclonal antibodies, preventative treatment.

Introduction

Migraine varies in its frequency, severity, and impact; treatment should consider these variations and the patient's needs and goals.[1] Treatment begins with a proper diagnosis and addressing the impact of the headache.[2] Education about adverse events, duration of therapy, and expectations is important.[3] Comorbidity is the association of two disorders more likely to occur by coincidence. Migraine comorbid disorders are listed in Table 1. Migraine treatment may be acute (abortive) or preventive (prophylactic), and patients may need both. Successful prevention reduces attack frequency. It may also decrease attack duration or severity and enhance the response to acute treatments, improve function, reduce disability,[3] and reduce healthcare costs.[4]

Acute Treatment

Medications are usually the acute treatment of choice. In a longitudinal study, 91.7% of 11,388 people with episodic migraine reported using pharmacologic treatment for their acute migraine attacks.[5] The objectives of acute treatment are to treat attacks early; to achieve quick, complete pain relief; to minimize or eliminate adverse events; to restore function; to decrease recurrence and the need for rescue treatment; and to reduce medical resource use.[6]

Acute pharmacologic treatment includes both migraine-specific medications, such as triptans and dihydroergotamine, and nonspecific medications such as acetylsalicylic acid (ASA), acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). It also includes medications for relief of associated symptoms, such as nausea. Adjunctive medications include antiemetics (eg, metoclopramide or prochlorperazine) and corticosteroids.

General Principles

1. The most effective strategy for patients with attacks of different severity is a "step care within attack" strategy. Early administration of treatment is most appropriate for consistently moderate or severe attacks that respond well to treatment. This recommendation should be guided by the frequency of the headache. For those with near-daily, daily, or continuous headache, caution is needed to avoid acute medication overuse.
2. The route of administration depends on the prior response to oral therapy, the temporal characteristics of the attack, and the presence and timing of nausea and vomiting. Early nausea and vomiting during an attack may impair absorption and bioavailability, diminishing the efficacy and/or consistency of acute medications.[7] Non-oral routes of administration include nasal spray, suppository, subcutaneous or transcutaneous injection, and inhalation.

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TABLE 1. Migraine comorbid disease

Cardiovascular	Neurologic
Raynaud's	Epilepsy
Patent foramen ovale (migraine with aura)	Fibromyalgia
Atrial septal defects (ASD), pulmonary AVMs	Positional vertigo
Mitral valve prolapse	Restless legs syndrome
Angina/myocardial infarction	Bell's palsy
Stroke	
Psychiatric	**GI**
Depression	Irritable bowel syndrome
Mania	Peptic ulcer disease
Panic disorder	
Anxiety disorder	
	Other
	Asthma
	Allergies

3. Adjunctive medications are useful for patients who respond partially to a single medication. Patients who do not consistently achieve an adequate response to a triptan, for example, may require concomitant therapy to treat nausea (antiemetic), or to achieve a more sustained response by reducing the risk of recurrence within a 24- to 48-hour period (NSAID).[8–11]
4. All patients need rescue therapy when acute therapy is not effective, even if they typically respond to their usual treatment.[12–15]

Acute Treatment Guidelines

According to an evidence-based guideline from the American Headache Society (Table 2), all currently available triptans, in various formulations, are effective (Level A) for the acute treatment of migraine for moderate or severe pain at the time of treatment. Dihydroergotamine nasal spray is effective (Level A), and ergotamine and intravenous ergotamine are probably effective (Level B) for acute treatment.

Effective nonspecific medications include aspirin (500 mg), acetaminophen (1000 mg), diclofenac (50 or 100 mg), ibuprofen, metamizole (dipyrone) (1 mg), naproxen (500 or 550 mg), rofecoxib (25 mg), butorphenol nasal spray, codeine, and a combination of acetaminophen/aspirin/caffeine (Level A). Ketoprofen, IV ketorolac, or magnesium; isometheptene compounds; and tramadol/acetaminophen are probably effective (Level B). There is not enough information available to determine if celecoxib (400 mg) is effective in migraine (Level U). The antiemetics prochlorpromazine, droperidol, chlorpromazine, and metoclopramide are probably effective (Level B).

