LEBDA MEDICAL JOURNAL, Vol. 10. No2.2025 Pages1-11

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

Received: September 01, 2025
Revised: September 23, 2025
Accepted: October 12, 2025
Published: October 30, 2025

A Review of Migraine as a Neurovascular Disorder: Causes, Biochemical Changes, and Comparative Treatments

Basma S.A. Kamel[a,*] , Mostafa M. Abdelhafeez[b]

[a] Lecturer of Biochemistry and Molecular Biology, Faculty of Pharmacy, Al-Asmarya Islamic University, Libya
[b] Assistant Professor, Department of Public Health, Faculty of Health Sciences, Al-Asmarya Islamic University, Libya
* Corresponding author, email: dr.basma.bio@gmail.com

ABSTRACT

Migraine is a chronic neurovascular disorder and one of the most disabling neurological conditions worldwide. It is characterized by recurrent attacks of unilateral, pulsating headache accompanied by nausea, photophobia, and phonophobia, with or without aura. Both genetic and environmental factors contribute to its pathogenesis. Genome-wide association studies have identified multiple susceptibility loci, while hormonal fluctuations, stress, sleep disturbance, and dietary factors act as common triggers. Biochemically, cortical spreading depression, activation of the trigeminovascular system, and release of calcitonin gene-related peptide (CGRP) and serotonin dysregulation are central to attack generation. Epidemiological studies reveal that migraine affects over one billion people globally, with a higher prevalence among women, particularly during reproductive years, underscoring the role of sex hormones. Acute management includes NSAIDs, triptans, gepants, and lasmiditan, with antiemetics for nausea. Preventive strategies are indicated in frequent or disabling attacks and include beta-blockers, topiramate, valproate, antidepressants, and the newer anti-CGRP monoclonal antibodies. Non-pharmacological approaches such as lifestyle modification, trigger avoidance, cognitive behavioral therapy, and neuromodulation devices complement drug therapy. Advances in targeted treatments have improved outcomes, but equitable access remains a challenge. Optimized, individualized therapy offers significant potential to reduce disability and improve quality of life for patients with migraine.

Keywords: *Migraine, Aura, Triggers, Triptans, Gepants*

1. Introduction

Migraine is classified as a primary headache disorder by the International Headache Society. It is typically characterized by episodes of throbbing or pulsating headache pain, usually unilateral (on one side of the head), lasting 4–72 hours when left untreated. The headache is characteristically moderate to severe in intensity and aggravated by routine physical activity; it is commonly accompanied by nausea and/or

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

photophobia and phonophobia (1). Migraines are broadly divided into two major subtypes: migraine without aura and migraine with aura. Migraine *with aura* is distinguished by transient focal neurological symptoms that precede or accompany the headache, most often visual disturbances such as flashes of light or blind spots. Aura symptoms typically develop gradually over 5–20 minutes and last less than 60 minutes, and may include visual zigzag lines, scotomas, sensory changes (like tingling), or speech disturbances (2). In migraine *without aura*, no such neurological warning occurs before the headache phase. Most migraineurs experience the headache phase with its associated features, and about one-third of patients have aura with some or all attacks (3). In addition, patients may experience a prodrome phase (hours to days before an attack, with symptoms like fatigue, neck stiffness, or food cravings) and a postdrome phase (after the headache, with symptoms like exhaustion or mild headache). Migraine is thus a clinical syndrome with well-defined diagnostic criteria, and diagnosis is made by history and exam, since imaging or lab tests are typically normal in primary migraine. Chronic migraine is defined by a high frequency of attacks (15 or more headache days per month, with at least 8 being migraine days) and represents an evolution of episodic migraine in some individuals (4).

2. Review Approach

This narrative review provides a thematic synthesis of current evidence on migraine and primary headache disorders, integrating insights from epidemiology, neurobiology, clinical diagnosis, and therapeutic strategies. Literature was primarily identified through targeted searches in PubMed, Google Scholar and Scopus (2014–2025), supplemented by manual screening of reference lists from key publications.

