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Review Article

Preventive Migraine Treatment: Newer Perspective

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Abstract

Background: Preventive management of migraine aims to diminish attack frequency, duration, and severity through pharmacologic and non-pharmacologic strategies.

Methods: Articles published between 2001 and June 2024 concerning migraine prevention were systematically reviewed.

Results: Current guidelines advocate preventive therapy for frequent or disabling migraines. Evidence supports beta-blockers, antiepileptics, antidepressants, and CGRP-targeted agents. Recent innovations include gepants, monoclonal antibodies, botulinum toxin, and neuromodulation devices.

Conclusion: CGRP-targeted therapies represent a major advance, recommended as first-line options alongside established pharmacologic and lifestyle interventions.

Keywords: *Migraine prevention, CGRP-targeted therapy, Preventive treatment, Neuromodulation*

Introduction

Preventive treatment for migraines aims to decrease severity, frequency and duration of migraine headache. This approach may include medications, changes in lifestyle, and other therapeutic options. Commonly prescribed medications include beta-blockers, antidepressants, antiseizure medications, and CGRP inhibitors, while modifications in lifestyle like managing stress and maintaining a regular sleep schedule can also prove beneficial. [1]

Methods

Article related to preventive migraine treatment were selected from 2001 to June 2024.

Results

The 2021 American Headache Society consensus guideline recommends the use of preventive medications for individuals who experience four or more debilitating migraine attacks per month, or one to two headaches per week, or highly disabling migraine attacks such as hemiplegic migraine or brainstem aura, migraine with associated complications, and chronic migraine (headache occurring 15 or more days per month for three months. [1] Preventive migraine treatments are broadly classified into non-specific and target-specific treatments.

Migraine Non-specific preventive medications

Many different classes of medications are used for the preventive treatment of migraine in episodic migraine and chronic migraine The choice of preventive medication is based on the side effects profile and contraindications of drugs, and underlying comorbidities. Propranolol, metoprolol, topiramate, and divalproex are the first line of drugs in migraine prophylaxis given higher efficacy and level A evidence in episodic migraine and chronic migraine.[2] Calcium channel blockers, especially flunarizine, have higher efficacy in the prevention of migraine with aura. [2] It takes 3–6 months of constant treatment to evaluate for response and these preventive drugs should be administered for 6–12 months depending on the evolution of the patient [Table 1]. [2, 3]

Table 1. Classes of treatment for preventive treatment of migraine (episodic and chronic migraine). [2,3]
[Mnemonic: $A^2B^2C^3DE$ of Migraine]

	Class	Drugs	Levels of evidence	Target Dosing of important medications with best evidence.
A	ACEI	Lisinopril	Level C	Lisinopril: 10-40 mg once daily
A	ARB	Candesartan	Level C	Candesartan:8-16 mg once daily
B	Beta Blockers	Propranolol, metoprolol, Timolol	Level A	Propranolol:60 mg once daily or 2 times a day maximum 240 mg/day Metoprolol:50 mg 2 times a day
B	Botulinum toxin	Botulinum toxin approved only for chronic migraine	Level A	155 units subcutaneous monthly
C	Calcium channel blockers	Verapamil, flunarizine, cinnarizine	Level A	Flunarizine: 5-10mg bed time. Verapamil : 120-240 mg Cinnarizine : 1.5mg/kg/day in children, adults 75 mg
C	CGRP monoclonal antibodies	Erenumab,eptinezumab, fremanezumab,and galcanezumab [mnemonic E^2FG]	N/A	Erenumab :70 mg or 140 mg subcutaneous monthly. Eptinezumab:100-300 mg IV every 3 months. Fremanezumab:225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months Galcanezumab:240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly
C	Cyproheptadine	Cyproheptadine belongs to antihistamines (used in children)	Level C	Cyproheptadine 4-8 mg once daily or divided 2 times a day
D	Depression treatment drugs: Antidepressants	Amitriptyline, nortriptyline, protriptyline,Venlafaxine and Duloxetine (SNRI)	Level B	Amitriptyline: 50 mg nightly Venlafaxine: 75-225 mg extended release once daily

Table 1 continued….