Dexamethasone is probably effective when given with rizatriptan (10 mg) (Level B). There is inadequate evidence for intravenous valproic acid (Level U). Butalbital is possibly effective (Level C).

Emerging Acute Therapies

While the triptans have significantly advanced acute migraine treatment, approximately one-fifth of migraineurs have cardiovascular contraindications that limit their use. Their efficacy is limited when considering the most robust patient-centered outcomes. In addition, triptans induce latent central sensitization and may promote the development of medication overuse headache (MOH).[16] Therefore, there is a large unmet treatment need for safe and effective acute migraine drugs that do not constrict vascular beds or induce MOH. In addition, new formulations of older drugs are being developed. U.S. Food and Drug Administration (FDA)-approved new formulations include sumatriptan needle-free injection (brand name Sumavel); sumatriptan epipen-like injection (brand name Alsuma); sumatriptan auto-injectors (Dr. Reddy's Zembrace, Sun, generic); and breath-powered powder sumatriptan intranasal treatment (brand name Onzetra).

Sumatriptan iontophoretic patch (brand name Zecuity) is off the market because of adverse events (AEs). Awaiting FDA approval are rizatriptan dissolvable film (RHB-103, VersaFilm) and dihydroergotamine (DHE) oral inhalation (brand name Semprana).

New medication devices in development include an intracutaneous microneedle system of zolmitriptan[17] and sumatriptan (Sofusa Dose Disc System Skin Patch), zolmitriptan oral inhalation (CVT-427), and sumatriptan oral spray (SUD-001).

5-HT 1F Receptor Agonists

Serotonin (5-hydroxytryptamine [5-HT]), a biogenic amine, was identified, crystallized, and named by Rapport and Page.[18] There are 7 types of 5-HT receptors, $5\text{-HT}_{1–7}$. All are G protein-coupled receptors except the $5\text{-HT}_{3\ \text{receptor}}$, which is a ligand-gated cation channel.[19] The 5-HT1 subfamily consists of 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F.[19]

Ergotamine targets $5\text{-HT}_{1A\text{-}1F}$; $5\text{-HT}_{2A\text{-}C}$, $D_{1\text{-}5}$ and α1 and α2 adrenergic receptor types.[20] The anti-migraine effects are due to agonist activity at the 5-HT_{1B}, 5-HT_{1D}, and possibly 5-HT_{1F} receptors on trigeminal nerve terminals.[21] Ergotamine causes vasoconstriction, which can cause hypertension and coronary vasoconstriction. Retroperitoneal fibrosis, pleuropulmonary fibrosis, and cardiac valvulopathy can occur with chronic use.

The triptans have high $5\text{-HT}_{1B\ \text{and}}$ 5-HT_{1D} receptor affinity. 5-HT1B receptors mediate vasoconstriction, and 5-HT1D receptors mediate inhibition of neuronal impulse transmission.[11] In addition, several triptans have affinity for the 5-HT_{1F} receptors subtype, which does not mediate vasoconstion.[22] Spiral and vestibular ganglion cells in rodents and primates express the

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TABLE 2. Acute treatment evidence