3. Causes and triggers

3.1. Genetic factors

Migraine is heritable. Twin studies estimate heritability at roughly 42%, indicating that almost half of the variability in susceptibility arises from genetic factors (5, 6). Genome-wide meta-analyses have now identified 122 independent loci and 181 credible sets linked to migraine, underscoring neuronal, vascular, and inflammatory pathways (7). Well-characterized monogenic forms such as familial hemiplegic migraine are caused by mutations in ion-channel genes (**CACNA1A**, **ATP1A2**, **SCN1A**) affecting excitatory neurotransmission. Epigenetic changes – reversible chemical modifications to DNA and histone proteins – are increasingly recognized as contributors to migraine. Environmental factors such as stress or inflammation can alter methylation patterns and regulate genes like **MEF2D** and **PRDM16**, thereby influencing susceptibility and chronification (8).

3.2. Hormonal and metabolic influences

Migraine prevalence is roughly two to three times higher in women than in men, suggesting a strong hormonal influence (9). Globally, recent global burden analyses confirm that women consistently bear a greater absolute burden despite a faster relative rise among men (10). Estrogen fluctuations modulate serotonin and calcitonin gene-related peptide (CGRP) levels. High estrogen levels enhance the excitability of cortical neurons and increase serotonin, lowering the threshold for cortical spreading depression and trigemino-vascular activation, while the drop in estrogen during menses can precipitate attacks. Risk is highest during reproductive years and declines after menopause (11, 12).

Other metabolic factors include obesity, dyslipidemia, hypertension, diabetes, and insulin resistance, which are associated with increased migraine risk (8).

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

3.3 Environmental and lifestyle triggers

Migraine attacks are often precipitated by environmental or behavioral triggers in genetically susceptible individuals. Stressful events are among the most common migraine triggers. In a retrospective survey of individuals with migraine, 80% reported stress, followed by hormonal changes (65%), skipped meals (57%), weather changes (53%), sleep disturbances (50%), and perfumes and chemicals (40%) (13-15).

Additional triggers include bright light, loud sounds, barometric pressure changes, alcohol (especially red wine), caffeine withdrawal, heavy exercise, fasting, and certain foods high in tyramine or aspartame (16). A large review identified lower socioeconomic status, high caffeine intake, medication overuse, head trauma, and sleep disorders as risk factors. Women often report menstrual migraine, for which short-term prophylaxis with triptans or NSAIDs may be effective. Alcohol is reported as a trigger by many patients, although evidence is mixed; some studies show a roughly 51% increased risk (8).

3.4. Comorbidities and psychological factors

Migraine often co-occurs with anxiety, depression, bipolar disorder, and other pain syndromes. Stress, anxiety, and phobic disorders have been identified as risk factors (17). Chronic sleep deprivation, shift work, and circadian rhythm disturbance are strongly linked to migraine attacks; people with migraines are more than three times as likely to experience insomnia (17, 18). Obstructive sleep apnea may also trigger headaches (19). Smoking, obesity, and high caffeine intake can worsen migraine frequency and severity (20). Post-traumatic headaches after mild traumatic brain injury may share pathophysiological mechanisms with migraine (21). Identifying and managing co-morbid conditions is therefore an essential component of migraine care.

4. Biochemical changes during a migraine attack

Migraine is considered a neurovascular disorder. Contemporary models emphasize the interplay between cortical excitability, activation of trigeminal nociceptive pathways, and release of vasoactive neuropeptides. Attacks often begin with cortical spreading depression (CSD), a wave of neuronal depolarization followed by a period of suppression that travels across the cortex. CSD can trigger aura symptoms and activate trigeminal afferents via pannexin-1 channels (22). Activation of the trigeminovascular system leads to the release of neuropeptides, including CGRP, substance P, neurokinin A, and pituitary adenylate cyclase-activating peptide (PACAP) from perivascular nerve endings. These peptides cause vasodilation and plasma protein extravasation, generating sterile neurogenic inflammation around meningeal blood vessels. CGRP is particularly important; its levels rise during migraine attacks, and infusion of CGRP can trigger migraine-like headaches (23, 24). Serotonin (5-HT) levels are also altered. Trigeminovascular neurons express 5-HT1B/1D receptors; low interictal serotonin and high CGRP promote trigeminal activation, while triptans act as 5-HT1B/1D agonists, normalizing serotonin and blocking CGRP release (25). Neuroimaging studies reveal changes in cortical and subcortical networks during attacks. Functional MRI demonstrates activation of the hypothalamus, brainstem nuclei, thalamus, and somatosensory cortex. The hypothalamus may orchestrate pre-monitory symptoms through connections to the trigeminal nuclei. Elevated nitric oxide and inflammatory cytokines further sensitize nociceptors, contributing to central sensitization and chronification. After the attack, there is often a post-drome phase with fatigue and cognitive slowing, suggesting widespread neural changes (26).