E	Epilepsy treatment drugs: Antiepileptics	Divalproex, topir-amate,gabapentin,zonisamide	Level A	Divalproex sodium :250-500 mg 2 times a day Topiramate:50 mg 2 times a day
M	Migraine other drugs:	Memantine, melatonin,	N/A	Memantine 10 mg 2 times a day
N	Nutritional supplements	Magnesium, Riboflavin, COQ10	Level B	Magnesium: 400-600 mg once daily :riboflavin: 400 mg once daily; COQ:300 mg once daily

Level A: established as effective; Level B: Probably effective; Level C: Possibly effective, ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CGRP: Calcitonin gene-related peptide, N/A: Not available; SNRI: Serotonin and norepinephrine reuptake inhibitors; COQ: Coenzyme Q

Migraine-specific preventive medication

The migraine preventive treatment landscape has been transformed by the development of monoclonal antibodies targeting CGRP or its receptor. These treatments, which are given subcutaneously or intravenously monthly or quarterly, have high efficacy and are well tolerated. [2] The CGRP receptor antagonist Atogepant, CGRP monoclonal antibodies, and neuromodulation devices are the latest treatments approved by the FDA for the preventive treatment of episodic and chronic migraine. Rimegepant is recently approved for the prophylactic treatment of episodic migraine in addition to its role in acute attacks.

CGRP monoclonal antibodies

CGRP (calcitonin gene-related peptides) is a neuropeptide found throughout the central and peripheral nervous systems that are intrinsically involved in migraine pathogenesis. CGRP monoclonal antibodies are monoclonal antibodies that act by binding to CGRP or its receptor and thus antagonize CGRP available in the nervous system and thus prevent migraine headaches. The first of these, erenumab, became available in May 2018 followed by three other CGRP monoclonal antibodies; fremanezumab,galcanezumab, and Eptinezumab.[2,4] The advantages of CGRP monoclonal antibodies include robust efficacy, a potentially lower side effect burden, and convenient monthly or quarterly dosing. CGRP monoclonal antibodies do not interact with other medications and are excellent for patients with polypharmacy. Six to nine months of treatment are provided [Table 2].

Table 2. Calcitonin gene related peptides monoclonal antibodies [4-7]

CGRP monoclonal antibodies	Route of administration & Mode of action	dose	Side effects
Eptinezumab	IV infusion Act on ligands	100 mg or 300 mg IV infusion every 3 months.	Constipation and injection site adverse reactions.
Erenumab	Subcutaneous Act on receptor	70-mg or140-mg subcutaneous dose once monthly.	Constipation and injection site adverse reactions Development of hypertension or worsening of pre-existing hypertension
Fremanezumab	Subcutaneous Act on ligands	225-mg subcutaneous dose once monthly or 675 mg (3, 225-mg injections) every 3 months	Injection site erythema and rash, constipation, and other gastrointestinal symptoms.
Galcanezumab	Subcutaneous Act on ligands	Subcutaneous loading dose of 240 mg (2, 120-mg injections) and then dosed at 120 mg once monthly.	Injection site reaction, erythema, pruritus, and sinusitis.