Level A	Level B	Level C	Level U	Others
Analgesic Acetaminophen 1000 mg (for non-incapacitating attacks)	**Antiemetics** *Chlorpromazine IV 12.5 mg Droperidol IV 2.75 mg *Metoclopramide IV 10 mg *Prochlorperazine IV/IM 10 mg; PR 25 mg	**Antiepileptic** Valproate IV 400-1000 mg	**NSAIDs** Celecoxib 400 mg	**Level B negative** **Other** Octreotide SC 100 μg
Ergots DHE *Nasal spray 2 mg Pulmonary inhaler 1 mg	**Ergots** DHE * IV, IM, SC 1 mg *Ergotaminc/caffeine 1/100 mg	**Ergot** *Ergotamine 1-2 mg	**Others** *Lidocaine IV *Hydrocortisone IV 50 mg	**Level C negative** **Antiemetics** *Chlorpromazinc IM 1 mg/kg *Granisctron IV 40-80 μg/kg
NSAIDs *Aspirin 500 mg Diclofenac 50, 100 mg Ibuprofen 200, 400 mg *Naproxen 500, 550 mg	**NSAIDs** *Flurbiprofen 100 mg Ketoprofen 100 mg Ketorolac IV/IM 30-60 mg	**NSAIDs** Phenazone 1000 mg		**NSAIDs** Ketorolac tromethamine nasal spray
Opioids *Butorphanol nasal spray 1 mg		**Opioid** *Butorphanol IM 2 mg *Codeine 30 mg PO *Meperidine IM 75 mg *Methadone IM 10 mg *Tramadol IV 100 mg		**Analgesic** Acetaminophen IV 1000 mg
Triptans Almotriptan 12.5 mg Eletriptan 20, 40, 80 mg Frovatriptan 2.5 mg *Naratriptan 1, 2.5 mg *Rizatriptan 5, 10 mg Sumatriptan *Oral 25, 50, 100 mg *Nasal spray 10, 20 mg Patch 6.5 mg *SC 4, 6 mg Zolmitriptan nasal spray 2.5, 5 mg *Oral 2.5,5 mg	**Others** $MgSO_4$ IV (migraine with aura) 1-2 g *Isometheptene 65 mg	**Steroid** Dexamethasone IV 4-16 mg		
Combinations *Acetaminophen/aspirin/caffeine 500/500/130 mg Sumatriptan/naproxen 85/500 mg	**Combinations** *Codeine/acetaminophen 25/400 mg Tramadol/acetaminophen 75/650 mg	**Others** *Butalbital 50 mg *Lidocaine intranasal		
		Combinations *Butalbital/acetaminophen/caffeine/codeine 50/325/40/30 mg *Butalbital/acetaminophen/caffeine 50/325/40 mg		

Level A: Medications are established as effective for acute migraine treatment based on available evidence. Level B: Medications are probably effective for acute migraine treatment based on available evidence. Level C: Medications are possibly effective for acute migraine treatment based on available evidence. Level U: Evidence is conflicting or inadequate to support or refute the efficacy of the medications for acute migraine. Level B negative: Medication is probably ineffective for acute migraine. Level C negative: Medication is possibly ineffective for acute migraine. NS = nasal spray.

5-HT1A, 5-HT1B, 5-HT1D, and 5-HT1F receptors. Hence, actions of ganglion cells might partly explain the efficacy of these agents in vestibular migraine and their vestibular AEs.[23]

Lasmiditan (COL-144) is a highly selective, potent 5-HT_{1F} receptor agonist.[24] In preclinical animal models, it inhibited dural plasma protein extravasation and reduced trigeminal nucleus caudalis c-Fos expression, following trigeminal ganglion stimulation.[25] Lasmiditan had no vasoconstrictor effect on the rabbit saphenous vein.[25] An intravenous formulation was effective in a proof-of-concept, dose-finding study. Intravenous lasmiditan, at a starting dose of 2.5 mg, was evaluated for the acute treatment of migraine in 130 subjects in a hospital

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setting.[24] Forty-two subjects received placebo and 88 received lasmiditan, in doses ranging from 2.5–45 mg. Of subjects treated in the 10, 20, 30, and 45 mg lasmiditan dose groups, 54–75% showed a 2-hour headache response, compared to 45% in the placebo group ($P < 0.0126$). AEs occurred in 65% of lasmiditan and in 43% of placebo subjects. Dizziness, paresthesia, and limb heaviness occurred more often with lasmiditan.

Oral lasmiditan (50, 100, 200, and 400 mg) was studied in a multicenter, double-blind, parallel-group, dose-ranging, acute migraine study.[26] Lasmiditan was superior to placebo, and showed a dose response effect at 2 hours. Treatment-emergent AEs were dose-dependent, and mild or moderate in intensity. Adverse events included vertigo, dizziness, paresthesia, fatigue, and somnolence.