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

5. Epidemiology

Migraine is one of the most prevalent neurologic disorders worldwide. A large systematic analysis estimated that there were approximately 1.1 billion prevalent cases of migraine worldwide in 2019. The global age-standardized prevalence increased by 1.7% between 1990 and 2019, making migraine a leading cause of disability (27). Migraine accounted for 16.3% of all neurological disorder disability-adjusted life years (DALYs) in 2016 and remains the second leading cause of years lived with disability worldwide (28). The current best estimate of global migraine prevalence is 14–15%, and, in terms of burden, migraine accounts for 4.9% of global ill health, quantified as years lived with disability. Prevalence peaks in early adulthood and declines after age 45 (27).

6. Sex differences and hormonal influence

Migraine is significantly more prevalent in women. Population studies estimate that about 17% of women and 6% of men experience migraine (29-31). The global age-standardised rate of years lived with disability (YLD) attributable to migraine was 525.5 per 100,000, up by 1.5% since 1990. Migraine burden is not evenly distributed. Prevalence is consistently higher in women, and age-specific prevalence rises into the 40–44 year age group before declining (27). The ratio peaks during reproductive years and declines after menopause. Female sex hormones modulate neurotransmitter systems implicated in migraine. Estrogen increases nitric oxide synthase activity and increases serotonin levels, promoting trigeminovascular activation; cyclic withdrawal of estrogen during menstruation is a common trigger (11). During pregnancy, high stable estrogen levels often improve migraine, while postpartum hormone fluctuations may worsen symptoms. Women also appear more susceptible to chronicity due to the interplay of hormones, stress, sleep disturbance, and depression (8).

7. Acute (abortive) treatment

Treatment goals for acute migraine are to relieve pain and associated symptoms quickly, restore normal function, and minimize recurrence. Early treatment during the headache phase improves efficacy. Because individual response varies, therapy should be personalized based on attack severity, associated symptoms, comorbidities, and patient preferences. Evidence-based guidelines support the following options:

7.1. General measures

Treatment choice depends on symptom severity, associated nausea or vomiting, comorbidities, and prior drug response. Early, single-dose treatment is usually more effective than repeated small doses. For patients unable to tolerate oral medications, nonoral routes or neuromodulation may be used. Key principles include patient education, use of migraine-specific drugs (eg, triptans, CGRP antagonists, lasmiditan), appropriate route of administration, rescue medication for severe attacks, and avoiding medication overuse headache (32).

For mild attacks without vomiting or severe nausea, simple analgesics such as NSAIDs (aspirin, ibuprofen, naproxen, diclofenac) or acetaminophen are first-line options. If ineffective, triptans may be added. Combining NSAIDs with triptans can be more effective than either alone. Antiemetics may be used when nausea is present (33, 34).

Patients with moderate to severe migraine often require triptans, with or without NSAIDs (35). Alternatives include CGRP antagonists, lasmiditan, or dihydroergotamine. For those with significant nausea or vomiting, subcutaneous, intranasal, or parenteral options are preferred (eg, subcutaneous sumatriptan, nasal triptans, parenteral dihydroergotamine) (36).

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

Prolonged attacks >72 hours (Status Migrainosus) may need intravenous fluids and parenteral therapy such as ketorolac, dopamine receptor blockers, valproate, or dihydroergotamine. Intravenous dexamethasone is often given to reduce relapse risk (37, 38).

7.1.1. Triptans

Triptans (e.g., sumatriptan, rizatriptan, eletriptan, zolmitriptan) are highly effective and specifically designed for migraine treatment. They act by vasoconstriction and blocking the trigeminal pathways. Different formulations (oral, subcutaneous, nasal) allow individualized use. Early administration improves outcomes (39). They should be avoided in patients with cardiovascular disease, hemiplegic migraine, or brainstem aura (40).

7.1.2. Combination Therapy

The best evidence supports the sumatriptan-naproxen combination, which is more effective than either drug alone (41, 42).

7.1.3. Antiemetics

Dopamine antagonists such as IV metoclopramide or prochlorperazine are effective for pain and nausea, either as monotherapy or in combination therapy (43, 44). Diphenhydramine is often co-administered to reduce dystonic reactions. Other antiemetics (chlorpromazine, droperidol, haloperidol, ondansetron) may be considered, though they are associated with a higher risk of adverse effects (45-47).

