Tackling migraines head-on: insights into pathophysiology, management and treatment

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Abstract

Migraines are complex neurological disorders characterised by recurrent episodes of moderate-to-severe headaches, often accompanied by sensory disturbances. Globally, migraine is one of the leading causes of disability and is classified into various subtypes based on individual characteristics and symptoms. Clinical presentation and diagnosis rely on the identification of specific symptoms and stages of migraine attacks, distinguishing them from other types of headache disorders. The pathophysiology of migraine involves a complex interplay between neurological, vascular, and biochemical factors, with the trigeminovascular system playing a central role. Migraine management includes both non-pharmacological and pharmacological approaches. Non-pharmacological strategies involve lifestyle modifications, dietary adjustments, and sleep and stress management. Pharmacological treatment involves therapies such as triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and calcitonin gene-related peptide (CGRP) antagonists, as well as preventive medications such as antihypertensives, antidepressants, antiepileptics, and newer biological therapies. Key challenges in migraine treatment include the accessibility of advanced therapies, the role of pharmacogenomics in personalised treatment, and the development of emerging therapies through clinical trials. Further research is needed to better understand the complex pathophysiology of migraine for the development of more effective and targeted treatment strategies.

Keywords: migraine, headache disorders, neurological disease, pain, pharmacological, non-pharmacological

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Introduction

The term "migraine" is derived from the Greek word "*hemicrania*," meaning "half of the skull".[1] It is a complex, genetically influenced neurological disorder marked by recurrent episodes of moderate to severe headache, typically affecting one side of the head.[1,2] These recurrent attacks are often accompanied by symptoms such as nausea and increased sensitivity to light, sound or movement.[2,3,4] These debilitating episodes can last from several hours to days, significantly impairing daily function and quality of life.[2,5] Globally, migraine is a leading cause of disability and work absenteeism.[6,7] In 2019, migraine ranked third among neurological diseases, after stroke and dementia, in terms of age-standardised disability-adjusted life years (DALYs).[8,9] From 1990 to 2019, the global age-standardised prevalence of migraine increased by 1.7%.[3,10] In 2019, 1.1 billion (0.98–1.3) prevalent cases of migraine were recorded.[3,11] As of 2021, 3.1 billion people (40% of the population) were affected by headache disorders, with women being disproportionately affected.[8,12] Migraines rank among the top three most prevalent neurological disorders across most age groups, beginning at age five and remaining in the top three until age 80 years.[8] The clinical course of migraine typically progresses through several phases, namely the premonitory phase, transient neurological symptoms known as aura, severe headache episodes, and postdrome phase.[2,5] The impact of migraine extends beyond physical health, influencing economic productivity, family dynamics, and performance in educational and professional settings.[13]

Triggers for migraine

Migraine triggers are diverse and can vary significantly between individuals. Common triggers include stress, hormonal changes (particularly in women), consumption of certain foods and beverages, environmental factors, and sleep disturbance (Figure 1).[2,14] Specific dietary triggers include alcohol, caffeine, chocolate, aged cheese, and foods containing additives such as monosodium glutamate (MSG).[15,16] Environmental triggers can include bright or flickering lights, loud noises, strong odours, and changes in weather or barometric pressure.[17,18] Physical factors such as intense exercise, lack of sleep, and changes in sleep patterns can also precipitate migraines.[4,19-22] In addition, certain medications and dehydration can trigger attacks.[23,24] Identifying and managing these triggers through lifestyle modifications and avoidance strategies are essential for migraine prevention and management.

