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Nutrition, Hormones, and CGRP in Migraine: An Integrative Review of Micronutrient and Mitochondrial Mechanisms

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ABSTRACT: Migraine is a neurological disorder characterized by severe throbbing and one-sided pain in the head. It is more than “just a headache”. It is associated with several other symptoms including nausea, vomiting, visual disturbances like spotting, and increased sensitivity to light, sound and smell. However, the exact cause of a migraine attack is not known. A migraine attack can be triggered by a multitude of factors including specific smells, loud sounds, bright flashes of light, sudden changes in temperatures, certain foods and drinks, hormonal fluctuations, sleep disturbances, physical exertion and even certain medications. About 1 billion people suffer from migraine attacks, most of them being women. Approximately three times as many women experience migraines compared to men. Hence, an attempt has been made to understand how specific dietary patterns and micronutrients influence hormonal fluctuations and analyze how these fluctuations are associated with migraine attack frequency and severity.

INTRODUCTION:

Migraine is an intensely prevailing neurological disorder portrayed by recurring occurrence of moderate to severe headache and a complex set of associated symptoms, impacting over a billion people globally. Its disabling nature makes it the second most common cause of years lived with disability worldwide, profoundly affecting not only individuals but also families, communities, and workplaces. Migraine is not merely a headache; it's a multisystem disorder involving genetic, environmental, and behavioral factors, producing attacks that can last for hours or even days and often disrupt daily functioning.¹

Epidemiology and Burden

Migraine affects approximately 6% of men and 18% of women on an annual basis, with the highest prevalence in people aged 20–40 years and those from socioeconomically disadvantaged groups.¹ The female dominance in migraine prevalence is attributed to hormonal fluctuations and genetic susceptibility.¹ The disorder is associated with comorbid conditions, particularly anxiety and depression, which further escalate the burden on patients and society.¹ Epidemiological studies confirm the global spread of migraine, reinforcing the need for improved awareness, diagnosis, and management strategies.^{1,2}

Historical Perspective

Historically, migraine's presence has been noted since ancient times; early records from Egypt's Ebers Papyrus (1500 BC) as well as Hippocratic texts (200 BC) described features such as visual aura and relief with vomiting. [1] The terminology “migraine” evolved from Galen’s description of “hemikrania” (half-head) to the French “migraine.” Over centuries, physicians have observed distinctions between migraine with aura and without aura, attempted treatments from trepanation to ergot derivatives, and incrementally deepened the understanding of migraine’s pathophysiology.^{1,2}

CLASSIFICATION AND TYPES:

Migraine is classified based on clinical features and the presence or absence of aura. The International Headache Society divides the primary migraine types as follows:

- **Migraine With Aura:** Characterized by reversible sensory, visual, or language symptoms preceding or accompanying the headache. Visual phenomena (scintillating scotomas, flashing lights), sensory changes (numbness, tingling), and language disturbances may appear gradually and typically resolve

within an hour.^{1,3,4}

- **Migraine Without Aura:** The most common type, marked exclusively by severe, recurrent headache, often unilateral, with no preceding aura.^{1,5}

- **Chronic Migraine:** Defined by a headache frequency of 15 or more days per month spanning over a trimester, where the symptom profile fulfills migraine criteria on a minimum of eight of those days.^{1,5}

- **Rare Forms:** Including hemiplegic migraine (transient paralysis or weakness on one side), status migrainosus (attack persistent over 72 hours), abdominal migraine, vestibular migraine, and silent migraine (aura without headache).^{1,5,6}

Diagnostic Criteria

Diagnosis relies primarily on clinical evaluation, using criteria from the International Headache Society.¹ For migraine with aura, at least two attacks with reversible sensory/visual/language symptoms, lasting between five minutes and an hour, and subsequent headache are required.^{1,4} Migraine without aura is diagnosed based on recurrent attacks (minimum two), headache duration of 4 to 72 hours, unilateral location, moderate to severe intensity, aggravated by activity, and associated symptoms such as nausea, photophobia, or phonophobia.^{1,5} The importance of a thorough history and examination cannot be overstated, as many secondary headache disorders mimic or coexist with migraine.^{1,7}

Pathophysiology

Migraine's pathogenesis is multifactorial, rooted in both genetic and environmental predispositions.^{1,8,9}

Genetic studies implicate mutations in genes encoding neural ion channels and transporters, such as CACNA1A, ATP1A2, and SCN1A, in familial migraine.^{1,10} The current consensus model attributes migraine attacks to abnormal neuronal excitability (especially in the cortex), triggering neurovascular changes, neurogenic inflammation, and altered pain processing.^{1,8} Cortical spreading depression, a wave of neuronal and glial depolarization, is postulated as the basis for aura phenomena. Activation of trigeminal nerve fibers induces release of vasoactive peptides (CGRP, substance P), causing neurogenic inflammation and vasodilation.^{1,11} Although earlier theories centered around vascular changes, newer models emphasize the role of neuropeptides, neurotransmitter (serotonin), and altered central pain pathways.^{1,8,12}

PHASES OF MIGRAINE:

A typical migraine attack evolves through recognizable phases, each marked by specific symptoms and neurochemical changes.^{1,5,15}

Prodromal Phase: Hours or days before the headache, patients may experience premonitory symptoms including yawning, mood changes, food cravings, neck pain, fatigue, visual blurring, and increased urination.

These can be mistaken for triggers but represent the prodrome of a migraine attack.^{1,5,12}

Aura: Observed in 20–30% of migraine patients, aura typically presents as visual (flashes, zigzag patterns, tunnel vision), sensory (pins and needles, numbness), or language (aphasia) disturbances, starting gradually and usually resolving within 60 minutes.^{3,4,5} Not all migraineurs experience aura; its pathophysiology has been tied to cortical spreading depression.^{1,8,4}

Headache (Attack Phase): The hallmark phase with throbbing, pulsating, often unilateral pain intensified by routine activity. Associated symptoms include nausea (80%), vomiting (50%), sensitivity to light, sound, odor, along with neck stiffness.^{5,12} Head pain may last 4–72 hours, and severe cases, such as status migrainosus, may persist longer, sometimes requiring hospitalization.^{1,5,15}

Postdrome Phase: Following headache resolution, patients report fatigue, cognitive impairment (“migraine hangover”), neck pain, mood disturbances, and gastrointestinal issues lasting for up to 48 hours.^{1,5,15}

Though headache is the chief complaint, migraine exhibits a constellation of symptoms that distinguish it from other headaches.^{5,7} A tension headache manifests as a bilateral, mild-to-moderate, steady ache, lacking sensory disturbances or aura. Cluster headache is sudden and intense, typically localized behind one eye, and is associated with autonomic symptoms (eye redness, eyelid drooping).^{5,7,13} Migraine pain is throbbing, worsens with movement, and may migrate; sensory sensitivities and gastrointestinal symptoms further support the diagnosis.^{5,13}

MIGRAINE RISK FACTORS AND TRIGGERS:

Genetic susceptibility is strong; four out of five people report a family history, and individual risk rises further if both parents are affected.⁵ Women experience migraines at three times the rate of men, and reproductive hormonal fluctuations (menstrual cycle, pregnancy, menopause) significantly impact frequency and severity.^{1,5,6} Other risk factors include comorbid psychiatric conditions (depression, anxiety, bipolar disorder, epilepsy), sleep disorders, and younger age at onset.^{2,5,11}

Common triggers for migraine attacks encompass a wide spectrum:

- Hormonal changes (menstrual cycle, contraceptives, menopause)
- Emotional stress, anxiety
- Sensory stimuli (bright lights, loud noise, strong odors)
- Weather changes (storm fronts, barometric shifts, altitude)
- Skipping meals, dehydration
- Physical exertion, sexual activity
- Tobacco, caffeine fluctuations (excess or withdrawal)
- Certain medications (vasodilators)
- Sleep disturbances (too much or too little)
- Foods: aged cheeses, alcohol, chocolate, processed meats, MSG, aspartame, nitrates

The role of dietary triggers is controversial; while many report food triggers, evidence is limited. Keeping a symptom and food diary helps identify individual triggers.^{5, 14}

TYPES OF MIGRAINE:

Migraine can present in numerous forms, many distinguished by unique symptom profiles and associated conditions:

- **Migraine With Aura (Classic Migraine):** This type features one or more reversible neurological symptoms preceding headache, most commonly visual disturbances.^{3,4,5}
- **Migraine Without Aura (Common Migraine):** Headache without premonitory neurological symptoms, but with typical migraine features.⁵
- **Menstrual Migraine:** Headaches linked specifically to the menstrual cycle, often more severe and resistant to treatment.^{5,6}
- **Silent (Acephalgic) Migraine:** Aura symptoms without headache, usually lasting only 20–30 minutes.⁵
- **Vestibular Migraine:** Presents as balance problems, vertigo, nausea, and vomiting, with or without headache.^{5,6}
- **Abdominal Migraine:** Stomach pain, nausea, vomiting, more prevalent in children, may transition to classic migraine later.⁵
- **Hemiplegic Migraine:** Brief paralysis or weakness on one side, may be accompanied by numbness, dizziness, and vision changes; needs urgent evaluation to rule out stroke.^{5,6}
- **Ocular (Ophthalmic) Migraine:** Temporary vision loss in one eye and a dull ache behind the eye, requires medical evaluation for possible nerve or vascular disorders.⁵
- **Migraine With Brainstem Aura:** Dizziness, confusion, balance loss; affects backs of the head, often in young women and tightly linked to hormonal changes.⁵
- **Status Migrainosus:** Severe, unremitting migraine lasting over 72 hours, often requiring hospitalization.⁵
- **Ophthalmoplegic Migraine:** Eye pain, droopy eyelid, double vision; often requires neuroimaging to exclude nerve or aneurysm pathology.⁵

Migraine is sub-classified based on frequency:

- **Episodic:** Sporadic attacks, as few as once a year up to several times monthly.⁵
- **High-Frequency Episodic:** 9–14 days/month over 3+ months.⁵
- **Chronic:** Headaches on over 15 days/month, at least eight qualifying as migraine; about one-third of migraine sufferers have chronic forms, which are severely disabling.⁵ Working with healthcare professionals is crucial for controlling chronic migraine.