Controlled phase 3 trials have been completed.[27] In the SAMURAI trial, 2,231 patients were randomized to lasmiditan (100 mg, 200 mg) or placebo; a second dose was permitted for rescue or recurrence. The primary endpoint was 2-hour pain freedom. The key secondary endpoint was the relief of the most bothersome symptoms (MBS) at 2 hours (before dosing, subjects noted whether nausea, phonophobia, or photophobia were present and which was "most bothersome"). About half of subjects found photophobia was their MBS (about one-quarter for nausea and vomiting). For the groups lasmitidan 100 mg, lasmitidan 200 mg, and placebo, 28.2%, 32.2%, and 15.3%, respectively, were free of pain at 2 hours and 40.9%, 40.7%, and 29.5%, respectively, were free of MBS at 2 hours (all < 0.001 compared to placebo). Headache pain relief was 59.4%, 59.5%, and 42.2%, respectively ($p < 0.001$). AEs were dose-dependent and included vertigo, dizziness, paresthesia, fatigue, and somnolence. In this trial, lasmiditan met its primary and secondary endpoints, and many subjects had cardiovascular risk factors or conditions. The GLADIATOR phase 3 long-term, open-label trial is ongoing.[28]

The SPARTAN trial, in addition to 100 mg and 200 mg lasmiditan groups, included a 50 mg group to find the lowest effective dose in acute migraine.[26] The primary and secondary outcome measures are like those of the SAMURAI trial. This trial was completed in June 2017.[29]

CGRP Receptor Antagonists (Gepants)

The CGRP family of neuropeptides consists of CGRP, calcitonin (CT), adrenomedullin (AM), and amylin (AMY). Human CGRP comes in 2 types: α and β. α-CGRP results from alternative splicing of the calcitonin gene; it is the main subtype in trigeminal neurons.[30] The canonical CGRP receptor has three parts: (1) calcitonin-like receptor, (2) receptor activity–modifying protein type 1, and (3) a receptor component protein.[31] CGRP receptors are present on trigeminal ganglia, primary dural sensory afferents, the periaquedactual gray (PAG), and on meningeal blood vessels.[30] The adrenomedullin receptors, AM1 and AM2, consist of CLR coupled with either RAMP2 or RAMP3, respectively. The calcitonin receptor (CTR) consists of only CTR. Amylin receptors are created by linking CTR with a RAMP; amylin AMY1-3 receptors consist of CTR plus RAMP1, 2, or 3, respectively. The amylin 1 receptor (CTR with RAMP1) also responds to CGRP.[32]

CGRP is important in migraine pathophysiology. CGRP infusion triggers attacks of migraine that are indistinguishable from spontaneous attacks in migraineurs[33]; triptans inhibit the release of CGRP[34]; migraine pain relief parallels the decline in circulating CGRP levels[35]; and its levels are increased in external jugular venous blood during an acute migraine attack.[35] The most compelling pieces of evidence are the results of several trials that evaluated the selective CGRP receptor antagonists (gepants) for acute migraine treatment. Gepants are not vasoconstrictors and have minimal adverse events. Gepants block both the canonical CGRP receptor and the Amylin 1 receptor. Five gepants are effective for acute migraine treatment.[36–40] Olcegepant, while effective, could only be given intravenously and was abandoned.[38] Olcegepant (2.5 mg IV) had a response rate of 66%, compared with 27% for placebo. Telcagepant (orally available) had 6 positive phase III trials.[30,41,42] AEs were similar to placebo, but it acted slower than triptans: 26% of subjects were pain free at 2 hours; placebo 11%; rizatriptan (10 mg) 41%; and almotriptan (12.5 mg) 35%.[42] Telcagepant development has been stopped because of significant elevations in liver transaminase levels. Another gepant, MK-3207, was terminated because of asymptomatic liver enzyme abnormalities.[39] Boehringer Ingelheim compared BI 44370 TA[37] (50, 200, and 400 mg) to eletriptan (40 mg) and placebo. More patients had pain freedom at 2 hours, which was significant in the 400 mg group (27.4 %) and the eletriptan group (34.8 %), compared to placebo. BMS-927711 (10, 25, 75, 150, 300, or 600 mg) was tested in a double-blind, placebo-controlled, dose-ranging study[40] using an adaptive design in comparison to sumatriptan 100 mg or placebo. Significantly more patients in the BMS-927711 75 mg (31.4%, $p < 0.002$), 150 mg (32.9%, $p < 0.001$), and 300 mg (29.7%, $p < 0.002$) groups and the sumatriptan group (35%, $p < 0.001$) were free of pain at 2 hours compared to placebo (15.3%). No serious treatment-related AEs were reported, and no patients discontinued because of AEs. Biohaven has acquired BMS-927711 (now called rimegepant) for acute migraine and BHV-3500 for migraine prevention from Bristol-Myers Squibb Company.