Gepants for the prevention of migraine

Gepants, which are small-molecule CGRP receptor antagonists, function by binding to CGRP receptors and preventing the interaction between CGRPs and their receptors. Rimegepant and atogepant are the two gepants approved for preventing migraines [Figure 1]. Rimegepant and atogepant are effective in preventive treatment of episodic migraine while atogepant has additional evidence as a preventive treatment of chronic migraine. [1 ,4,5 ,6]

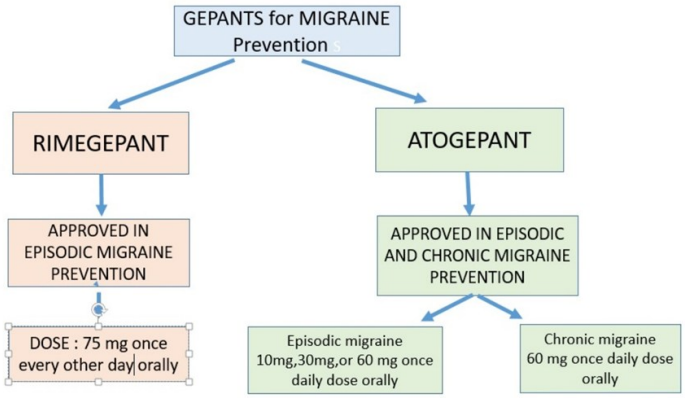

Figure 1. Gepants for migraine prevention.

The AHS 2024 has recently released a position statement update stating that CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without any requirement for prior failure of other classes of migraine preventive treatment. [7]

Neuromodulatory devices

Neuromodulatory devices can help prevent migraine headaches. All five devices are approved for the preventive treatment of episodic and chronic migraine with or without aura in patients 12 years of age or older. [8, 9] These devices are external trigeminal nerve stimulation, single-pulse transcranial magnetic stimulation, non-invasive vagus nerve stimulation, remote electrical neuromodulation, and external concurrent occipital and trigeminal neurostimulation. Dosing and duration vary in the preventive treatment of migraine [Table 3].

Table 3. Neuromodulation devices for migraine prophylaxis [8, 9, 11].

Device	Dose	Side effects
Electrical trigeminal nerve stimulation	20 minutes daily session at low frequency (60 Hz)	Paraesthesia, fatigue, insomnia, headache, and local skin allergy to the electrode
Vagus nerve stimulation	two 2-minute self-administered stimulations delivered 5–10 minutes apart to the right side of the neck at 3 prespecified times every day: (1) within 1 hour of awakening; (2) 6–8 hours after the first treatment; and (3) 6–8 hours after the second treatment.	Facial pain, gastrointestinal symptoms, and upper respiratory tract infection
Remote electronic neuromodulation	The device is applied for 45 min to the lateral upper arm every alternate days.	Topical peripheral sensations of warmth, itching, arm pain, redness, and numbness.
Single -pulse transcranial magnetic stimulation	Twice-daily treatment with 4 pulses (2 consecutive pulses, wait 15 min, then repeat another 2 consecutive pulses).	Light-headedness, tingling, and tinnitus .
Combined occipital and trigeminal nerve stimulation	6 cycles of electric pulses to 6 branches of both occipital and trigeminal nerve (unlimited stimulation for 48 hours)	No serious adverse events

Botulinum toxin injection for migraine

Botulinum toxin administration is approved by the FDA only for chronic migraines for people 18 years and older.[40] The injection protocol for Onabotulinumtoxin A should be followed as per the PREEMPT (Phase III Research Evaluating Migraine Prophylaxis Therapy) guidelines, which involve administering 155 U–195 U to 31–39 sites every 12 weeks.[2] Seven muscle groups associated with the trigeminal, occipital, and cervical sensory nerves, are sampled for onabotulinumtoxin A injection. These muscle groups are corrugator, procerus, frontalis, temporalis, occipital, cervical, paraspinal, and trapezius muscles [Figure 2].