DIAGNOSIS:

Diagnosis is clinical, involving detailed personal and family history and careful symptom tracking. Physicians rely on criteria regarding episode characteristics, onset pattern, triggers, and associated symptoms.^{1,5} In ambiguous cases or when secondary causes are suspected, blood tests, MRI, CT scans, or EEG may be ordered.^{2,5,8} The MIDAS (Migraine Disability Assessment Scale) is used to measure attack intensity and its functional impact across work, family, and social domains.⁵

Severity Assessment

The MIDAS rating helps segment migraine by degree of disability:

- Grade 1: Little to none
- Grade 2: Mild
- Grade 3: Moderate
- Grade 4: Severe

MANAGEMENT AND TREATMENT:

Migraine treatment aims to reduce attack frequency, severity, and duration, as well as improve quality of life. Strategies combine acute therapies for immediate relief, preventive approaches, neuromodulation, and supportive non-drug interventions.^{5, 14}

Pharmacological Therapies:

- **Acute Medications:** OTC pain relievers (acetaminophen, aspirin, ibuprofen, caffeine combinations) often work for mild attacks; overuse can cause rebound headaches or dependence.^{5,14}
- **Triptans:** Selective serotonin receptor agonists (sumatriptan, rizatriptan, eletriptan, zolmitriptan) offer targeted relief by balancing brain chemical activity.^{5,14}
- **Ditans:** Lasmiditan is a newer agent acting on serotonin pathways, especially for those with cardiovascular risks.^{5,14}
- **Gepants:** Rimegepant, ubrogepant, zavegepant—all inhibit CGRP to block pain signaling.^{5,14}
- **Ergotamines:** Older drugs (cafergot) work on brain chemicals; caution advised due to vascular risks.⁵
- **Antiemetics:** Metoclopramide and others help with nausea/vomiting.⁵
- **Preventive Medications:** Prescribed for frequent, severe, or poorly controlled attacks. Include anticonvulsants, beta-blockers, calcium channel blockers, antidepressants, and CGRP blockers (erenumab, fremanezumab, galcanezumab, eptinezumab, atogepant).^{1,5}

Device-Based and Neuromodulation Treatments:

Several FDA-approved devices deliver magnetic or electrical stimulation to target pain pathways:

- eNeura (transcranial magnetic stimulation)
- Cefaly (trigeminal nerve stimulation)
- GammaCore (vagal stimulation)
- Nerivio (remote arm stimulation)
- Relivion (combined trigeminal/occipital neurostimulation)⁵

Botox Therapy:

OnabotulinumtoxinA injections are approved for chronic migraine, providing significant attack reduction for many patients.^{1,5}

Surgical Options:

Rarely considered; nerve decompression and neurectomy are reserved for refractory cases where other measures have failed.⁵

Non-pharmacological Management:

Lifestyle adjustments play a pivotal role:

- Stress reduction (meditation, yoga, relaxation exercises)
- Keeping a regular sleep and meal schedule^{1,5,14}
- Avoiding identified triggers (using diaries and symptom apps)
- Staying hydrated and getting enough rest^{5,14}
- Regular moderate exercise

The treatment prospectives have been discussed later in detail in this review.

Complementary and Alternative Approaches:

- Biofeedback for early attack control
- Nutritional supplements (magnesium, riboflavin, coenzyme Q10, feverfew, melatonin, butterbur)^{1,14}
- Physical therapies (acupuncture, massage, chiropractic care)
- Cognitive behavioral therapy (CBT) to reframe stress and pain perceptions⁵

Complications

Serious complications such as migrainous infarction (stroke during migraine), persistent aura, seizures, and chronic psychological problems (depression, anxiety, insomnia) are seen, although most migraines do not cause lasting harm.^{1,5,6} Severe attacks (status migrainosus, hemiplegic migraine) require immediate medical

attention.^{5,6}

Living With Migraine

Chronic migraine entails substantial lifestyle and psychosocial challenges. Coping strategies include keeping diaries, stress management, regular routines, hydration, and working with healthcare teams.^{1,5} Migraine is considered a disability if it restricts major life activities, recognized under legislation in some countries.⁵

Conclusions and Future Perspectives

Migraine remains underdiagnosed, undertreated, and underestimated despite decades of research and therapeutic advances.^{1,5} The complexity of its presentation, multiple triggers, and heterogeneity highlight the need for personalized medicine and heightened awareness. Patients frequently misuse pain medications and delay seeking specialist care, often aggravating their condition.^{1,5} Advancements in acute and preventive medication, devices, and non-pharmacological strategies provide hope for better disease control. Ongoing research on genetics, neurophysiology, and biomarkers promises brighter prospects for migraine management and possibly, prevention.^{1,5,6,8}

IMPACT OF MICRONUTRIENTS ON MIGRAINE

As we know Migraine is a neurovascular disease caused due to various factors like genetics, hormonal, severe brain injury, and lack of micronutrients.²⁰ Micronutrients are the substance which we intake or uptake in daily basis to let a healthy lifestyle.^{20,26} While genetics can play a role in the development of migraine, many internal and external factors such as everyday diet, specific trigger foods, alcohol consumption, hormonal shifts, stress, and lifestyle habits, can influence how severe or long-lasting an attack becomes. Migraine also tends to occur more frequently in women than in men, possibly because the hypothalamic–pituitary–ovarian axis, which controls estrogen levels, may affect cortical sensitivity or blood vessel dilation.²⁷

According to the International Headache Society, migraines are generally classified into two main forms:

-Migraine without aura: This type involves repeated headache episodes lasting between 4 and 72 hours. The pain is usually moderate to severe and often worsens with everyday activities like walking or climbing stairs. Nausea, along with sensitivity to light or sound, is also common.²⁷

-Migraine with aura: These episodes include neurological symptoms, such as visual, sensory, motor, or declamation disturbances, that evolve slowly and typically last five to sixty minutes, followed by a headache.²⁷

Various triggers can provoke migraines, including specific foods, environmental factors like weather changes or strong odors, certain medications, dehydration, stress, and tiredness. Deficiencies in certain vitamins or minerals may also play a role in migraine occurrence, and correcting these imbalances with supplements may benefit some individuals.²⁷ A range of factors can influence the likelihood of developing migraines, including genetics, age, obesity, hormonal fluctuations, changes in vascular neurotransmitters, low socioeconomic conditions, stress, and dietary habits. Nutrient intake, in particular, has been linked to migraine risk over the long term in both men and women, with a stronger association often observed in women. However, despite growing interest in this area, only a limited number of studies have examined how diet relates to migraine. Among the existing research, results are inconsistent; some cross-sectional studies suggest that consuming foods such as chocolate,

caffeinated beverages, milk, cheese, and alcohol may elevate the risk of migraine episodes.^{17,20,26} Micronutrients can be simply termed as the vitamins, minerals that has a serious effect in development of body, if there is lack of nutrients or excess of various supplements containing micronutrients can cause toxic or noxious effect to body.^{17,20,21}

Micronutrients which are really important in preventing migraine are magnesium (mg), Niacin or vitamin B3 (it is a very crucial aqua-soluble vitamin that converts the food we uptake into energy (ATP) and nourish the hair, skin and nerves. Riboflavin or vitamin B2, cobalamin is another form of vitamin B12 (which is responsible for proper nerve function), Coenzyme Q10 is essential in put a stop to congestive heart failure as well as migraine. Migraine maybe caused if there is any mitochondrial dysfunction and impaired antioxidant status in body, in this condition the Micronutrients such as carnitine can help in aiding mitochondrial energy building along with antioxidant effect. Alpha-lipoic acid (ALA) is a naturally occurring substance that acts as both an antioxidant and a pro-oxidant. It is commonly used in the management of diabetic neuropathy. Vitamin D also plays a vital role in preventing migraine.^{18,20}

Because each food contains a unique mix of nutrients, eating a varied diet is the best way to ensure you get a full range of vitamins and minerals. The body needs sufficient amounts of all micronutrients to function at its best, as every vitamin and mineral serves a distinct purpose. These nutrients are essential for key processes such as growth, immune defense, brain development, and many other vital activities. Depending on what they do in the body, some micronutrients also contribute to disease prevention and support your body's ability to

fight illness.^{16,18}

Biochemical Roles of Micronutrients

1. Metabolic cofactors:

Certain trace minerals support metabolic processes by helping enzymes work properly or by forming part of enzyme structures. For instance, zinc is involved in the activity of hundreds of enzymes, and selenium is present as selenocysteine in the antioxidant enzyme glutathione peroxidase.³³

2. Coenzymes:

Many vitamins, or the molecules derived from them, are required for key biochemical reactions. Riboflavin and niacin participate in the electron transport chain, while folate is essential for reactions that transfer methyl groups. These processes are fundamental for generating energy and producing proteins and nucleic acids.³³

3. Gene expression regulation:

Proteins containing zinc-finger domains bind to DNA and play an important role in controlling gene activity. They help regulate receptors for steroid hormones and other critical signaling molecules.³³

4. Antioxidant defense:

A number of micronutrients function as antioxidants. Since everyday metabolic activity produces reactive oxygen species that can harm DNA, cell membranes, and other cellular structures, the body depends on certain vitamins and enzymes for protection. Vitamin E and carotenoids can directly neutralize free radicals, while enzymes like superoxide dismutase (which requires zinc, copper, or manganese) and glutathione peroxidase (which relies on selenium) help eliminate oxidative by-products as shown in the fig.(1)¹⁶

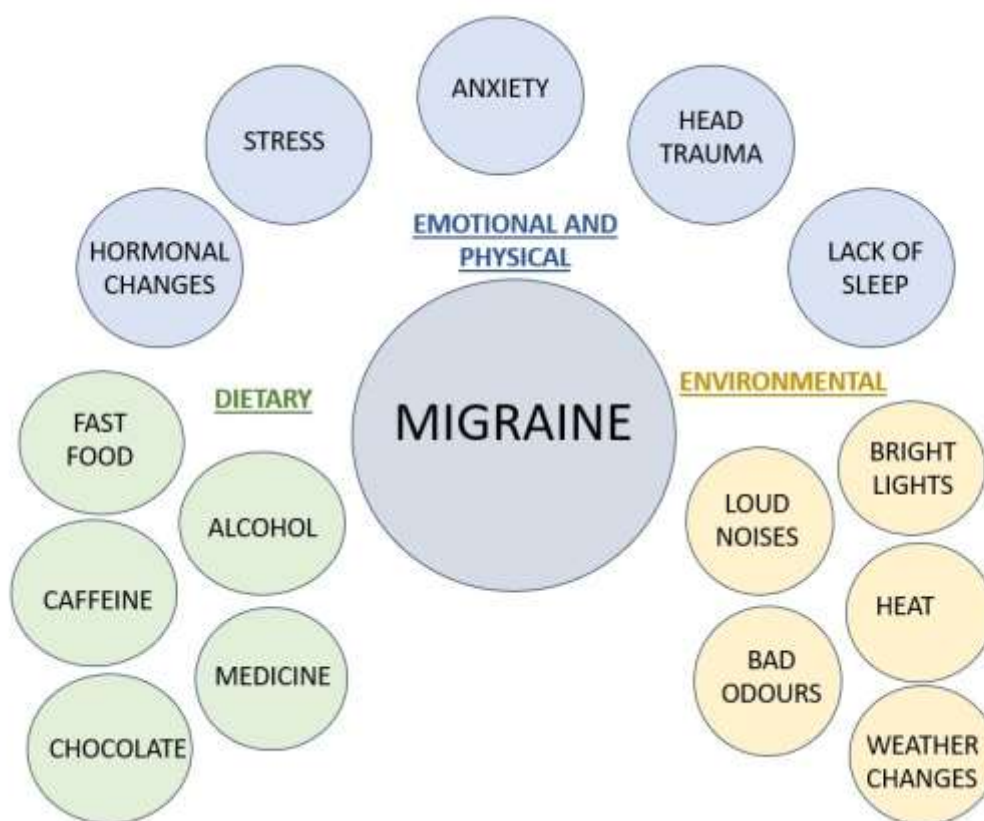


Fig. (1). Migraine triggers are factors that can cause migraines. Migraine triggers may be emotional or physical causes like stress, anxiety, hormonal changes, head trauma, and lack of sleep or dietary triggers like fast food, caffeine, chocolate, alcohol, and medicines. Environmental causes of migraines include bright lights, noise, odours, heat, and weather changes.