7.1.4. CGRP Antagonists

Oral “gepants” (ubrogepant, rimegepant) and intranasal zavegepant are effective for acute migraine, especially in patients who cannot take triptans. They provide pain relief and reduce associated symptoms, though long-term safety data are still emerging (48, 49).

7.1.5. Lasmiditan

Lasmiditan, a selective 5-HT1F agonist, is effective without vasoconstrictive effects. Common side effects include dizziness and somnolence, and patients must avoid driving for 8 hours after each dose (50).

7.1.6. Ergots

Dihydroergotamine is useful for severe attacks and status migrainosus, particularly when combined with antiemetics. Ergotamine is less effective and associated with more side effects; it is rarely used (51).

7.1.7. Non-pharmacological and device-based treatments

Acupuncture, relaxation training, cognitive-behavioral therapy, and biofeedback demonstrated modest benefit in acute and preventive treatment. External trigeminal nerve stimulation devices such as Cefaly and single-pulse transcranial magnetic stimulation have received regulatory approval for acute therapy and prevention. These devices are non-invasive, well-tolerated, and may be considered for patients preferring non-drug options (36).

8. Preventive (prophylactic) treatment strategies

Preventive therapy aims to reduce the frequency, severity, and duration of attacks; improve responsiveness to acute therapy; and minimize disability. Prophylaxis is considered for patients with frequent attacks (≥3 per month or ≥8 headache days per month), debilitating attacks despite appropriate acute treatment, medication overuse headache, prolonged aura, or patient preference. Selection of prophylactic therapy depends on migraine type (episodic vs chronic), comorbidities, contraindications, and patient goals. Treatment usually starts at a low dose and is increased slowly; efficacy should be assessed after 2–3 months, and therapy continued for 6–12 months before tapering (52). The following modalities are evidence-based:

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

8.1. First-line pharmacological options

8.1.1. Anti-CGRP monoclonal antibodies

Erenumab (CGRP-receptor antibody), fremanezumab, galcanezumab, and eptinezumab (CGRP-ligand mAbs) specifically inhibit CGRP signaling and are administered via monthly or quarterly injections. A 2025 international guideline summarizing recommendations reported erenumab 70 mg or 140 mg every four weeks, fremanezumab 225 mg monthly or 675 mg quarterly, galcanezumab 120 mg monthly, eptinezumab 100 mg or 300 mg quarterly, and topiramate 100–200 mg orally for episodic migraine. For chronic migraine, onabotulinumtoxinA 155–195 IU intramuscularly, atogepant 60 mg oral, eptinezumab 100 mg or 300 mg quarterly, fremanezumab 675 mg quarterly or 225 mg monthly, galcanezumab 120 mg monthly, and erenumab 70 mg or 140 mg every four weeks were strongly recommended (53). These treatments show responder rates, defined as a ≥50% reduction in monthly migraine days, range from 30–62% versus 17–38% with placebo. They are well tolerated, with injection-site reactions and constipation being the most common adverse effects. Anti-CGRP antibodies should be used cautiously in patients with cardiovascular or cerebrovascular disease and are not recommended during pregnancy or breastfeeding. Treatment response is usually assessed at 4–12 weeks; non-responders may try another agent. Anti-CGRP therapies offer a relatively rapid onset of benefit (often within the first month) and simplicity of monthly dosing, but their high cost can limit accessibility (36).

8.1.2. Topiramate

Topiramate is an antiepileptic that blocks voltage-dependent sodium channels, enhances GABAergic activity, and inhibits excitatory glutamatergic transmission. It has comparable efficacy to propranolol and is recommended as a first-line option for episodic and chronic migraine. Typical doses are 50–200 mg/day, titrated gradually to minimize adverse effects such as paresthesias, cognitive slowing, and weight loss. Topiramate is contraindicated in pregnancy due to the risk of fetal malformations and in patients with a history of kidney stones or glaucoma. The 2025 guideline categorizes oral topiramate 100 and 200 mg as strongly recommended and lower doses (50 mg) as weakly recommended for episodic migraine (53).