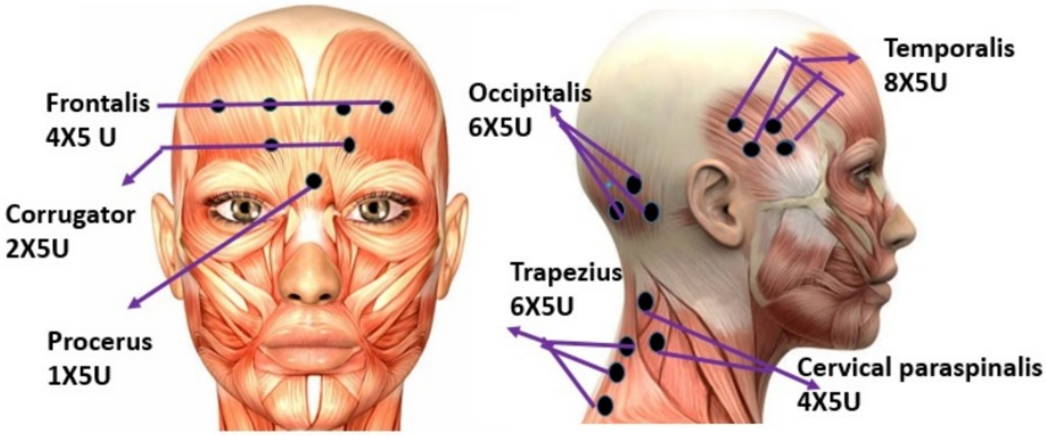

Figure 2. *Sites for botulinum toxin injections.*

General consideration in preventive treatment of migraine

There are short-term and long-term prevention strategies. Short-term prevention strategies in prodrome phase and menstrual migraine. Long-term prevention is indicated if there is disability (attacks impaired with activities of daily living) due to the severity of migraine attacks. Disability is considered a MIDAS [10] score of greater than 11. There is an indication of preventive treatment if a person with migraine has 6 or more headache days per month. [5] For people with less than 6 days of migraine headaches per month, preventive treatment is initiated by the presence of migraine-related disability. The goals of preventive treatment are to reduce the frequency, severity, duration, and disability associated with migraine attacks and overall improve the health-related quality of life.

Emerging therapies:

Central Neuromodulation: Involves invasive techniques, such as cranial nerve stimulation, spinal cord stimulation, and deep brain stimulation. It's useful for treating medically refractory migraines, for more aggressive treatment, for those who prefer non-medication options, and for those who have experienced adverse effects from medications. [11] Transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) devices, occipital nerve stimulation (ONS) devices, and exposure to green light may modulate nociception and have a role in intractable chronic migraine. [9]

Cannabis nasal spray: Medical cannabis(MC) is an alternative therapy for migraines and is 51% more effective than non-cannabis products.Medical cannabis significantly reduced nausea and vomiting associated with migraine attacks after 6 months of use. Also, MC reduced the number of days of migraine after 30 days, and the frequency of migraine headaches per month. MC was 51% more effective in reducing migraines than non-cannabis products. Compared to amitriptyline, MC aborted migraine headaches in some (11.6%) users and reduced migraine frequency. The use of MC for migraines was associated with the occurrence of medication overuse headaches (MOH), and the adverse events were mostly mild and occurred in 43.75% of patients who used oral cannabinoid preparations .[12]

***Lifestyle modification**:* There are multiple triggers for migraine attacks that vary from person to person, hence lifestyle changes can prevent and improve migraine. Proper sleep, diet, and exercise help reduce attacks. The SMART mnemonic for a healthy lifestyle stands for Sleep (S), Meals (M), Activity (A), Relaxation (R), and Trigger (T). Establish a regular sleep schedule with consistent sleep times, limit naps, avoid screens before bed, and aim for 9-11 hours of sleep each night. One should eat consistent meals and not skip meals, snack as needed, drink plenty of water, and dilute high-sugar electrolyte drinks with water. Limit screen time to 2 hours per day and aim for 30 minutes of physical activity, 3-5 days per week. To reduce stress and anxiety that can cause migraines, relaxation training like deep breathing, yoga, or mindfulness apps are recommended. During an attack, the use of a strong stimulus like an ice pack or candy can distract from the pain. To avoid experiencing migraines in the future, it is important to identify and eliminate triggers such as stress, certain food items, weather changes, and poor sleep habits. Keeping track of your responses to these triggers through a headache log can help avoid them and prevent migraines. All individuals who suffer from migraines should be educated on the significance of maintaining regular sleep patterns, meal times, and participating in aerobic exercise. [13