Recognizing the elements that lead to migraines can help people pinpoint their own triggers and handle episodes more efficiently. In recent years, significant attention has been given to finding effective approaches for preventing and treating neurological conditions, including promising strategies centered around dietary modifications.²⁵

Foods like spinach, milk, egg, nuts, meat, green veggies, enriched flour, oily fish, whole grains, etc. is the source of magnesium, riboflavin, vitamin, protein, Coenzyme Q10 which prevent the disease, if there is deficiency in this diet, attack of many infectious and neuro related diseases like neurodegenerative, seizures, epilepsy, Alzheimer.^{28,30} Research indicates that various dietary patterns may help lower how often migraines occur. Some examples include:

- Ketogenic (keto) diet
- Modified Atkins diet
- Diets rich in folate
- Low-fat diets
- High omega-3 combined with low omega-6 intake
- Low-glycemic diets
- Low-sodium diets, especially in older adults

Studies suggest that the keto and modified Atkins diets may be more effective than standard eating habits in decreasing migraine frequency.^{28, 30}

This benefit may be linked to ketosis, a metabolic state in which the brain uses ketones instead of glucose for energy. These diets typically emphasize low-carbohydrate, high-fat foods such as fish, eggs, and non-starchy vegetables.²⁸

However, it's important to stay cautious-some foods allowed on keto diets can still trigger migraines in certain individuals. Consulting a doctor or a registered dietitian is recommended before beginning a keto plan, as it carries potential risks.²⁸

For people who need to prioritize heart health, keto may not be ideal. In such cases, heart-friendly eating patterns like the Mediterranean or DASH diets might also be helpful for easing migraine symptoms.^{28,32}

Vitamin E

Many women experience migraines alongside menstrual symptoms. Vitamin E appears to help reduce these “menstrual migraines” by lowering levels of arachidonic acid-a compound that is later converted into substances linked to migraine attacks during menstruation. Foods such as sunflower seeds, almonds, and spinach are rich sources of vitamin E. Increasing intake in the days leading up to menstruation and during the cycle may help ease various symptoms. Research has shown that women with higher vitamin E levels tend to report reduced pain and decreased sensitivity to sensory triggers.³²

Micronutrients

Micronutrients can be administered by patient as supplements containing vitamin, minerals, antioxidants etc. which helps in preventing migraine. As the main properties of micronutrients are to prevent by acting as an antioxidant, causing mitochondrial energy production. Magnesium (mg) plays a key role in the body, helping more than 300 enzymes carry out metabolic processes and support proper nerve activity. Not getting enough magnesium can increase the chances of problems related to brain function and metabolism, and low magnesium levels are often seen in people who suffer from migraines.³¹

Vitamin-D

Because of limited sunlight exposure, Vitamin D deficiency is common among people. Fortunately, introducing a Vitamin D supplement can be a safe, low-risk approach to reducing the frequency and severity of migraines.

While the supplement is highly tolerated and safe for general use and is even actively recommended during pregnancy, unlike many other medications- it is still possible to take too much. Because excessive levels can lead to toxicity, it is best to consult with a healthcare professional to determine the ideal, personalized dosage. Overall, Vitamin D serves as an excellent option to incorporate into a preventative health routine.³¹

Coenzyme Q10

Coenzyme Q10 helps the cells produce energy and reduces oxidative stress, a factor that has been associated with migraine development.

Vitamin B complex

B-vitamins such as B6, B12, and folic acid play a vital role in producing neurotransmitters, which support healthy brain activity and help maintain emotional balance.

Eliminating foods based on IgG antibodies testing may help lower how often migraine attacks occur, and findings from clinical research generally suggest that this approach can be effective.^{22,24}

Omega-3 fatty acids

Omega-3 fatty acids have demonstrated potential in attenuating the activity of select cytokines- bioactive proteins critically implicated in the mediation of inflammatory responses and pain signaling pathways. Docosahexaenoic acid, in particular, appears to exert a suppressive influence over multiple downstream inflammatory mediators, positioning it as a compound of notable therapeutic interest. Beyond their anti-inflammatory properties, these beneficial lipids are also capable of generating bioactive derivatives that collectively serve to diminish nociceptive signaling and confer protection against oxidative cellular damage. Nevertheless, the precise magnitude of their clinical efficacy in the prophylactic or symptomatic management of

migraine disorder remains incompletely elucidated, necessitating further rigorous investigation to establish definitive therapeutic parameters.^{24,40}

Omega-3 fatty acids constitute fundamental structural components of cellular membrane phospholipids, playing an indispensable role in maintaining membrane integrity and fluidity. Their dietary consumption has been consistently correlated with a measurable reduction in circulating inflammatory biomarkers, encompassing C-reactive protein, pro-inflammatory eicosanoids, cytokines, chemokines, and an array of additional inflammatory mediators implicated in disease pathogenesis as shown in the fig.(2)

A substantial body of clinical evidence has substantiated the therapeutic benefits of omega-3 supplementation across a diverse range of inflammatory and autoimmune conditions, including Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, and migraine disorder. The breadth of conditions implicated across these findings collectively reinforces the expansive immunomodulatory capacity of these essential fatty acids. Consequently, omega-3 fatty acids have garnered considerable recognition as a viable complementary or alternative therapeutic avenue, warranting continued exploration within both preventive and adjunctive clinical frameworks.⁴⁰

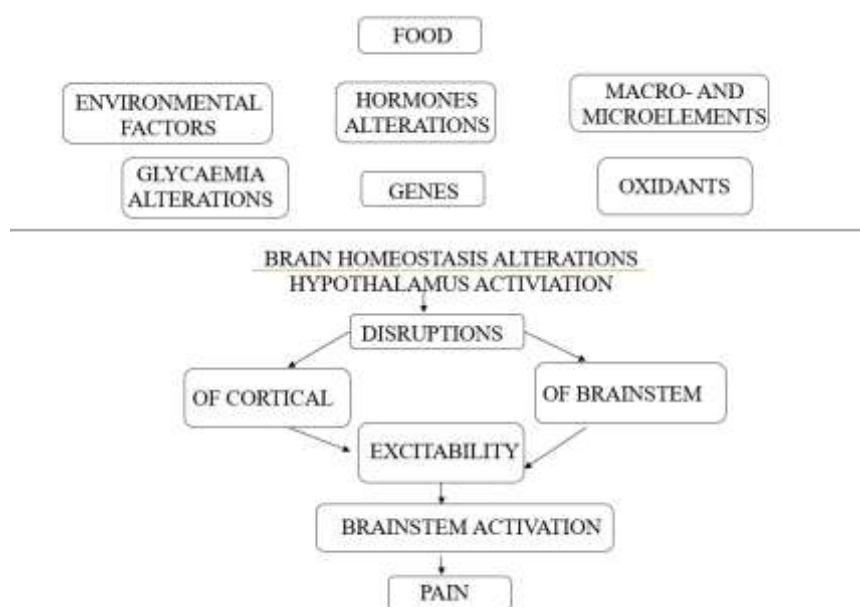


Fig. (2). The external factors include food, hormones, genetics, oxidants, changes in glycaemia, and the environment, which disrupt the homeostasis of the brain, activate the hypothalamus, and lead to dysfunctions in the cortical and brain stem regions, enhanced excitability, and a trigger for migraine pain through the activation of the brain stem.

The above image represents the Neural mechanisms within the brain that contribute to the development of migraine pain. Nutritional deficiencies usually present with a range of symptoms that develop gradually. Severe deficiency disorders typically appear only after a long period of insufficient intake. A primary vitamin deficiency occurs when the diet does not provide enough of a particular nutrient to meet the body's needs. In contrast, a secondary deficiency develops when intake is adequate, but the body is unable to properly use the nutrient because of problems with digestion, absorption, transport, or cellular metabolism.²¹ Since the brain relies heavily on glycolysis for its energy needs, mitochondrial function may significantly influence the development of migraines.^{19,21}

Various approaches have been recommended by government bodies and community organizations to address micronutrient deficiencies in different population groups.

These strategies include food-based interventions, improving the nutrient density of meals, fortifying commonly consumed foods, adding nutrient powders to homemade dishes, providing dietary supplements, and enriching staple items such as flour, cereals, salt, water, and cooking oils.¹⁹ These nutrients play an important role in supporting overall brain function. Including

foods high in these vitamins, minerals, and antioxidants or using supplements when needed-may help in reducing or managing migraine symptoms.³⁶ Magnesium (Mg) is a cell cofactor in which it helps in high production of energy (ATP). Magnesium is a vital mineral that supports a wide range of bodily functions. It is needed for energy-dependent metabolic reactions, helps build proteins, maintains cell membrane stability, supports nerve signal transmission, influences muscle and nerve activity, assists in muscle movement, aids hormone release, and plays an important part in various metabolic pathways. are essential for maintaining the brain's energy balance, and problems in how they function can contribute to migraine development. These organelles generate most of the brain's ATP, and when their activity is reduced, the resulting energy shortage can set off a migraine episode. Such mitochondrial issues are also associated with oxidative stress. This connection helps explain why factors like certain highfat diets and supplements such as coenzyme Q10 and riboflavin may reduce migraine frequency; they help improve or support mitochondrial performance.³⁶

These micronutrients act by the mechanism of action- Magnesium acts by binding to NMDA (N-methyl-Daspartate) receptor, a type of glutamate receptor. Glutamate receptors play an important role in migraine development because they influence pain signaling, promote central sensitization, and contribute to cortical spreading depression (CSD). Research has found that people with migraine often have elevated glutamate levels, and treatments that act on these receptors, such as magnesium, topiramate, and ketamine, have shown some benefit in reducing migraine symptoms. Magnesium binds as an antagonist, by binding to the glutamate receptor it blocks the influx of calcium ion channel which causes the prevention of excessive neuronal transmission in brain causing the sensitivity of pain in nerve. The magnesium can reduce the oxidative stress which is the imbalance state of free radicals and antioxidant. When these nutrients are insufficient, nerve cells become less resilient. They're more likely to develop energy shortages, experience oxidative damage, and become overly reactive, all of which can play a role in triggering migraines and increasing sensitivity to light and sound. Reactive Oxygen Species (ROS) are highly reactive molecules that have the potential to harm cells as shown in the fig.(3). Migraines are closely associated with oxidative stress- a condition that arises when the body produces more ROS than it can counteract with its antioxidant defenses. This imbalance can injure cells and is thought to amuse a vital role on triggering migraine attacks and contributing to symptoms such as pain and aura.³⁶

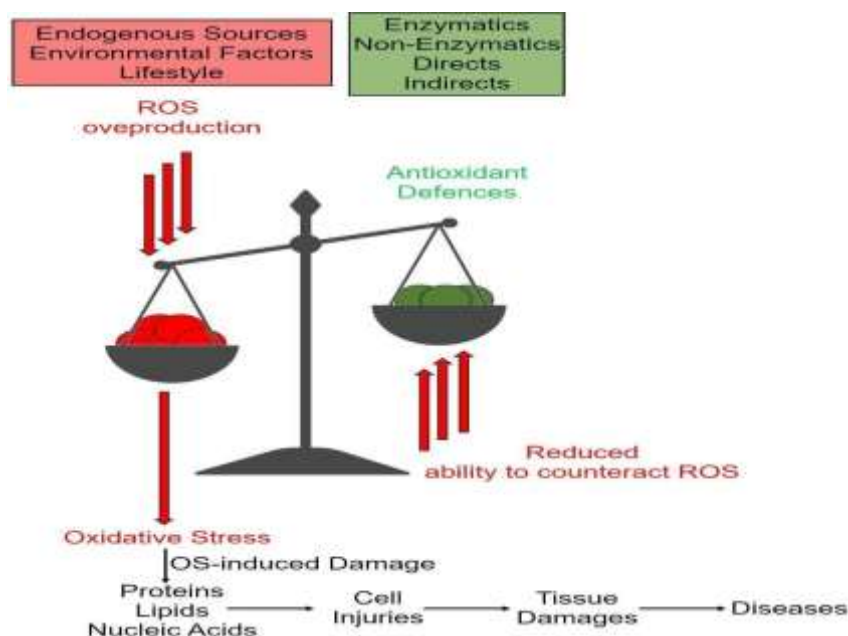


Fig. (3). The figure below represents a balance scale. On the left side, there is an increased amount of ROS (roses) that overwhelm the antioxidant defenses (greens) and induce oxidative stress. Overall, this leads to the oxidation of proteins, lipids, and nucleic acids, causing cell injury, tissue damage, and disease.