8.1.3. OnabotulinumtoxinA

Botulinum toxin type A is approved for the prevention of chronic migraine. It is injected into 31 sites across the head and neck muscles every 12 weeks. OnabotulinumtoxinA reduces monthly migraine days by about two more days compared with placebo, and it is particularly beneficial in patients with medication-overuse headache. It is not effective for episodic migraine. Adverse effects include injection-site pain, neck stiffness, and muscle weakness. The 2025 guideline issued a strong recommendation for onabotulinumtoxinA in chronic migraine (53).

8.2. Other oral preventive medications

8.2.1. Beta-blockers

Propranolol is among the most widely used beta-blockers and is an effective first-line agent. Metoprolol and atenolol are alternatives, particularly for patients with comorbid hypertension or anxiety. Common adverse effects include fatigue, dizziness, and potential worsening of depression; contraindicated in patients with asthma and severe bradyarrhythmia. The 2025 guideline gives a weak recommendation for propranolol (160 mg/day oral) in episodic migraine prevention (53).

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

8.2.2. Antiepileptic drugs

Topiramate is among the most effective preventive therapies for migraine and is supported by strong evidence, but its use is limited by safety concerns. Besides topiramate, valproic acid (divalproex) is also an established preventive agent with strong supporting evidence; however, it is contraindicated in women of childbearing potential due to high teratogenic risk and generally avoided in patients with liver disease. Lamotrigine has weaker evidence and is considered when first-line agents fail (54).

8.2.3. Antidepressants

Tricyclic antidepressants (TCA) such as amitriptyline (10–100 mg/day, titrated as tolerated) and nortriptyline provide benefit, particularly in patients with comorbid depression or insomnia. Nortriptyline is frequently used as an alternative with fewer anticholinergic effects, although evidence is less robust. Venlafaxine, a serotonin–norepinephrine reuptake inhibitor, is also probably effective with modest supporting evidence, particularly for patients with comorbid depression or anxiety. Antidepressants are commonly used as migraine preventives. Amitriptyline has the best evidence for use in migraine prevention. Common adverse effects of TCAs include weight gain, dry mouth, constipation, sedation, and possible QT prolongation, while venlafaxine may cause nausea, insomnia, or elevated blood pressure (53, 55).

8.2.4. Memantine and other agents

Memantine, an NMDA receptor antagonist considered when conventional preventives fail, has limited evidence but is included in the 2023 VA/DoD guideline as an option for episodic migraine (56). Riboflavin (vitamin B2), magnesium, and coenzyme Q10 combination (57).

8.3. Non-pharmacological preventive strategies

8.3.1. Lifestyle modifications

Regular sleep, consistent meals, adequate hydration, moderate and consistent caffeine intake (avoiding both excess and withdrawal), and avoidance of identified triggers form the foundation of migraine prevention. Aerobic exercise, such as brisk walking or cycling, three times per week, significantly reduces headache frequency and intensity, likely through endorphin release and improved vascular health (58, 59). Relaxation techniques, mindfulness, cognitive behavioral therapy, and biofeedback improve coping and may reduce migraine frequency. Patients should maintain a headache diary to correlate attacks with sleep patterns, stress, and dietary factors (60, 61). Weight reduction may benefit obese patients. Smoking cessation and limiting alcohol intake are advisable (62).

8.3.2. Neuromodulation devices

Several devices are available to help identify patterns and triggers. Transcutaneous supraorbital nerve stimulation (Cefaly) is FDA-cleared for both acute treatment and daily preventive use, with evidence of modest but clinically meaningful benefit. Single-pulse transcranial magnetic stimulation has demonstrated efficacy in reducing migraine days and is approved for both acute and preventive treatment of migraine with aura. Non-invasive vagus nerve stimulators provide modest benefit in acute and preventive therapy. Occipital nerve blocks or implantable neurostimulation may be considered for refractory chronic migraine under specialist supervision (63, 64). Evidence remains limited, and these interventions are typically reserved for patients who fail conventional treatments.

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

9. Conclusion

Migraine is a common and disabling brain disorder with complex genetic, hormonal, and environmental determinants. Understanding the pathophysiological underpinnings – from cortical spreading depression to trigeminovascular activation and neuropeptide release – has led to targeted therapies such as triptans, ditans, gepants, and anti-CGRP monoclonal antibodies. Evidence-based guidelines emphasize individualized care: simple analgesics and NSAIDs for mild attacks, triptans or gepants for moderate to severe attacks, and avoidance of opioids. Preventive therapy should be offered when attacks are frequent, severe, or disabling. Anti-CGRP antibodies, and atogepant represent major advances, with onabotulinumtoxinA for chronic migraine and traditional agents such as topiramate, beta-blockers, valproate, and antidepressants remaining valuable. Non-pharmacological strategies – trigger avoidance, lifestyle modifications, behavioral therapy, and neuromodulation – complement pharmacologic measures and empower patients. Because migraine disproportionately affects women and those of lower socioeconomic status, patient education and equitable access to care are imperative. Ongoing research will refine our understanding of migraine mechanisms and expand therapeutic options, offering hope for improved quality of life for the millions of people worldwide living with migraine.