Recently Allergan acquired 2 CGRP small molecule receptor antagonists from Merck: ubrogepant

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(MK-1602) for acute migraine treatment and atogepant (MK-8031) for migraine prevention. These different chemical entities are believed to not cause the liver AEs of prior gepants. Voss *et al*[43] studied ubrogepant for the acute migraine treatment in a Phase 2b randomized, double-blind, placebo-controlled trial. Ubrogepant (1 mg, 10 mg, 25 mg, 50 mg, 100 mg) was compared to placebo in a 1:1 ratio. Ubrogepant 100 mg was significantly superior to placebo for pain freedom (25.8% versus 8.9%), but not for headache response at 2 hours. Overall AEs were similar to placebo. Further trials are underway. In aggregate, these studies confirm that gepants are effective for acute migraine treatment and, like lasmiditan, lack vasoconstrictor activity.

Preventive Treatment

Principles

Recent guidelines[44–49] have established criteria for considering migraine preventive treatments and their efficacy (Table 3):

1. Disabling attacks despite appropriate acute treatment
2. Frequency (≥ 4 attacks or ≥ 8 headache days/month)
3. Acute treatment failure, overuse, or bothersome AEs
4. Patient choice
5. Hemiplegic migraine; basilar migraine; frequent, prolonged, or uncomfortable aura symptoms; or migrainous infarction[44,45,50]

A preventive treatment is successful when it decreases migraine by half.

General guidelines for instituting preventive therapy

- Start at a low dose and slowly increase until it is effective, the maximum dose is reached, or there are intolerable AEs.
- Consider comorbidity disorders (Table 1).[46,51–58]
- Do not use contraindicated drugs (coexistent or comorbid illnesses).
- Have an adequate trial (2–6 months).
- Have realistic goals.
- Periodically revaluate therapy.
- Women need to be aware of drug effects on a fetus.[59]
- Involve patients; discuss their treatment and their expectations.
- Discuss AEs.

Monotherapy is a treatment goal but is often not attainable. Polytherapy may enable therapeutic adjustments based on the status of coexistent disorders.

New Preventive Medications

Small molecule CGRP antagonists (gepants)

Gepants block both the canonical CGRP receptor and the amylin 1 receptor. Ho *et al*[60] evaluated telcagepant in a migraine preventive trial. The trial was terminated due to hepatotoxicity concerns. Telcagepant was effective, but the aminotransferase elevations led to its discontinuation. Allergan acquired the rights to 2 new CGRP small molecule receptor antagonists from Merck, including atogepant (MK-8031), for the prevention of migraines. Biohaven acquired 2 new gepants from