Mitochondrial Problems: Increased oxidative stress can interfere with how mitochondria work, lowering their ability to produce energy. This malfunction can also cause even more ROS to form, creating a cycle that may set off a migraine attack. Malfunction or dysfunction of mitochondria can also lead to oxidative stress as shown in fig.(4). Studies have shown that when magnesium levels drop in the platelets of people with migraines, there is a rise in cyclic AMP, while cyclic GMP levels

remain unchanged. These changes are thought to influence the release of neurotransmitters involved in early migraine-related disturbances in blood vessel regulation and the development of cortical spreading depression (CSD).³⁷

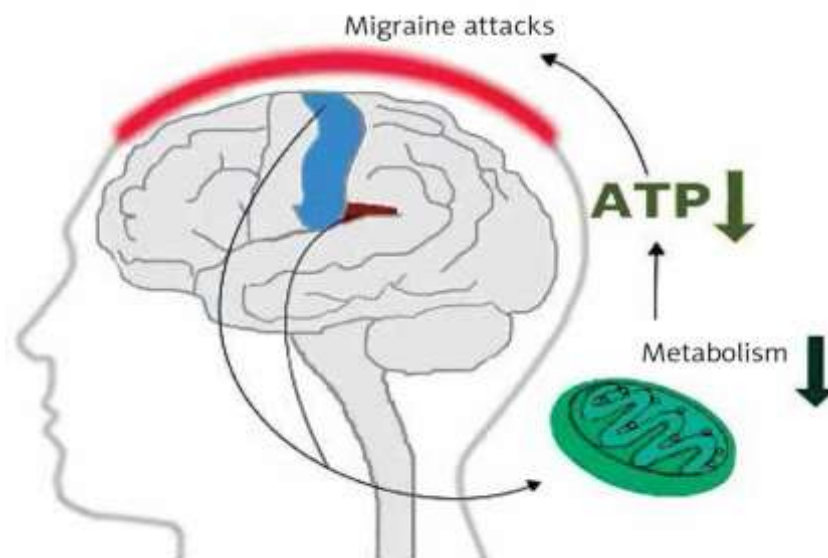


Fig. (4). The figure shows how decreased metabolic activity and ATP production by mitochondria contribute to the decrease in the threshold for cortical spreading depression, which underlies migraine attacks.

CSD cortical spreading Depression is Decreased ATP production due to dysfunction of mitochondria leads to decreased threshold which consequently leads to Cortical spreading depression (CSD). Spreading depression (SD) is a slowly moving wave in which neurons and glial cells undergo a brief but intense depolarization, followed by a prolonged period where normal electrical activity is greatly reduced. This process is accompanied by complex shifts in blood vessel diameter, cerebral blood flow, and energy use. While it is best known in the cerebral cortex-where it is referred to as cortical spreading depression (CSD)-similar events have been documented in many parts of the nervous system, including the hippocampus, cerebellum, and retinal.³⁷

CSD triggers cell swelling, releases a wide range of neurotransmitters and signaling molecules, and causes major shifts of ions across cell membranes. Some of these chemical and ionic disturbances help initiate or propagate the wave, while others function as protective or restorative responses following the event. As described in the related article by C. Ayata, many elements involved in CSD- such as ion channels, membrane transporters, neurotransmitter release systems, receptors, and vascular signaling mechanisms-could serve as potential targets for new therapies. Beyond migraine, CSD-like mechanisms may also contribute to conditions such as hemorrhagic and ischemic stroke, subarachnoid hemorrhage, traumatic brain injury, and epilepsy as shown in fig.(5).^{37, 38}

Coenzyme Q10 is a naturally present essential enzyme which are used as an antioxidant and helps in production of energy, acts by the same mechanism as magnesium (mg) Coenzyme Q10, recognized for its naturally occurring and potent antioxidant properties, has emerged as a promising therapeutic adjunct in the management and prophylaxis of a broad spectrum of clinical conditions. Its potential utility spans multiple disease categories, encompassing cardiovascular disorders, metabolic dysregulation, autoimmune pathologies, and neurodegenerative conditions-reflecting the widespread biological significance of this compound across diverse physiological systems.^{38,39} Coenzyme Q10 Due to its involvement in the mitochondrial electron transport chain, this supplement is thought to offer a preventive benefit against migraine episodes. CoQ10 is a fat-soluble, vitamin-like molecule that serves two major roles in the body: it works as an antioxidant and participates in mitochondrial energy production by transferring electrons from complexes I and II to cytochrome coenzyme Q10 does not have any specific receptor to bind with, it simply reduces the body CGPR (Calcitonin gene related peptide) reduction in CGPR will help in reducing the migraine constancy in nerve endings which in turn reduces the pain caused by.^{39,40}

Riboflavin It is also known as Vitamin B is a water-soluble vitamin which is also responsible for reducing the oxidative stress and mitochondrial dysfunction by increasing the neuroinflammation prevention. Riboflavin also increases the mitochondrial production.⁴⁰

Migraine is disease which is not curable but can be managed by adapting into a new diet, exercise, good amount of spinach, etc.²⁴

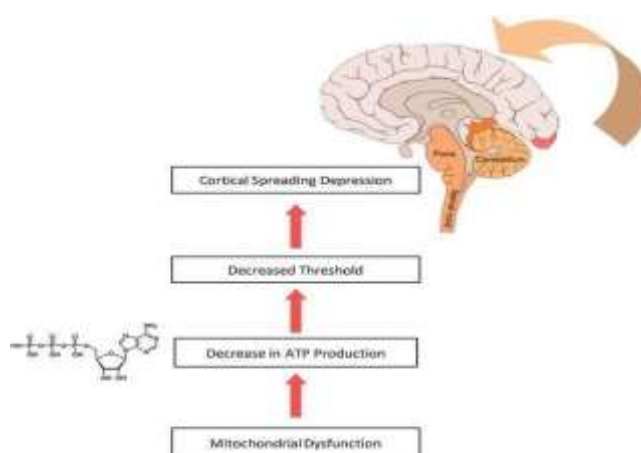


Fig. (5). The figure below represents the flowchart of the relationship between mitochondrial malfunction, reduced ATP production, cortical spreading depression, and a lowered threshold. The diagram also includes the image of the brain, as well as the molecule of ATP.

Low antioxidant intake and increased oxidative stress can raise the likelihood of migraine attacks by promoting inflammation. When inflammatory molecules such as tumor necrosis factor (TNF)- α , are released, they can trigger neuroinflammation and contribute to migraine episodes by enhancing cellular permeability and altering how cells interact.^{24,26} In a statistical analysis included vitamins D, A, K, C, B6, B2, B1, B3, B9, B12, as well as carbohydrates, protein, total fiber, magnesium, and calcium. Factor scores for each participant were calculated by multiplying the frequency of nutrient intake by the corresponding factor loadings and then summing these values. This analysis identified three nutrient patterns. The first pattern was characterized by higher levels of calcium, vitamins A, K, C, B6, and B2, along with magnesium. However, in that statistical study they concluded that calcium intake commonly obtained from foods like milk and cheese, showed an inverse association with migraine-related disability. Calcium and magnesium work concurrently in formation of various neurotransmitters and inflammatory mediators. Because of this, both minerals support healthy nervous system function and may help ease nerve tension.^{23,26}

Studies indicate that around 27–30% of individuals with migraine report that certain foods can provoke their headaches. In one cross-sectional study involving 123 migraine sufferers, basically 2.4% stated that they did not react to any dietary triggers. Frequently reported foods and ingredients that may provoke migraine attacks include chocolate, caffeine, cheese, milk, alcoholic drinks, and additives like monosodium glutamate (MSG) and aspartame.²³

Responses to these dietary triggers can vary widely among different migraine types.²³ It is important to include micronutrients such as vitamins, minerals, antioxidant which are present in vegetable, fruits, meat, fish can be taken as a supplement in daily bases to maintain, prevent, treat many diseases like Migraine etc.²³

MIGRAINE AND HORMONAL INFLUENCE:

Migraine ranks among the most burdensome and frequently encountered neurological disorders worldwide, affecting approximately 15% of the global population. Decades of cumulative research have consistently demonstrated a striking sex-based disparity in prevalence, with women experiencing migraine at nearly three times the rate observed in their male counterparts. A substantial proportion of affected women further report a perceptible intensification of migraine symptomatology during particular phases of the menstrual cycle, underscoring the profound influence of hormonal fluctuations on headache pathophysiology. Furthermore, a subset of women undergoing exogenous hormonal therapy—whether through oral contraceptive use or hormone replacement regimens—report a notable amelioration in the frequency and severity of their

migraine episodes over the course of treatment, suggesting a complex and individualized relationship between hormonal modulation and migraine expression.⁴²

Hormonal shifts throughout the female reproductive cycle can have a strong impact on migraine activity.⁴⁴

Hormones can play a dual role in migraines, both triggering their onset and amplifying the associated pain.⁴⁹ The regulation of these hormones depends on coordinated interactions among the hypothalamus, pituitary gland, and ovaries. The hypothalamus produces a substance called gonadotropin-releasing hormone (GnRH), which acts on the anterior pituitary gland and stimulates the anterior pituitary to secrete gonadotropic hormones like follicle-stimulating hormone (FSH) along with luteinizing hormone (LH). During the early part of a typical 28-day menstrual cycle, FSH and LH promote the growth of an ovarian follicle, which then releases estrogen and progesterone. When estrogen reaches a certain threshold, it triggers a sharp rise in LH, resulting in ovulation around the midpoint of the cycle. If fertilization does not occur, the luteal phase continues with initially elevated estrogen and progesterone levels produced by the follicle. Toward the end of this phase, the drop in progesterone levels leads to the onset of menstruation.⁴⁴

Fluctuations in the levels of estrogen have a significant part in triggering migraine episodes, with the drop in estrogen before menstruation being one of the most common triggers. Among adolescent girls and adult women who use combined oral contraceptives (COCs), headaches frequently worsen during the pill-free or placebo week, when estrogen levels fall. A similar estrogen decline happens after childbirth, making the postpartum period particularly susceptible to hormonally driven migraine attacks.⁴⁴

Ovarian hormones play a major role in influencing the central nervous system in women who experience migraines. Key reproductive stages, such as the onset of menstruation, pregnancy, and menopause often coincide with shifts in how migraine symptoms present. Migraine attacks frequently occur when estrogen levels drop, particularly in the premenstrual days and the days during menstruation. This results in a strong body of clinical evidence supports the idea that fluctuations in ovarian hormones have a direct impact on migraine patterns.⁴³ The female menstrual cycle is governed by the Hypothalamic-Pituitary-Ovarian (HPO) axis, which controls the levels of the female sex hormones that are estrogen and progesterone. Shifts in the concentrations of these two hormones, along with the positive- negative feedback mechanisms, controls processes such as the 28-day female reproductive cycle, pregnancy, the postpartum period after delivery, and the menopausal phase.⁴¹

Migraine headaches often comply to a recognizable temporal pattern in a female's life, reflecting changes in the levels in estrogen across various reproductive stages. The estrogen withdrawal hypothesis underlies many of the current assumptions regarding this relationship. In contrast, the effects of other hormones and the influence of estrogen and progesterone on other primary headache disorders have been far less extensively

Studied as shown in the figure.(6)⁵⁴

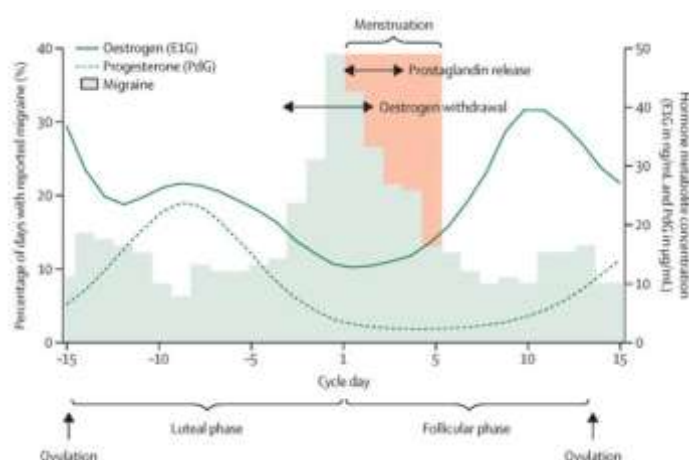


Fig .(6). The graph tracks oestrogen and progesterone across the menstrual cycle, showing migraine frequency peaking around menstruation when oestrogen withdraws and prostaglandins are released, with luteal and follicular phases and ovulation marked.