ETHICAL STATEMENT

Not Applicable.

CONFLICT OF INTEREST

There is no conflict of interest to be declared.

AUTHORS' CONTRIBUTIONS

Basma S.A. Kamel and Mostafa M. Abdelhafeez developed the concept and structure of the review together. Basma S.A. Kamel led the literature search and drafted the initial manuscript, provided critical revisions.
Mostafa M. Abdelhafeez contributed additional sources, and enhanced the analytical discussion. Both authors read and approved the final version.

References

1. Maity MK, Naagar M. A review on headache: epidemiology, pathophysiology, classifications, diagnosis, clinical management and treatment modalities. International Journal of Science and Research (IJSR). 2022;11(7):506-15.
2. Levin M. International Classification of Headache Disorders and Diagnosis of Migraine and Its Subtypes. Comprehensive Review of Headache Medicine. 2025:101.
3. Wider B, Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database Syst Rev. 2015;4(4):Cd002286.
4. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, et al. Migraine. Nature Reviews Disease Primers. 2022;8(1):2.
5. Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Häppölä P, Mitchell AA, et al. Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families. Neuron. 2018;98(4):743-53.e4.
6. Polderman TJC, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nature Genetics. 2015;47(7):702-9.
7. Hautakangas H, Palotie A, Pirinen M, Consortium IHG. Fine-mapping a genome-wide meta-analysis of 98,374 migraine cases identifies 181 sets of candidate causal variants. medRxiv. 2024.
8. Amiri P, Kazeminasab S, Nejadghaderi SA, Mohammadinasab R, Pourfathi H, Araj-Khodaei M, et al. Migraine: A Review on Its History, Global Epidemiology, Risk Factors, and Comorbidities. Front Neurol. 2021;12:800605.
9. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: updated age, sex, and socioeconomic-specific estimates from government health surveys. Headache: The Journal of Head and Face Pain. 2021;61(1):60-8.