TABLE 3. Classification of migraine preventive therapies

Level A: Effective	Level B: Probably effective	Level C: Possibly effective	Level U: Inadequate or conflicting data	Ineffective, probably or possibly effective
AEDs	**Antidepressants**	**ACE inhibitors**	**α-Agonists**	**Ineffective**
Divalproex sodium	Amitriptyline	Lisinopril	Clonidine	Lamotrigine
Sodium valproate	Venlafaxine	**Angiotensin blockers**	**Antidepressants**	**Probably ineffective**
Topiramate	**ß-Blockers**	Candesartan	Fluoxetine	Clomipramine
ß-Blockers	Atenolol	**AEDs**	Fluvoxamine	**Possibly ineffective**
Metoprolol	Nadolol	Carbamazepine	Protriptyline	Acebutolol
Propranolol		**Antihistamines**	**AEDs**	Clonazepam
Timolol		Cyproheptadine	Gabapentin	Nabumetone
		ß-Blockers	**ß-Blockers**	Oxcarbazepine
		Nebivolol	Bisoprolol	Telmisartan
			Pindolol	
			Ca++ blockers	
			Cyclandelate	
			Nicardipine	
			Nifedipine	
			Nimodipine	
			Verapamil	

Abbreviations: ACE = angiotensin-converting-enzyme; Ca++ blockers = calcium channel blockers; MRM = menstrually related migraine; SSNRI = selective serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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Bristol-Myers Squibb Company including BHV-3500 for migraine prevention.

Monoclonal antibodies (mABs)

Monoclonal antibodies (mABs) to CGRP and its receptor now exist. How do they differ from small molecules? MABs function extracellularly, while small molecules function both extra- and intracellularly. They are more specific, do not affect QT intervals, and have limited, off-target toxicity. They do not cross the blood–brain barrier and have few central nervous system AEs. mABs are large molecules and cannot be administered orally. Their half-life is weeks, allowing for long-dosing intervals. They are not eliminated through the liver or kidneys. Humanized mABs contain 85% to >90% human protein. Fully human or human mABs contain both heavy and light chains from human origins.[61]

Three mABs that target CGRP, and one that targets the canonical CGRP receptor, are being developed. Lilly is developing Galcanezumab (LY2951742), a humanized monoclonal antibody against CGRP. Galcanezumab blocks capsaicin-induced increases in skin blood flow. Capsaicin stimulates dermal neurons to release CGRP, resulting in increased dermal blood flow. CGRP mAB receptor antagonist effects last for at least a week.[62] The time to Cmax after subcultaneous (SC) ranges from 7 to 13 days, with a 28 days elimination half-life. A phase 2 study in episodic migraine has been completed. Patients (18–65) were randomly assigned (1:1) to galcanezumab (n = 108) or placebo (n = 110) (SC) every 2 weeks for 12 weeks. The primary endpoint (mean change migraine headache days/28-day period) was assessed at 9–12 weeks. The mean change in migraine headache days was –4·2 (SD 3.1; 62.5% decrease), with galcanezumab group compared with –3.0 (SD 3·0; 42.3% decrease) with placebo. AEs more frequent than placebo included injection site pain, erythema, upper respiratory tract infections, and abdominal pain. Galcanezumab thus is beneficial in migraine prevention and provides support for the role of CGRP in the pathogenesis of migraine.[63] There are a number of ongoing trials:

- EVOLVE-2 study (NCT02614196): a phase 3, randomized, D-B, P-C study in episodic migraine
- REGAIN study (NCT02614261): a phase 3, randomized, D-B, P-C study in chronic migraine
- Studies in episodic (NCT02397473) and chronic (NCT02438826) cluster headache[64]

Teva acquired fremanezumab (TEV-48125, formerly LBR-101) from Labrys. It is a humanized mAB against isoforms (α and β) of CGRP.[65] In phase 1 studies, it was given to 94 subjects (0.2–2000 mg) once (day 1) intravenously (IV), or up to 300 mg given twice (day 1 and day 14). The drug was very well-tolerated, with about 1.4 treatment-emergent AEs compared to 1.3 on placebo. Overall treatment-related AEs occurred in 21.2% of the active group and in 17.7% of the placebo group.