More recent research indicates that calcitonin gene-related peptide (CGRP) holds a major role via triggering these migraine headaches. CGRP is a neuropeptide, a signaling molecule in the brain that works alongside neurotransmitters⁴²

Since the 1980s, researchers have recognized that intense migraine pain is linked to the giving out of CGRP from nerve cells located in the head, face, and neck, specifically those belonging to the trigeminal nerve. When CGRP is released, it triggers a number of reactions in the surrounding tissues. One major effect is the widening of nearby arteries, caused by CGRP acting on the smooth muscle cells within the arterial walls. This discovery has allowed scientists to design increasingly effective treatments for migraine. Today, many of the most successful migraine therapies work by blocking CGRP or interfering with its activity.⁴²

The decline in estrogen that happens during menstruation leads to a rise in CGRP levels. As a result, migraine attacks become more frequent during this stage of the menstrual cycle. In other words, a decrease in estrogen tends to promote migraine activity.⁴²

The results also indicate that measuring CGRP in tears may be more informative than assessing it in the bloodstream. This is because CGRP is produced by many organs throughout the body, so blood tests reflect the total amount coming from all these sources. In contrast, the CGRP found in tears is primarily released by cells of the trigeminal nerve. For this reason, tear-based measurements may offer a more precise indication of migraine-related CGRP activity. The researchers note, however, that this testing approach is still new, and additional studies are required before it can be used routinely.⁴²

Menstrual-related headaches are a frequent type of headache in women, sparked by the decrease in the levels of estrogen during the menstrual cycle. Effective treatment requires accurate diagnosis with respect to the menstrual cycle or coordination with external hormone therapy, typically beginning two days before the beginning of menstruation and continuing through the day three of menstrual cycle.⁴⁵

The correlation between the female sex hormones like estrogen with migraine is intricate, including both genetic and non-genetic mechanisms. The levels of calcitonin gene-related peptide (CGRP) are higher in females of reproductive age compared with males. Cyclical changes in hormones influence CGRP release and, in turn, affect the trigeminal-vascular system. Obese women are at more than twice the danger of developing both episodes of migraine attacks as well as chronic migraine, likely because of abnormal fluctuations in estrogen production in adipose tissue. Estrogen also impacts serotonergic neurotransmission by enhancing the expression of the enzyme, tryptophan hydroxylase and reduction in expressing the serotonin reuptake transporter. Additionally, prolactin may have a modulatory effect on migraine.⁴⁶ Prolactin (PRL) is a hormone primarily involved in lactation and breast development, as well as numerous other functions essential for maintaining homeostasis. Chemically, prolactin is correlated with the growth hormone and placental lactogen. Animal studies have shown that elevated prolactin levels increase trigeminal pain sensitivity in the meninges, affecting CGRP signaling specifically in female rodents. In humans, higher the serum prolactin levels have been observed in individuals affected by migraine. Additionally, it is seen that people with prolactin-secreting pituitary tumors exhibit an increased frequency of headaches and migraine attacks.⁴⁹

A recent study on monoclonal antibodies targeting prolactin receptors offers new insights into the integrated relationship between prolactin hormone and CGRP. However, prolactin receptors if blocked in humans carries potential adverse risks, as it may disrupt the hormone's numerous other physiological functions.⁴⁹

Calcitonin gene-related peptide (CGRP) involved in peripheral as well as central pain pathways, which includes those that are associated with migraine. Its vasoactive effects contribute to meningeal irritation plus neurogenic inflammation as well. When CGRP is released from the axons of primary nociceptive neurons in the trigeminal nerves, it induces processes like plasma extravasation, vasodilation, and the meningeal mast cell degranulation. The levels of CGRP are elevated in individuals with migraine, and reproductive hormones influence its release. Blood CGRP concentrations are generally higher in women than men, increase during pregnancy and with combined hormonal contraceptive use, and change after menopause.⁵⁰

Substance P represents an additional vasoactive neuropeptide of considerable clinical relevance. It is synthesized and released by trigeminal nociceptive fibers innervating the cranial meninges, where its liberation serves as a principal driver of neurogenic inflammation within these pain-sensitive structures. This neuroinflammatory cascade is widely regarded as a fundamental underlying mechanism responsible for the characteristic pain experienced during migraine episodes. Notably, exogenous estrogen supplementation has demonstrated a measurable capacity to attenuate circulating plasma concentrations of Substance P, suggesting a meaningful modulatory role for estrogenic compounds in mitigating neuropeptide-mediated pain signaling.⁵⁰

It is known that migraine is a condition that affects women far more often than men. This is attributed to the life stages and hormonal events such as menarche, monthly periods, duration of gestation, menopause, and the use of hormonal contraceptives as well as hormone-replacement therapies, that women go through and that can all impact how often migraines occur. Migraine commonly begins after the onset of menstruation, becomes more frequent in the days leading up to or during a period, and often improves during pregnancy or after menopause.⁴¹ Research indicates that migraine is less common after menopause than during the perimenopausal period. The transition to menopause appears to increase the incidence of occurrence of migraine headaches. Women with a history of premenstrual syndrome (PMS) tend to get affected by more migraines in the period of late perimenopause, while frequency of attack generally decreases once menopause is reached.⁴⁶ These changes are largely driven by fluctuations in estrogen, which can alter neuronal sensitivity and affect brain blood vessels.⁴¹

However, adding external hormones can sometimes worsen migraines and might also multiply the danger of vascular problems in females who already experience migraines. Migraine with aura, in particular, is linked with a higher risk of stroke, heart disease, as well as vascular-related death. Research shows that females with migraine who are on combined oral contraceptives may face an increased risk of ischemic stroke. Therefore, combined hormonal contraceptives should be prescribed with great caution in women who experience auras/migraines.⁴¹

Combination Oral Contraceptives and their correlation with migraine

A variety of hormonal contraceptive options exist, including combined oral contraceptives (COCs), progestin-only pills, extended-cycle 91-day COCs, combination contraceptive patches, and vaginal contraceptive rings. Beginning hormonal contraception can influence migraine patterns in different ways, depending on the individual.⁴¹ Growing apprehension surrounding dose-dependent adverse health outcomes- most notably venous thromboembolism and cardiovascular complications, both of which have been extensively implicated in association with ethinylestradiol -has driven considerable pharmaceutical innovation toward the development of refined contraceptive formulations. These emerging alternatives encompass reduced ethinylestradiol concentrations, the incorporation of naturally derived estrogens, the utilization of progestogens with diminished androgenic activity, and the exploration of novel delivery routes that circumvent conventional oral administration.

Among the available combined hormonal contraceptive options, combined oral contraceptives retain their position as the most widely prescribed and broadly utilized formulation globally. They are offered across a broad spectrum of hormonal compositions, varying in the specific type of estrogen and progestogen employed, the magnitude of their respective doses, and the structural design of the dosing regimen -affording clinicians considerable flexibility in tailoring therapy to individual patient profiles and therapeutic needs.⁵⁰

Combined oral contraceptives (COCs) are often prescribed to adolescent girls not only for pregnancy prevention but also for conditions such as heavy menstrual bleeding and acne. Modern COCs contain a mix of progestin and a low dose of ethinyl estradiol. Some medications used for migraine prevention can increase the breakdown of COCs in the body, reducing their effectiveness.⁴⁴ With progestin-only contraceptive methods including pills, subdermal implants, depot injections, and levonorgestrel-releasing intrauterine systems, headaches are commonly reported at the start of therapy but typically improve within a few months. These methods are not associated with worsening migraines; in fact, they can lead to a major reduction in both the occurrence and intensity of attacks. Approximately 10% of users discontinue treatment due to side effects, most commonly breakthrough spotting.⁴⁶

COCs can have varying effects on migraine, they may lessen symptoms, make them worse, or produce no noticeable change. In individuals sensitive to hormonal fluctuations, migraines often intensify during the pill-free week due to falling estrogen levels. For some, using extended-cycle COCs, where the placebo week is skipped and active pills are taken for 12 continuous weeks, can reduce headache frequency.⁴⁴

Higher circulating estrogen levels from COCs can sometimes trigger aura in people who previously never experienced it, and migraines may even appear for the first time in women who start using COCs. Similar effects can occur in other high-estrogen states, such as pregnancy. Migraine itself, especially migraine with aura is an independent danger factor for ischemic stroke. For women aged 25–30 with aura migraine, the yearly risk of ischemic stroke while using COCs rises to about 18 per 100,000, compared with roughly 3 per 100,000 in those who have migraine without aura.⁴⁴

Providing supplemental estradiol around the time of menstruation, maintaining the use of hormonally active pills, or using extended transdermal hormone delivery has been linked to a general diminishing in both frequency and intensity of migraine attacks.⁴¹ Potential contraceptive approaches for reducing headaches include extended-cycle combined hormonal contraceptives, progestin-only methods, or newer formulations such as estradiol valerate.⁴⁶

EVALUATION:

Headaches associated with the menstrual cycle are diagnosed predominantly through thorough clinical evaluation rather than investigative testing. In the vast majority of cases, neuroimaging yields entirely unremarkable results. Nevertheless, magnetic resonance imaging may occasionally demonstrate focal areas of white matter hyperintensity. These signal abnormalities are attributed to a constellation of underlying mechanisms, namely aberrant cerebral hyper perfusion, disruption of blood-brain barrier integrity, and regionally confined cerebral edema- rather than being a direct consequence of primary ischemic injury.