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

10. Dong L, Dong W, Jin Y, Jiang Y, Li Z, Yu D. The global burden of migraine: A 30-Year trend review and future projections by age, sex, country, and region. Pain and Therapy. 2025;14(1):297-315.
11. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine—interactions of oestrogen, oxytocin and CGRP. Nature Reviews Neurology. 2021;17(10):621-33.
12. Raffaelli B, Do TP, Chaudhry BA, Ashina M, Amin FM, Ashina H. Menstrual migraine is caused by estrogen withdrawal: revisiting the evidence. The journal of headache and pain. 2023;24(1):131.
13. Li S, Liu Q, Ma M, Fang J, He L. Association between weather conditions and migraine: a systematic review and meta-analysis. Journal of Neurology. 2025;272(5):346.
14. Alsuwayt SS, Aljaied YS, Ahmed AA, Al Hussain FA, Alawami HM, Alamer ZB, et al. Did Primary Healthcare Patients in Riyadh Experience Their First Migraine Episodes After a Stressful Event, and What Triggers and Relievers Do They Commonly Report? Cureus. 2024;16(11):e74712.
15. Ceren Akgor M, Vuralli D, Sucu DH, Gokce S, Tasdelen B, Gultekin F, et al. Distinct Food Triggers for Migraine, Medication Overuse Headache and Irritable Bowel Syndrome. J Clin Med. 2023;12(20).
16. Kaniecki RG. Trigger identification and elimination. Integrative Headache Medicine: An Evidence-Based Guide for Clinicians: Springer; 2021. p. 17-41.
17. Dresler T, Caratozzolo S, Guldolf K, Huhn J-I, Loiacono C, Niiberg-Pikksööt T, et al. Understanding the nature of psychiatric comorbidity in migraine: a systematic review focused on interactions and treatment implications. The journal of headache and pain. 2019;20(1):51.
18. Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, et al. Migraine and sleep disorders: a systematic review. The journal of headache and pain. 2020;21(1):126.
19. Wang Y-P, Wei H-X, Hu Y-Y, Zhang C, Niu Y-M. Causal association between obstructive sleep apnea and migraine: a bidirectional Mendelian randomization study. Nature and Science of Sleep. 2025:183-94.
20. Zhang L, Yin J, Li J, Sun H, Liu Y, Yang J. Association between dietary caffeine intake and severe headache or migraine in US adults. Scientific Reports. 2023;13(1):10220.
21. Schwedt TJ. Post-traumatic headache due to mild traumatic brain injury: current knowledge and future directions. Cephalalgia. 2021;41(4):464-71.
22. McLeod GA, Josephson CB, Engbers JD, Cooke LJ, Wiebe S. Mapping the migraine: Intracranial recording of cortical spreading depression in migraine with aura. Headache: The Journal of Head and Face Pain. 2025;65(4):658-65.
23. Song X, Zhu Q, Zhang J, Yang J, Zhang X, Song Q. Trigeminal nerve-driven neurogenic inflammation linking migraine to glioblastoma invasion: a literature review. Frontiers in Immunology. 2025;16:1632154.
24. Kuburas A, Russo AF. Shared and independent roles of CGRP and PACAP in migraine pathophysiology. The Journal of Headache and Pain. 2023;24(1):34.
25. Pleş H, Florian I-A, Timis T-L, Covache-Busuioc R-A, Glavan L-A, Dumitrascu D-I, et al. Migraine: Advances in the pathogenesis and treatment. Neurology international. 2023;15(3):1052-105.
26. Schramm S, Boerner C, Reichert M, Baum T, Zimmer C, Heinen F, et al. Functional magnetic resonance imaging in migraine: A systematic review. Cephalalgia. 2023;43(2):03331024221128278.
27. Safiri S, Pourfathi H, Eagan A, Mansournia MA, Khodayari MT, Sullman MJM, et al. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. PAIN. 2022;163(2):e293-e309.
28. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019;18(5):459-80.
29. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41(7):646-57.
30. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.
31. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 2017;16(1):76-87.
32. Haghdoost F, Togha M. Migraine management: Non-pharmacological points for patients and health care professionals. Open Medicine. 2022;17(1):1869-82.
33. Qaseem A, Tice JA, Etxeandia-Ikobaltzeta I, Wilt TJ, Harrod CS, Cooney TG, et al. Pharmacologic treatments of acute episodic migraine headache in outpatient settings: a clinical guideline from the American College of Physicians. Annals of internal medicine. 2025;178(4):571-8.
34. Gartlehner G, Dobrescu A, Wagner G, Chapman A, Persad E, Nowak C, et al. Pharmacologic treatment of acute attacks of episodic migraine: a systematic review and network meta-analysis for the American College of Physicians. Annals of Internal Medicine. 2025;178(4):507-24.