Bigal *et al*[66] studied fremanezumab in the prevention of high-frequency episodic migraine (phase 2b). They randomly assigned patients to 3 28-day treatment cycles of subcutaneous (SC) fremanezumab (225 mg or 675 mg) or placebo. Migraine days decreased from baseline to weeks 9–12 by –3.46 days in the placebo group, compared to –6.27 days for 225 mg, and –6.09 days for the 675 mg group. In this trial, fremanezumab was safe, well-tolerated, and effective as a preventive treatment of high-frequency episodic migraine.[66] Bigal *et al* then studied 2 doses of fremanezumab in chronic migraine prevention. They randomly assigned patients to 3 28-day treatment cycles of SC fremanezumab (675 mg in the first and 225 mg in the second and third treatment cycles), fremanezumab (900 mg each treatment cycle), or placebo. The mean decrease from baseline in headache-hours during weeks 9–12 was –59.84 hours in the 675/225 mg group, –67.51 hours in the 900 mg group, compared to –37.10 hours for placebo. Most AEs were mild (injection-site pain and pruritus). Fremanezumab SC was tolerable and effective.[67]

Trials underway include the following:

- A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens for episodic migraine prevention (NCT02629861)
- A second study for chronic migraine prevention (NCT02621931)
- A randomized, double-blind, placebo-controlled, parallel-group study of 2 dose regimens for episodic cluster headache prevention (NCT02945046)
- A second study for chronic cluster headache (NCT02964338)[64]

Alder developed eptinezumab (ALD403) a desialylated, humanized IgG1 mAB that binds to both α and β forms of human CGRP. The plasma elimination after T ½ is 31 days. Dodick *et al*[68] studied eptinezumab for migraine prevention in a phase 2 trial. Patients (18–55) who had 5 to 14 migraine days/28-days were randomized to IV eptinezumab 1000 mg or placebo. Safety was assessed 12 weeks later. The primary endpoint was the change from baseline to weeks 5–8 in migraine day frequency. AEs occurred in 57% of patients in the eptinezumab group and 52% in the placebo group. The mean change in migraine days was –5.6 (SD 3.0) for the eptinezumab group compared with –4.6 (3.6) for placebo (difference –1·0, 95% CI –2·0 to 0·1; one-sided p = 0·0306). No safety issues were found. In this study, eptinezumab was effective in high-frequency, episodic migraine prevention.

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Dodick *et al*[69] studied single IV infusions of eptinezumab 300 mg, 100 mg, 30 mg, and 10 mg versus placebo in the prevention of chronic migraine. Subjects were randomized, and received either a single infusion of eptinezumab 300 mg, 100 mg, 30 mg, 10 mg, or placebo by a 1-hour IV infusion. The study met the primary 12-week post-infusion efficacy endpoint: % difference in patients achieving a 75% reduction in migraine days from baseline: eptinezumab 300 mg (33%) and 100 mg (31%) versus placebo (21%) (weeks 1–12). Significantly more patients had a 50% reduction in migraine days from baseline for eptinezumab 300 mg, 100 mg, and 30 mg versus placebo (weeks 1–12). Eptinezumab was safe, well-tolerated, and met the primary endpoint of ≥ 75% reduction in migraine days compared to placebo.

Erenumab (AMG 334), developed by Amgen, is a human mAB of the IgG2 subtype against the canonical CGRP receptor, not CGRP. The CGRP receptor is a G protein-coupled receptor that is composed of the calcitonin receptor-like receptor and receptor activity-modifying protein 1 (RAMP1) subunits. Erenumab has high affinity (Kd 20 pM) competitively and reversible receptor binding. Its estimated elimination T ½ is 21 days.