Management of migraine in special situations:

There are several types of migraines, such as vestibular migraine, menstrual migraine, status migrainosus, and migraine with aura, that require different treatment from the standard treatment discussed [Table 4]. [14,15,16,17,18,19]

Additionally, the treatment of migraine in children, pregnancy, and lactation is also different.

Table 4. Showing preventive medication of migraine in special circumstances [14-19].

Special scenario	Preventive medication
Vestibular migraine	Lamotrigine, propranolol, topiramate, Valproic acid, and flunarizine. Lamotrigine is preferred if vertigo is more frequent than headache. Cyproheptadine for pediatric vestibular migraine. Vestibular rehabilitation.
Menstrual Migraine	Mini prevention for 10 days 2 days prior to menstrual migraine onset. Mini prevention contains NSAIDS and longer-acting triptans for 10 days as first-line treatment. Combination with specific hormonal contraceptives. Avoid hormonal contraceptives in menstrual migraine with aura.
Pediatric migraine	Propranolol, topiramate, cinnarizine, and amitriptyline with cognitive behavior therapy (CBT) in children. CGRP receptor antagonists are indicated in adolescence when headache (moderate-severe intensity) is more than 8 days/month.
Status migrainosus	Same as migraine prophylaxis
Pregnancy and migraine	Propranolol, amitriptyline, and verapamil are safe in pregnancy.
Lactating mother and migraine attack.	Propranolol, verapamil, amitriptyline, and gabapentin. Avoid using flunarizine, cinnarizine, zonisamide, atenolol, and Lisinopril.
Hemiplegic migraine.	Initial treatment with verapamil, flunarizine or acetazolamide followed by lamotrigine is recommended. Acetazolamide in familial hemiplegic migraine.
Migraine with aura	Migraine prophylaxis drugs can be used, preferred is calcium channel blocker -flunarizine.

Discussion

The latest development in the preventive treatment of migraines involves medication targeting CGRP. This includes parenteral monoclonal antibody injections such as eptinezumab, erenumab, fremanezumab, and galcanezumab approved in adults with either episodic or chronic migraine However, the initial preventive treatment drug is oral conventional medications among the various classes of drugs available. The treatment benefits of CGRP-targeted therapy occur rapidly when compared to conventional non-specific migraine preventive medication. Hence, instead of waiting for the failures of two traditional migraine drugs, the AHS 2024[7] has recently released a position statement update stating that CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments and preventive treatment [Figure 3] [4, 7] has been illustrated. The choice between non-pharmacological and pharmacological treatments depends on the individual's needs and preferences.