During prolonged migraine episodes exceeding 48 hours in duration, a diffuse and bilaterally symmetrical pattern of hyper perfusion is frequently documented across key neural structures, including the cerebral cortex, thalamus, and basal ganglia. Neuroimaging is generally reserved for clinical scenarios in which the presenting headache deviates meaningfully from a patient's established pattern-whether in terms of its qualitative character, anatomical distribution, or temporal duration-thereby warranting further investigation to exclude secondary or structural causes.⁴⁵

Migraine attacks involve pathological widening of intracranial blood vessels alongside heightened sensitization of the trigeminal nerve, culminating in neurogenic inflammation within pain-responsive meningeal structures. This cascade compromises the integrity of the blood-brain barrier and stimulates the liberation of various proinflammatory substances into the surrounding tissue. The choice of an optimal neuroimaging technique is governed by several intersecting factors, including the clinical presentation, the diagnostic yield of available modalities, institutional access to computed tomography or magnetic resonance technology, the interpretive proficiency of the reviewing radiologist, and any patient-specific contraindications that may preclude certain examinations. Vascular assessment necessitates the administration of intravenous contrast agents to achieve adequate vessel opacification. Both computed tomography angiography and magnetic resonance angiography offer robust visualization of arterial and venous architecture. Magnetic resonance imaging of the head, however, frequently yields unremarkable findings in migraine patients and may therefore function as a diagnosis of exclusion, especially within acute care or emergency environments.⁴⁵ **Migraine and Hormonal Replacement Therapy (HRT).**

Hormonal replacement therapy is widely used to relieve symptoms associated with menopause as well as the menopausal transition, and it can have a notable impact on migraine patterns.⁴⁶ These therapies contain female hormones, most often estrogen, but stabilizing hormone levels with HRT does not always effectively prevent migraines. Similar to hormonal contraceptives, estrogen can have variable effects, it may reduce migraine frequency, provoke attacks, or have no noticeable effect at all.⁴⁷

HRT formulations containing less doses of natural estrogens are generally associated with a minimal risk of thromboembolism, unlike combined oral contraceptives. However, HRT should be discontinued immediately if a woman develops new-onset migraine with aura, or experiences a marked increase in migraine occurrence, shows deteriorating symptoms of migraine accompanied with aura, or develops a transient ischemic attack or other vascular complications.⁴⁶

Menstrual migraines

The symptoms of migraine associated with menstruation are comparable to those of typical migraine. By strict definition, menstrual migraine refers to attacks that occur from two days before the start of menstruation to three days after it begins, in a minimum of 66% of cycles.⁴⁸

Menstrual migraine can be further classified based on its timing within the menstrual cycle:

1. Pure menstrual migraine: Attacks occur exclusively around menstruation.
2. Menstruation-related migraine: Attacks can occur at any time, but symptoms are noticeably worse during menstruation.

3. End-menstrual migraine: Attacks begin several days after bleeding starts and are often linked to transient iron deficiency rather than hormonal fluctuations.⁴⁸

Research indicates that menstrual-related migraine attacks tend to be more intense and longer-lasting than migraines occurring at various other times of the month. Studies suggest that these attacks can last up to 35% longer than non-menstrual migraines.⁴⁸

TREATMENT OF MIGRAINE:

Migraine ranks as the sixth most common disease worldwide, representing a leading cause of inability, as well as carrying a substantial personal as well as socio-economic burden. Treatment is often limited to inadequate therapeutic response, necessitating individualized management strategies.⁶² Migraine management involves both acute and preventive pharmacologic therapies, along with various non-drug interventions. Despite the availability of these treatments and well-defined diagnostic criteria, clinical care is often inadequate, with misdiagnosis and under-treatment representing significant public health concerns.⁶¹

Between 1970 and 2020, the FDA has given approval for seventeen medicaments for the acute therapy of migraines. These medications generally fall into two main categories. The first category encompasses medications specifically developed for acute migraine management, including 5-HT (serotonin) receptor agonists and anti-CGRP agents. The second comprises general analgesic agents, notably COX (cyclooxygenase) inhibitors, which are broadly utilized across a wide spectrum of pain-related conditions.⁶²

- Analgesics: Mild to moderate migraine attacks can initially be given treatment with analgesics like acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (NSAIDs). These medications can also be effective in some cases of severe attacks.⁵⁹
- Triptans (5-HT_{1B/1D} agonists): Triptans include drugs like Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. These agents exhibit the most superior efficacy in the management of acute migraine attacks and are particularly recommended when conventional analgesics or NSAIDs prove inadequate. Among available formulations, subcutaneous sumatriptan carries the most potent therapeutic value for acute migraine relief. Within the oral triptan class, eletriptan and rizatriptan stand out as the most clinically effective options. Furthermore, combination therapy pairing triptans with naproxen has consistently demonstrated greater therapeutic benefit compared to triptan monotherapy alone.⁵⁹
- Ergotamines are effective but less well-studied and have more adverse effects when compared with triptans; therefore, they are no longer considered first-line therapy. Triptans are superior to ergot alkaloids in terms of efficacy. Early administration of acute migraine medication improves effectiveness.⁵⁹
- Anti-emetics are effective for treating nausea and vomiting that are major symptoms accompanying during migraine attacks.⁵⁹

The effectiveness of non-pharmacological interventions for acute migraine has not been adequately studied.

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MIGRAINE PREVENTION OR PROPHYLACTIC MEDICATION:

Preventive medications for migraine are often underused in clinical practice. Understanding the principles of preventive therapy is essential to enhance adherence, reduce adverse effects, and improve overall patient outcomes. The selection of a preventive treatment should take into account comorbid conditions, patient preferences, reproductive considerations, and the best available clinical evidence.⁶⁴ Prophylactic medication should be given to those patients who experience frequent migraine attacks, severe symptoms, or persistent aura, in addition to educational and behavioral approaches. Selection of a prophylactic medication should consider frequency of migraine attacks (episodic or chronic), comorbidities, plus individual patient needs.⁵⁹

Randomized studies have demonstrated the efficacy of the following.

- Beta-adrenergic blocking agents, most notably metoprolol and propranolol.

- Calcium channel antagonists, most prominently flunarizine.
- Antiepileptic agents, particularly topiramate and valproic acid.
- Antidepressants like amitriptyline, nortriptyline

Other drugs that are less extensively studied, but might be potentially effective options include bisoprolol, lisinopril, and candesartan. Topiramate and onabotulinum toxin A are also drugs that are effective in chronic migraine, including cases with medication overuse.

- Non-medicament interventions such as behavioral therapy (e.g., relaxation techniques) should complement pharmacologic therapy.
- Regular aerobic exercise is recommended.
- Psychological approaches, including stress management and coping strategies, are advised for patients with reduced quality of life due to migraine.⁵⁹

Migraine pharmacotherapy, regardless of the patient's stage of life, can be broadly classified into two principal approaches: acute and preventive. Among the most frequently employed agents across both categories are nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic medications, beta-blockers, and tricyclic antidepressants.⁵¹

Lifestyle modifications can help in controlling migraines and include maintaining proper sleep hygiene, eating a balanced diet with regular meals, engaging in consistent physical activity, and staying away from known causes that aggravate migraines like stress, excessive or even little alcohol, weather changes, as well as triggers that influence hormonal fluctuations.⁴⁵

Management of menstrual-related headaches begins with identifying their timing in relation to the patient's menstrual cycle. For patients using oral contraceptives, adjusting the hormone regimen, such as lowering the estrogen dose, can help prevent premenstrual declines that trigger these headaches.⁴⁵

First line drugs for migraine treatment include NSAIDs and Triptans.

ANTI-INFLAMMATORIES (NSAIDS AND ACETAMINOPHEN):

Robust evidence indicates that acetaminophen and oral NSAIDs- including aspirin, diclofenac, ibuprofen, and naproxen-serve as highly effective first-line interventions for managing mild to moderate migraine episodes.⁶³ NSAIDs remain a foundational pillar in migraine management, backed by the most compelling and well-established evidence for their therapeutic effectiveness.⁵⁶ Nonsteroidal anti-inflammatory drugs, which exert their effects through the inhibition of both COX-1 and COX-2 enzymes, frequently demonstrate sufficient efficacy as standalone therapy. Mefenamic acid, in particular, has been extensively investigated in the context of acute menstruation-associated headaches and has additionally shown notable benefit in relieving general dysmenorrhea.⁴⁵ Pharmacological agents such as ibuprofen, naproxen sodium, acetylsalicylic acid (ASA), and diclofenac potassium have all exhibited well-documented efficacy across double-blind, randomized controlled trials and systematic reviews. Equally noteworthy, acetaminophen-both as a standalone agent and in combination formulations incorporating aspirin and caffeine-has demonstrated reliable and consistent effectiveness in the acute management of migraine attacks.⁵⁶

Mechanism of Action

NSAIDs exert their analgesic effects in migraine by suppressing prostaglandin synthesis through the reversible blockade of cyclooxygenase enzymes COX-1 and COX-2. Among these, agents that specifically curtail the production of prostaglandin E2 prove particularly valuable in addressing acute migraine episodes. Aspirin, by contrast, operates through a distinct mechanism, functioning as an irreversible inhibitor of both COX-1 and COX-2 enzymes.⁵⁶

Contraindications and Cautions

Absolute contraindications for NSAID use include hypersensitivity reactions. Careful clinical judgment is warranted when considering NSAID use in patients with significant cardiovascular disease, compromised renal function, erosive gastrointestinal conditions, bleeding diatheses, or those concurrently receiving anticoagulant therapy such as warfarin.⁵⁶

TRIPTANS:

Triptans constitute a distinct class of pharmacological agents developed exclusively for the acute treatment of migraine. Acting as serotonin (5-HT) receptor agonists, they selectively target 5-HT₁ receptor subtypes and are structurally classified as synthetic analogues of serotonin, closely mirroring its molecular architecture while conferring more targeted and potent therapeutic properties.⁵⁶ Triptans are broadly recognized as the gold standard in the symptomatic management of acute migraine attacks, representing the cornerstone against which other therapeutic interventions are measured and evaluated.⁶⁴ Triptans are widely regarded as a firstline therapeutic option for the management of moderate to severe migraine episodes; however, their efficacy is not universal, and they may not yield consistent or adequate relief in every patient or across all migraine attacks.⁶³ Seven triptans have received FDA approval for the acute treatment of migraine, encompassing sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan. However, as a pharmacological class, triptans carry a considerably higher cost burden compared to NSAIDs and are therefore typically reserved for circumstances in which first-line therapies-such as NSAIDs or acetaminophen-have proven inadequate, or when the severity of the headache warrants a more potent therapeutic intervention.⁵⁵ Triptans are divided further to two groups depending on their onset of action:

Group 1: Sumatriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan are characterized by a comparatively rapid onset of action, enabling a more prompt and expeditious initiation of therapeutic relief following administration.

Group 2: Naratriptan and frovatriptan are distinguished from other agents within the triptan class by their notably slower onset of action, rendering them comparatively delayed in the initiation of therapeutic effects.⁵⁶

Mechanism of Action

Triptans exhibit high binding affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Their antimigraine mechanism is believed to stem from the activation of postsynaptic 5-HT_{1B} receptors in conjunction with presynaptic 5HT_{1D} receptors located on trigeminal nerve endings and dorsal horn neurons-a dual action that collectively serves to attenuate vasodilation and suppress neurogenic inflammation, thereby alleviating the cardinal features of a migraine attack.⁵⁵

Adverse Effects

Frequently reported adverse effects encompass sensations of pressure or tightness localized to the chest, throat, or jaw, along with myalgia and generalized fatigue. Less commonly encountered symptoms include cutaneous flushing, paresthesia, dizziness, muscular weakness, and cognitive clouding-a transient impairment of mental clarity and concentration.⁵⁵

Contraindications

Given their potential to elevate blood pressure, triptans are contraindicated in patients with poorly controlled or high-risk hypertension, ischemic heart disease, cerebrovascular disease, or peripheral vascular disorders. Their use is further contraindicated in individuals diagnosed with hemiplegic or basilar migraine, as well as in those with underlying hepatic impairment, where compromised liver function may significantly alter drug metabolism and tolerability.⁵⁵

Other medications have also demonstrated efficacy in treating migraine but are typically reserved as secondline options due to concerns about side effects, administration route, cost, or potential for misuse.⁶³

DITANS:

Although triptans are generally well tolerated, concerns exist regarding their vasoconstrictive effects. As evidence increasingly supported migraine as primarily a neurological disorder, researchers explored whether drugs with a predominantly neuronal action could effectively treat migraine. This has led to the development of a newer class of medications known as ditans, with lasmiditan being the only one currently marketed.⁶⁴