Sun *et al*[70] studied erenumab in migraine prevention in a double-blind, placebo-controlled, phase 2 trial. Patients (18–60) who had 4 to 14 migraine days per month were randomized (3:2:2:2 ratio) to monthly SC placebo, erenumab 7 mg, 21 mg, or 70 mg. The primary endpoint, the mean change in monthly migraine days (baseline to the last 4 weeks of the 12-week, double-blind treatment phase), was −3.4 days with erenumab 70 mg versus −2.3 days with placebo (difference −1.1 days, $p = 0.021$). The mean reductions in monthly migraine days with the 7 mg (−2.2) and the 21 mg (−2.4) doses were not significantly different from placebo. AEs occurred in 54% of those who received placebo compared to 50% to 54% in the erenumab groups. Erenumab 70 mg is a potential therapy for prevention of episodic migraine. Two trials are underway for rrenumab in episodic migraine prevention: ARISE (NCT02483585) and STRIVE (NCT02456740).[64]

Tepper *et al*[71] studied erenumab in subjects with chronic migraine (18–65 years). Patients received erenumab (70 mg or 140 mg) or placebo every month by SC injection. The primary endpoint was the change from baseline in monthly migraine days. The secondary endpoints were the proportion of patients with ≥ 50% reduction in monthly migraine days, change from baseline in acute migraine-specific medication use days, and change from baseline in cumulative headache hours. Both erenumab doses [70 mg (−6.64) and 140 mg (16.63)] had statistically significant clinically meaningful reduction in monthly migraine days compared with placebo (−4.8). Erenumab 70 mg (39.9%) and 140 mg (41.1%) also showed statistically significant improvements in ≥ 50% responder rate compared to placebo (23.5%). Safety and tolerability were like placebo. One trial is underway for erenumab in chronic migraine prevention (NCT20120295).[64]

Orexin receptor antagonists (rexants)

The orexins (A and B) are a pair of hypothalamic neuropeptides that may be involved in nociception. Both neuropeptides are cleaved from the same precursor, preproorexin, and act on 2 G-coupled receptors termed the orexin 1 (OX1R) and 2 (OX2R) receptors. Orexin A shows equal efficacy for both receptors, while orexin B is relatively selective for the OX2R. Filorexant, a dual orexin receptor antagonist, was not effective in a phase 2a trial for migraine prevention.[72] However, preclinical evidence suggests that orexin A is anti-nociceptive, whereas orexin B was pro-nociceptive. Perhaps antagonism of the OX2R or agonism of the OX1R may be beneficial.[73]

Nitric oxide synthase inhibitors (NOS)

NOS produces nitric oxide triggering CGRP release. NOS inhibitors (neuronal and inducible) were not effective for acute or preventive migraine treatment.[74,75]

Botulinum toxin (BoNT) for migraine

Seven BoNT serotypes (A, B, C1, D, E, F, and G) are produced by *Clostridium botulinum*. All inhibit acetylcholine release, but they differ in targets, characteristics, and potencies.[76,77] Botulinum toxin type A (BoNTA) is the most commonly studied serotype.[76] BoNT is available as onabotulinumtoxinA (botulinum toxin type A), abobotulinumtoxinA (another type A), and BoNTB (rimabotulinumtoxinB).

BoNT is approved for chronic migraine prevention and may be effective in high-frequency episodic migraine. The mechanism of action of BoNT in headache is still uncertain.

Conclusion

Pharmacologic treatment is a cornerstone of migraine management. Preventive medication can not only reduce attack frequency, but can also improve acute treatment response and quality of life. Many migraine patients need prevention, but few get it. Many preventive medications are available, and guidelines for their selection and use have been established. Comorbid medical and psychological illnesses must be considered when choosing preventive drugs,[75] but there are no characteristics predictive of response to acute or preventive treatment.

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1. According to treatment guidelines, ergotamine is considered:
   A. Effective (Level A)
   B. Probably effective (Level B)
   C. Possibly effective (Level C)
   D. Unknown (Level U)

2. Lasmiditan, in Phase 3 trials for the treatment of acute migraine, acts at what receptors?
   A. 5HT1B
   B. 5HT1F
   C. 5HT2C
   D. 5HT3

3. Preventive treatment for migraine is considered successful when it reduces migraine by:
   A. One third
   B. One half
   C. Two thirds
   D. Three fourths

4. Monoclonal antibodies (mABs) to CGRP and its receptors function:
   A. Extracellularly
   B. Intracellularly
   C. Both extra- and intracellularly

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