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

35. Becker WJ. Acute migraine treatment in adults. Headache: The Journal of Head and Face Pain. 2015;55(6):778-93.
36. Diener H, Förderreuther S, Kropp P. Treatment of migraine attacks und preventive treatment of migraine, S 1 guideline, 2022, DGN and DMKG. Deutsche Gesellschaft für Neurologie (Pub), Guidelines for diagnosis and treatment in neurology. 2022.
37. Iljazi A, Chua A, Rich-Fiondella R, Veronesi M, Melo-Carrillo A, Ashina S, et al. Unrecognized challenges of treating status migrainosus: An observational study. Cephalalgia. 2020;40(8):818-27.
38. Marmura MJ, Hou A. Inpatient management of migraine. Neurologic Clinics. 2019;37(4):771-88.
39. Karlsson WK, Ostinelli EG, Zhuang ZA, Kokoti L, Christensen RH, Al-Khazali HM, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. bmj. 2024;386.
40. Petersen CL, Hougaard A, Gaist D, Hallas J. Risk of stroke and myocardial infarction among initiators of triptans. JAMA neurology. 2024;81(3):248-54.
41. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database of Systematic Reviews. 2016(4).
42. Silberstein S, Mannix L, Goldstein J, Couch J, Byrd S, Ames M, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. Neurology. 2008;71(2):114-21.
43. Friedman BW, Irizarry E, Solorzano C, Latev A, Rosa K, Zias E, et al. Randomized study of IV prochlorperazine plus diphenhydramine vs IV hydromorphone for migraine. Neurology. 2017;89(20):2075-82.
44. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 2: neuroleptics, antihistamines, and others. Headache: The Journal of Head and Face Pain. 2012;52(2):292-306.
45. Desouza IS, Anthony N, Thode Jr H, Allen R, Belyavskaya J, Koos J, et al. Effectiveness and safety of pharmacologic therapies for migraine in the emergency department: a systematic review and Bayesian network meta-analysis. Annals of Emergency Medicine. 2025;85(4):313-29.
46. Kazi F, Manyapu M, Fakherddine M, Mekuria K, Friedman BW. Second-line interventions for migraine in the emergency department: a narrative review. Headache: The Journal of Head and Face Pain. 2021;61(10):1467-74.
47. Cisewski D, Long B, Gottlieb M. Emergency medicine updates: droperidol. The American Journal of Emergency Medicine. 2022;53:180-4.
48. Dodick DW, Goadsby PJ, Schwedt TJ, Lipton RB, Liu C, Lu K, et al. Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. The Lancet. 2023;402(10419):2307-16.
49. Lipton RB, Blumenfeld A, Jensen CM, Croop R, Thiry A, L'Italien G, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: pooled results from three phase 3 randomized clinical trials. Cephalalgia. 2023;43(2):03331024221141686.
50. VanderPluym JH, Singh RBH, Urtecho M, Morrow AS, Nayfeh T, Roldan VDT, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. Jama. 2021;325(23):2357-69.
51. Smith TR, Winner P, Aurora SK, Jeleva M, Hocevar-Trnka J, Shrewsbury SB. STOP 301: A Phase 3, open-label study of safety, tolerability, and exploratory efficacy of INP104, Precision Olfactory Delivery (POD®) of dihydroergotamine mesylate, over 24/52 weeks in acute treatment of migraine attacks in adult patients. Headache: The Journal of Head and Face Pain. 2021;61(8):1214-26.
52. Dayal R, Sulindro AD. Prophylaxis of Migraine Protocols and Options. Migraine: Emerging Innovations and Treatment Options: Springer; 2021. p. 51-73.
53. Ornello R, Caponnetto V, Ahmed F, Al-Khazali HM, Ambrosini A, Ashina S, et al. Evidence-based guidelines for the pharmacological treatment of migraine. Cephalalgia. 2025;45(4):03331024241305381.
54. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. Cephalalgia. 2015;35(1):51-62.
55. Burch R. Antidepressants for preventive treatment of migraine. Current treatment options in neurology. 2019;21(4):18.
56. Sico JJ, Antonovich NM, Ballard-Hernandez J, Buelt AC, Grinberg AS, Macedo FJ, et al. 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Headache. Annals of internal medicine. 2024;177(12):1675-94.
57. Vikelis M, Dermitzakis EV, Vlachos GS, Soldatos P, Spingos KC, Litsardopoulos P, et al. Open label prospective experience of supplementation with a fixed combination of magnesium, vitamin B2, feverfew, Andrographis paniculata and coenzyme Q10 for episodic migraine prophylaxis. Journal of clinical medicine. 2020;10(1):67.
58. Amin FM, Aristeidou S, Baraldi C, Czapinska-Ciepiela EK, Ariadni DD, Di Lenola D, et al. The association between migraine and physical exercise. The journal of headache and pain. 2018;19(1):83.
59. Woldeamanuel YW, Oliveira ABD. What is the efficacy of aerobic exercise versus strength training in the treatment of migraine? A systematic review and network meta-analysis of clinical trials. The Journal of Headache and Pain. 2022;23(1):134.
60. Starling AJ. SEEDS for success: Lifestyle management in migraine. Cleveland Clinic journal of medicine. 2019;86(11):741.
61. Barnard ND. Migraine. 2025.
62. Agbetou M, Adoukonou T. Lifestyle modifications for migraine management. Frontiers in neurology. 2022;13:719467.

Corresponding author: dr.basma.bio@gmail.com

Lebda Medical Journal; [LMJ]; {Online ISSN:2520-095X}

Lebda Medical Journal Homepage:
https://lebmedj.elmergib.edu.ly/index.php/LMJ/en

63. Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lantéri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. The Journal of Headache and Pain. 2020;21(1):142.
64. Tiwari V, Agrawal S, TIWARI V. Migraine and neuromodulation: a literature review. Cureus. 2022;14(11).

Corresponding author: dr.basma.bio@gmail.com