Lasmiditan is a 5-HT_{1F} receptor agonist. Because 5-HT_{1F} receptors are mainly located on neuronal membranes, lasmiditan does not produce significant vasoconstriction. Animal studies have also suggested that lasmiditan may act as a partial agonist at 5-HT_{1B/1D} receptors. Clinical trials demonstrated that lasmiditan was resolving the most bothersome symptom, reducing photophobia, and restoring normal functioning. Posthoc analyses indicated that it is safe for patients with cardiovascular risk factors and older adults.⁶⁴

However, central nervous system side effects, likely related to lasmiditan's lipophilic properties, can occur. Patients should be cautioned about its potential to impair driving and other activities requiring alertness.⁶⁴

OPIOIDS AND ERGOT ALKALOIDS:

The administration of opioids is broadly discouraged in migraine management, as these agents have the potential to precipitate enduring molecular alterations within the central nervous system and are strongly associated with the development of medication-overuse headaches-a complication that significantly undermines long-term therapeutic outcomes.⁴⁵ In the majority of patients, these agents demonstrate inferior efficacy when compared to alternative therapeutic options, and their frequent or prolonged use considerably elevates the risk of developing medication-overuse headaches (MOH)- a debilitating condition that further complicates the overall management of migraine.⁵⁶ Dihydroergotamine mesylate, by contrast, additionally suppresses prostaglandin release from glial cells, thereby attenuating the activation of the trigeminal nucleus caudalis. While it carries a comparatively more favorable side effect profile than ergotamine tartrate, dihydroergotamine mesylate retains the capacity to provoke considerable nausea and vomiting, particularly when administered via intravenous, intramuscular, or subcutaneous routes.⁵⁶

Dihydroergotamine functions as an alpha-adrenergic blocker, a vasoconstrictor, and a potent agonist at serotonin 1b/1d receptors. Its use is generally reserved for severe, refractory, or intractable migraine episodes, including those meeting the criteria for status migrainosus.⁴⁵ Parenteral dihydroergotamine (DHE 45) is widely employed in the management of refractory migraine cases that have proven unresponsive to conventional therapeutic approaches.⁶³

Adverse Effects

Nausea and vomiting represent the most commonly reported adverse effects associated with ergotamine use, and may be effectively mitigated through concurrent administration of an appropriate antiemetic agent. Dysphoria constitutes another potential unwanted effect, the emergence of which is thought to be mediated through central 5-HT_{1A} receptor agonism.⁵⁵

Contraindications

Ergotamines are contraindicated in individuals with underlying cardiovascular disease and should be avoided in this patient population. Their peripheral vasoconstrictive properties are considerably more pronounced than those associated with triptans, a distinction attributable to the fact that ergotamines exert their effects through both adrenergic and 5-HT_{2A} receptor pathways- mechanisms that triptans do not engage.⁵⁵

BETA-BLOCKERS:

Beta-adrenergic blockers, commonly referred to as beta-blockers, exert their therapeutic effects through competitive inhibition of β -receptors, yet they differ considerably in terms of receptor specificity-most notably with respect to β ₁-selectivity-as well as in their individual pharmacokinetic profiles. Notably, beta-blockers possessing intrinsic sympathomimetic activity, including acebutolol, alprenolol, oxprenolol, and pindolol, have not demonstrated effectiveness in migraine prophylaxis and are therefore not considered suitable candidates for preventive therapy.⁵⁸

The precise mechanisms underlying the antimigraine efficacy of beta-adrenergic blockers (BABs) have yet to be fully elucidated, though inhibition of β ₁-mediated effects is widely regarded as central to their prophylactic action. Blockade of β ₁ receptors is thought to suppress the release of noradrenaline (NA) and attenuate the activity of tyrosine hydroxylase- the rate-limiting enzyme governing NA biosynthesis. Furthermore, BABs are capable of modulating the activity of periaqueductal gray (PAG) neurons via a GABA-mediated pathway. Both of these mechanisms are believed to collectively contribute to their overall antimigraine properties.⁵⁸

Some beta-blockers also interact with the serotonergic system by antagonizing 5-HT_{2C} and 5-HT_{2B} receptors. Since serotonin plays a key role in migraine pathophysiology, these effects may further explain the prophylactic benefits of beta-blockers in migraine management.⁵⁸

Adverse Effects

Among the most frequently encountered adverse effects of beta-blockers are somnolence, fatigue, dizziness, and generalized weakness. A broader spectrum of reported side effects encompasses weight gain, symptomatic hypotension, nausea, vomiting, diarrhea, peripheral coldness of the extremities, xerosis, dry eyes or mouth, bradycardia, bronchospasm, dyspnea, alopecia, visual disturbances, insomnia, sexual dysfunction, and various metabolic derangements.⁵⁵

Contraindications

Beta-blockers are broadly avoided in patients with asthma or chronic obstructive pulmonary disease, given the heightened risk of precipitating bronchospasm in these individuals. Cocaine intoxication similarly represents a recognized contraindication, owing to the potential for inducing coronary vasospasm-though this particular recommendation continues to be a subject of clinical debate.

CALCIUM CHANNEL BLOCKERS:

Calcium channel blockers have been employed in migraine prophylaxis since the 1980s, establishing a longstanding role in preventive treatment strategies. Flunarizine, a nonselective calcium antagonist, extends beyond simple calcium channel blockade by also inhibiting voltage-gated sodium channels- an action that may contribute to dampening neuronal excitability and restoring cortical hyperexcitability commonly implicated in migraine pathophysiology. Furthermore, flunarizine exerts an antagonistic effect on D₂ dopamine receptors, further broadening its therapeutic mechanism of action.⁵⁸ Beyond flunarizine, additional calcium antagonists employed in migraine prophylaxis include verapamil and cinnarizine, with verapamil emerging as the most widely utilized and frequently prescribed agent among these options for preventive migraine management.⁵⁵

Mechanism of Action

The precise mechanism by which calcium channel blockers confer their prophylactic benefits in migraine management has yet to be fully elucidated. Flunarizine, in particular, exhibits a broad and multifaceted pharmacological profile-encompassing calcium channel blockade, inhibition of voltage-gated sodium channels, antagonism of D₂ dopamine receptors, and the capacity to elevate circulating leptin levels.^{55,58}

Adverse Effects

Frequently reported adverse effects encompass constipation, dizziness, headache, nausea, vomiting, cutaneous flushing, peripheral edema, somnolence, hypotension, and cardiac conduction disturbances-the latter becoming more pronounced at elevated doses. Less commonly encountered reactions may include sexual dysfunction, gingival hyperplasia, and hepatic impairment.⁵⁵

Contraindications

Calcium channel blockers are contraindicated in several clinical scenarios, including known hypersensitivity to the agent, acute coronary syndrome, hypertrophic obstructive cardiomyopathy, severe stenotic valvular heart disease, and underlying cardiac conduction disturbances.⁵⁵

ANTIEMETICS:

Nausea ranks among the most prevalent and distressing symptoms experienced during migraine episodes. When attacks present with concurrent nausea and vomiting, antiemetic agents may be administered alongside analgesics or triptans as combined therapeutic approach, although current clinical evidence does not confirm that antiemetics meaningfully augment the systemic absorption of co-administered migraine treatments.

The most frequently employed antiemetics in this context are metoclopramide (10 mg) and domperidone (10 mg), both of which are well-established options in migraine management. Additional agents-including prochlorperazine, droperidol, and

chlorpromazine-have demonstrated potential in alleviating symptoms during acute migraine episodes, though the body of evidence supporting their routine use remains relatively limited.⁶⁰

When migraine attacks are accompanied by nausea or vomiting, antiemetic agents prove especially valuable in managing these debilitating symptoms. They may be deployed either in conjunction with NSAIDs or triptans as part of a combined regimen, or on select occasions, administered independently as monotherapy.

Among the currently available antiemetic options, metoclopramide stands out as the most robustly supported by clinical evidence, demonstrating notable efficacy in migraine symptom control and establishing itself as a reliable and effective first-line therapeutic choice.⁵⁵

Mechanism of Action

Metoclopramide, a pharmacological agent belonging to the benzamide chemical class, exerts its mechanistic effects through dopamine D2 receptor antagonism at subtherapeutic concentrations, while at elevated dosing thresholds, it additionally demonstrates inhibitory activity at serotonergic 5-HT₃ receptors. Prochlorperazine and chlorpromazine, both classified as dopamine D2 receptor antagonists, exert a dual therapeutic utility simultaneously conferring potent antiemetic properties and delivering meaningful analgesic relief in the context of migraine management.⁵⁵

Detrimental consequences

Many antiemetics carry a risk of torsades de pointes. Metoclopramide, prochlorperazine, and chlorpromazine can also cause extrapyramidal symptoms, including dystonia, tardive dyskinesia, and akathisia. Additional adverse effects are less common and may include headaches or severe allergic reactions.⁵⁵

Contraindications

Contraindications for dopamine antagonist antiemetics include known hypersensitivity.⁵⁵ **ANTIDEPRESSANTS:**

Among the antidepressant agents most extensively investigated in the context of migraine prophylaxis, the tricyclic antidepressant amitriptyline and the selective serotonin reuptake inhibitor fluoxetine have garnered the most substantial body of clinical scrutiny and research attention.⁵⁵ With respect to antidepressant pharmacotherapy, the findings of more than three placebo-controlled clinical investigations collectively substantiate the superior prophylactic efficacy of the tricyclic antidepressant amitriptyline and the selective serotonin reuptake inhibitor fluoxetine in the prevention of migraine. Notably, these beneficial therapeutic effects are demonstrable even among patient populations devoid of comorbid depressive pathology, and the pharmacological doses requisite for migraine prophylaxis are characteristically considerably lower than those conventionally prescribed for the management of depressive disorders.⁵⁸ Alternative tricyclic antidepressants, alongside the serotonin-norepinephrine reuptake inhibitor venlafaxine, may similarly demonstrate prophylactic utility in migraine management; however, the corroborating clinical evidence underpinning such assertions remains comparatively sparse and insufficiently robust.⁵⁵

Mechanism of Action

Amitriptyline: This agent operates as a dual serotonin-norepinephrine reuptake inhibitor, while concurrently exerting a repertoire of supplementary pharmacological actions, encompassing agonistic activity at alpha₂adrenoceptors, inhibition of sodium channel conductance, antimuscarinic and antihistaminergic properties, and the modulation of cortical spreading depolarization.⁵⁵

Fluoxetine: Inhibits serotonin reuptake, increasing serotonin levels. At higher doses, it can also inhibit noradrenaline reuptake.⁵⁵

Detrimental Effects

TCA: Anticholinergic adverse effects-including oral dryness, ophthalmological blurring, bowel motility impairment, vesical urinary retention, pyrexia, and profuse perspiration-in addition to morning-onset sedation, elevated cardiac rhythm, vivid and disturbing dream experiences, progressive weight accumulation, hemodynamic hypotension, impairment of sexual functioning, acute confusional states, and electrocardiographic QT interval elongation.⁵⁵

SSRIs: Sexual dysfunction, drowsiness, weight gain, insomnia, dizziness, headache, dry mouth, blurred vision, nausea, rash, tremors, constipation, and potential QT prolongation.⁵⁵

Contraindications

TCAs: Avoid coadministration with monoamine oxidase inhibitors (MAOIs) due to serotonin syndrome risk; also contraindicated with hypersensitivity or concurrent cisapride use.