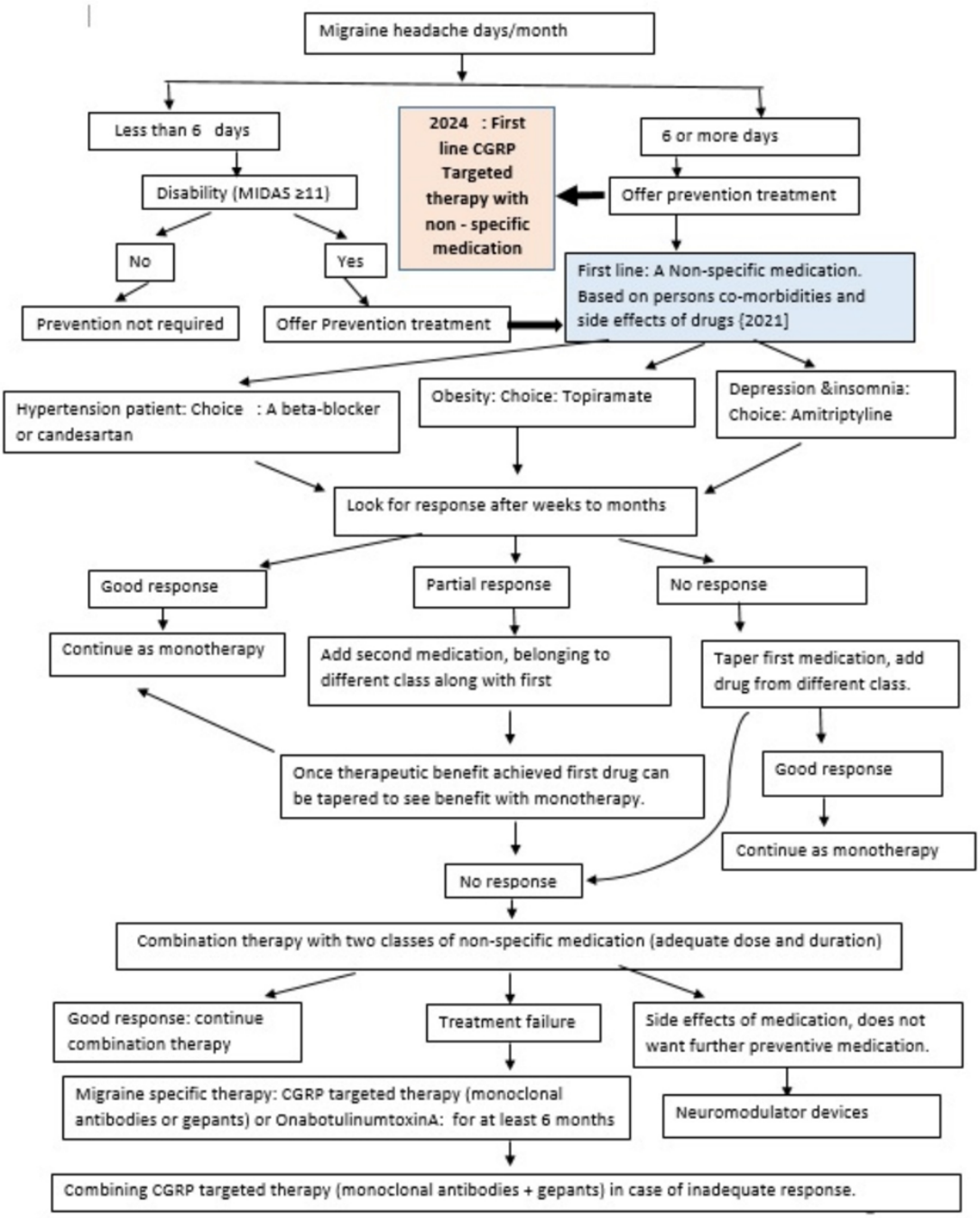

Figure 3. *Algorithm showing preventive treatment of migraine and first line treatments.*

This review has some limitations, as it does not cover the triggers of migraine, various subtypes, detailed descriptions of each type with management, or comparisons between individual drugs.

This review offers healthcare professionals a detailed strategies for prevention of migrane, along with current advancements and potential treatments. It also emphasizes the need for more research on CGRP-targeted therapy and neuromodulation devices, particularly for specific migraine subtypes and age groups where knowledge is lacking.

Conclusion

Migraines can be treated in various ways, both in the short and long term. The latest treatments focus on the CGRP pathway. To prevent migraines, it is recommended to use first-line CGRP-specific therapy along with non-specific therapy. Effective migraine prevention involves a combination of lifestyle changes, managing triggers, and medications that are supported by scientific evidence. Therapies that focus on CGRP provide further advantages by decreasing the frequency of attacks and enhancing overall quality of life, making them as first line therapy for migraine prevention.

Conflicts of Interest

The authors declare no conflicts of interest.

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