SSRIs: Concomitant administration with monoamine oxidase inhibitors (MAOIs), linezolid, methylene blue, pimozone, or thioridazine is strongly contraindicated, owing to the substantial risk of precipitating adverse hypersensitivity reactions.⁵⁵

ANTIEPILEPTICS (AEDS):

Several AEDs have demonstrated to be efficient in migraine prevention, with topiramate and valproate having the strongest evidence base.⁵⁵ Multiple antiepileptic drugs (AEDs) that act at various pre- and post-synaptic sites have been investigated and shown to be effective for migraine prevention. However, not all AEDs are equally effective for migraine compared to their efficacy in epilepsy. Drugs with a more selective or narrow mechanism of action generally appear less effective for migraine prophylaxis.⁵⁸

Mechanism of Action

Topiramate exerts its pharmacological effects through a multifaceted mechanism of action, encompassing the blockade of voltage-gated sodium and calcium channels, the attenuation of glutamate-mediated excitatory neurotransmission, the potentiation of GABA-A-mediated inhibitory signaling, the suppression of carbonic anhydrase activity, and the diminution of CGRP secretion emanating from trigeminal neuronal populations. Valproate, conversely, achieves its therapeutic effects through the augmentation of GABAergic inhibitory tone, the obstruction of excitatory ion channel conductance, and the transcriptional downregulation of CGRP expression within cerebral tissue.⁵⁵

Detrimental Effects

Topiramate: Nausea, vomiting, diarrhea, dizziness, somnolence, paresthesias, fatigue, nasopharyngitis, weight loss, tachypnea, palpitations, mood changes, dysuria, hematuria, and increased urination frequency.⁵⁵

Valproate: Nausea, emesis, diarrhea, abdominal discomfort, cephalgia, somnolence, alopecia, tremulous episodes, vertigo, visual perturbations, tinnitus, alterations in appetite and corporal weight, cognitive disorientation, profound sedation, hemorrhagic manifestations, and inflammatory responses.⁵⁵

Contraindications

Topiramate: Hypersensitivity to the drug.

Valproate: Impaired hepatic function, mitochondrial pathology, hypersensitivity reactions, disruptions of the urea cycle, and the gravid state.⁵⁵

HORMONE REPLACEMENT THERAPY:

Among the therapeutic interventions specifically tailored to the perimenopausal phase, hormone replacement therapy (HRT) stands as a particularly pertinent consideration. This transitional period is distinctively characterized by progressively intensifying hormonal oscillations, which are frequently implicated in a discernible escalation in both the incidence and severity of migraine episodes. The pharmacological stabilization of these endocrine fluctuations through the administration of HRT may constitute a viable prophylactic strategy against migraine, drawing parallels with established approaches employed in the management of menstrual migraine. Nonetheless, the existing body of clinical evidence pertaining to the efficacy of HRT as a preventive measure for migraines during the perimenopausal transition remains notably sparse and considerably inconsistent.⁵³

CGRP(R) MONOCLONAL ANTIBODIES:

Monoclonal antibodies targeting either calcitonin gene-related peptide (CGRP) or its receptor-collectively designated as CGRP-mAbs-are presently regarded as the most efficacious and favorably tolerated therapeutic option within the domain of

migraine prophylaxis, with gepants emerging as a closely comparable alternative. Pharmacological agents belonging to earlier generations of preventive treatment classifications represent an older stratum of the migraine prevention armamentarium.⁵⁷

Certain findings indicate that CGRP(r) monoclonal antibodies (mAbs) and gepants are one of the most effective and one of the main well-tolerated options for migraine prevention. Among oral preventive medications, high discontinuation rates have been particularly noted with amitriptyline, topiramate, and valproate.⁵⁷

ACUPUNCTURE:

Acupuncture, a therapeutic modality premised upon the precise insertion of fine needles into designated anatomical loci across the body, constitutes a cornerstone of Eastern medical traditions and has garnered widespread acceptance and favorable reception among the general population. Although it was introduced in Europe as early as the 17th century, skepticism about its effectiveness persists. Research has shown that acupuncture can be beneficial for a variety of medical conditions, including migraine prevention. Several clinical trials have examined its efficacy for migraine, but results have been mixed, particularly when comparing true acupuncture to sham acupuncture, as sham procedures may produce similar effects.⁶⁴

NEUROMODULATION:

Neuromodulation involves the use of externally applied electrical currents to reversibly modify the function of the nociceptive system, with the goal of altering pain signaling.⁶⁴

Transcranial Magnetic Stimulation (TMS)

TMS delivers fluctuating magnetic fields through the scalp, inducing small electrical currents in the brain.

This is thought to disrupt cortical spreading depression (CSD), a key mechanism in migraine. Single-pulse TMS (sTMS) has shown effectiveness in acute migraine treatment, suggesting that repetitive TMS (rTMS) may have potential for migraine prevention.⁶⁴

Occipital Nerve Stimulation (ONS)

Percutaneous ONS is an invasive approach initially explored for chronic cluster headaches.⁶⁴

Supraorbital Nerve Stimulation (SONS)

The first report of percutaneous SONS successfully treating intractable cluster headache was published in 2007. While no studies have examined SONS alone for migraine, it has been combined with ONS to manage chronic migraine. A newer noninvasive device, the supraorbital transcutaneous stimulator (STS), shows promise for migraine therapy.⁶⁴

Hence, a variety of pharmacologic and non-pharmacologic strategies exist for both acute and preventive migraine management. Treatment should be individualized based on patient needs, expectations, and potential side effects. First-line preventive medications include topiramate, amitriptyline, and propranolol. Noninvasive neuromodulation techniques such as TMS and Cefaly are likely to become more widely accessible as costs decrease. Invasive procedures like percutaneous ONS or SONS should be reserved for patients who have not responded to or tolerated conventional therapies, due to associated risks and limited long-term safety data.⁶⁴ A substantial array of pharmacological agents presently employed in the acute management of migraine have yielded compelling evidence of efficacy across rigorous clinical investigations. The identification of the most appropriate therapeutic regimen for any given patient is an inherently individualized process, necessitating careful consideration of the patient's distinct clinical profile, concurrent comorbidities, and personal therapeutic preferences. Arriving at a well-informed clinical decision is greatly facilitated by a comprehensive and nuanced understanding of the pharmacodynamic mechanisms and pharmacokinetic characteristics that define each of the available treatment modalities.⁶⁴

CONCLUSION:

Globally, migraine is distinguished as the sixth most frequently occurring disease, underscoring its substantial burden on public health. Classified as a debilitating neurological disorder, it is defined by cyclically recurring episodes of moderate to severe head pain, often presenting alongside a broad array of accompanying symptoms—such as nausea, heightened sensitivity to light and

auditory stimuli, phosphoric visual phenomena, somatosensory disturbances including numbness and tingling, generalized fatigue, and episodes of dizziness. Distinct from an ordinary headache, migraine is a nuanced condition rooted in disruptions to cerebral neural activity, vascular regulation, and afferent nerve signalling. Characteristically, the pain manifests as a unilateral, rhythmically pulsating or throbbing sensation, with attack duration ranging from a matter of hours to several days. Among the well-documented precipitants of migraine episodes are psychosocial stress, hormonal oscillations, inadequate sleep, consumption of certain foods, exposure to potent olfactory stimuli, fluctuations in atmospheric conditions, and excessive luminous stimulation.

Managing lifestyle triggers and comorbid conditions in migraine patients can significantly improve their outcomes. It is important to identify and address factors such as sleep disturbances, dietary triggers (including certain types of alcohol, cheese, citrus fruits like oranges, and chocolate), dehydration, and excessive caffeine intake. The preservation of an optimal body weight, coupled with consistent participation in physical exercise, confers substantial therapeutic benefit. Depending on a person's individual triggers, behavioural therapy, psychological interventions, and physical therapy may offer additional relief.

Some patients use natural preventive supplements such as magnesium, riboflavin (vitamin B₂), coenzyme Q10, and feverfew. However, their effectiveness varies, and the scientific evidence supporting them is limited, so they are not considered first-line treatments. As micronutrients bring abundant change in health if it is taken in less or even in excess amount it may cause toxicity to the body. Pathology of migraine by oxidative stress and mitochondrial dysfunction oxidative stress is due to the reaction of free radical and antioxidants along with mitochondrial dysfunction if there is any damage in mitochondria there will be a decrease of production of energy (ATP) impact of micronutrients in Migraine, micronutrients such as vitamin B12, B6, D, riboflavin, minerals, magnesium, coenzyme Q10 etc. which can prevent or treat migraine. The source of micronutrients are Fish, meat, vegetables like spinach, fruits. These micronutrients can be administered as supplements also by combining all the vitamins in different dosage forms as multi vitamin syrup, tablets. These micronutrients work by various mechanism. Magnesium (mg) acts by binding to the receptor NMDA and acts as an antagonist of glutamate receptor. Which in turn, by binding reduces or blocks the calcium ion influx in nerve cells which leads to decrease sensitivity of neuronal transmission and reduces nerve tension. Coenzyme Q10 acts by acting on mitochondria present in cell which will increase production of energy ATP and reduce the oxidative stress.

Migraine is a condition that affects women far more often than men. This phenomenon is ascribed to the distinct physiological milestones and hormonal transitions that women uniquely navigate throughout their lives-encompassing menarche, menstrual cycles, gestation, and menopause-as well as the exogenous hormonal influences introduced through the use of contraceptives or hormone replacement therapies, all of which bear considerable capacity to alter migraine frequency and susceptibility. Hormonal shifts throughout the female reproductive cycle can have a strong impact on migraine activity. Menstrual-related headaches are a frequent type of headache in women, triggered by the drop in estrogen levels during the menstrual cycle. Effective treatment requires accurate diagnosis in relation to the menstrual cycle or coordination with external hormone therapy. The decline in estrogen that happens during menstruation leads to a rise in CGRP levels. As a result, migraine attacks become more frequent during this stage of the menstrual cycle. Cyclic hormonal variations serve as a significant modulator of CGRP release, thereby exerting downstream effects on trigeminovascular function. Calcitonin gene-related peptide (CGRP), a neuropeptide of sensory origin, is intricately implicated in the transmission of pain signals across both peripheral and central pathways- most notably within the context of migraine. Through its vasoactive mechanisms, CGRP contributes to meningeal irritability and the propagation of neurogenic inflammatory cascades. Serum CGRP concentrations are characteristically higher among women than their male counterparts, demonstrate a pronounced elevation during pregnancy and with the administration of combined hormonal contraceptives, and undergo notable alterations in the post-menopausal period.

Regardless of the patient's stage of life, migraine management strategies can be broadly classified into acute intervention and prophylactic approaches. Among the most frequently employed pharmacological agents are nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic compounds such as topiramate and valproate, beta-adrenergic antagonists like propranolol, and tricyclic antidepressants encompassing amitriptyline and nortriptyline. Lifestyle modifications can help in controlling migraines and include maintaining proper sleep hygiene, eating a balanced diet with regular meals, engaging in consistent physical activity, and avoiding known triggers such as stress, alcohol, weather changes, and hormonal fluctuations. Acupuncture and neuromodulation are also part of migraine therapy. Management of menstrual-related headaches begins with identifying their timing in relation to the patient's menstrual cycle. For patients using oral contraceptives, adjusting the hormone regimen such

as lowering the estrogen dose can help prevent premenstrual declines that trigger these headaches. A variety of pharmacologic and non-pharmacologic strategies exist for both acute and preventive migraine management. Treatment should be individualized based on patient needs, expectations, and potential side effects. A well-informed decision relies on a comprehensive grasp of the pharmacodynamic and pharmacokinetic characteristics inherent to each available therapeutic alternative.

ABBREVIATIONS: We have ensured that all abbreviations are defined in the text where they first appear.

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