Signs and symptoms of migraine

Migraines are often preceded by warning signs, such as fluctuations in mood, food cravings, neck stiffness, excessive yawning, and visual disturbances.[5,25-29] Individuals may experience throbbing head pain (often localised to one side of the head), increased sensitivity to light, sound, and smell, as well as nausea, vomiting, dizziness, and fatigue.[4,25] In some individuals, migraines are accompanied by an aura, transient neurological symptoms

Figure 1: Triggers for migraine (created using BioRender)

that may include visual changes, tingling, speech difficulties, or muscle weakness.[5]

Categories of migraine

According to the International Classification of Headache Disorders (ICHD-3), migraines are categorised into several subtypes based on their specific characteristics and associated symptoms.[1,4,30] This classification system helps healthcare professionals accurately diagnose and manage different forms of migraine more effectively.

Migraine without aura

Migraine without aura is the most frequently diagnosed form of migraine, accounting for the majority of migraine cases seen in clinical practice.[2,30] It is characterised by recurrent headaches typically lasting between 4–72 hours if not treated effectively or if left untreated.[2,31] These headaches typically present with unilateral, pulsating (throbbing) pain of moderate-to-severe intensity.[2] Additional symptoms may include nausea, vomiting, photophobia, and phonophobia.[2,32] Physical activity, such as walking or climbing stairs, often exacerbates pain, leading many sufferers to seek rest in quiet, dark rooms.[2]

Migraine with aura

Migraine with aura is characterised by fully reversible neurological symptoms, collectively referred to as an aura.[2] Aura symptoms serve as warning signs and can significantly affect an individual's daily activities. These aura symptoms typically develop gradually over 5–20 minutes and last for less than 60 minutes.[5,33] Common aura manifestations include visual disturbances (flickering lights, spots, or lines, temporary blindness), sensory symptoms (pin-and-needle sensations or numbness), and speech or language problems (disorientation, confusion, fainting).[5] Although less common, some individuals may experience motor weakness.

Chronic migraine

Chronic migraine is a debilitating form of migraine characterised by headaches occurring on 15 or more days per month for at least three consecutive months, with migraine features present on at least eight of those days.[1,2,25,34] Symptoms include frequent headaches, increased sensitivity to light, sound, and smell, as well as nausea and vomiting.[25] Additional symptoms may include visual disturbances, speech difficulties, numbness or pins and needles, dizziness, and vertigo.[35] This subtype significantly affects the quality of life of an individual, often leading to significant physical, emotional, and social impairment, requiring intensive management strategies.

Probable migraine

Probable migraine fulfils some, but not all, criteria for typical migraine.[1,36] This category is used when there is insufficient evidence to make a definitive diagnosis of migraine. However, the clinical presentation strongly suggests a migraine disorder.[2]

Additionally, episodic syndromes are associated with migraine, particularly in children and adolescents. These include recurrent gastrointestinal disturbances (such as cyclic vomiting syndrome and abdominal migraine), benign paroxysmal vertigo (characterised by the sudden onset of vertigo in otherwise healthy children), and benign paroxysmal torticollis (involving recurrent episodes of head tilt).[1,37,38]

Complications of migraines

Complications of migraine may develop in some patients, further adding to its complexity. Among these, *status migrainosus* refers to a severe migraine attack lasting longer than 72 hours, often leading to dehydration and requiring emergency medical intervention or hospitalisation.[2,39] Persistent aura without infarction involves prolonged aura symptoms, such as visual disturbances, that last for more than one week but without any evidence of brain infarction on neuroimaging findings.[40] In contrast, migrainous infarction occurs when one or more migraine aura symptoms are associated with ischaemic lesions visible on brain imaging.[41] Another rare but notable complication is migraine aura-triggered seizures, also known as *migralepsy*, in which a seizure occurs during or shortly after a migraine with aura.[42] In addition to these specific complications, migraine is associated with broader health risks. Chronic daily headaches, often resulting from medication overuse, may develop in some individuals, leading to more than 15 headache days per month and significantly diminishing the quality of life of an individual.[23] Migraine has also been linked to an increased risk of cardiovascular and cerebrovascular diseases, highlighting the need for careful monitoring.[43] Moreover, the burden of chronic migraine is compounded by its frequent association with mental health disorders, such as anxiety and depression.[44]

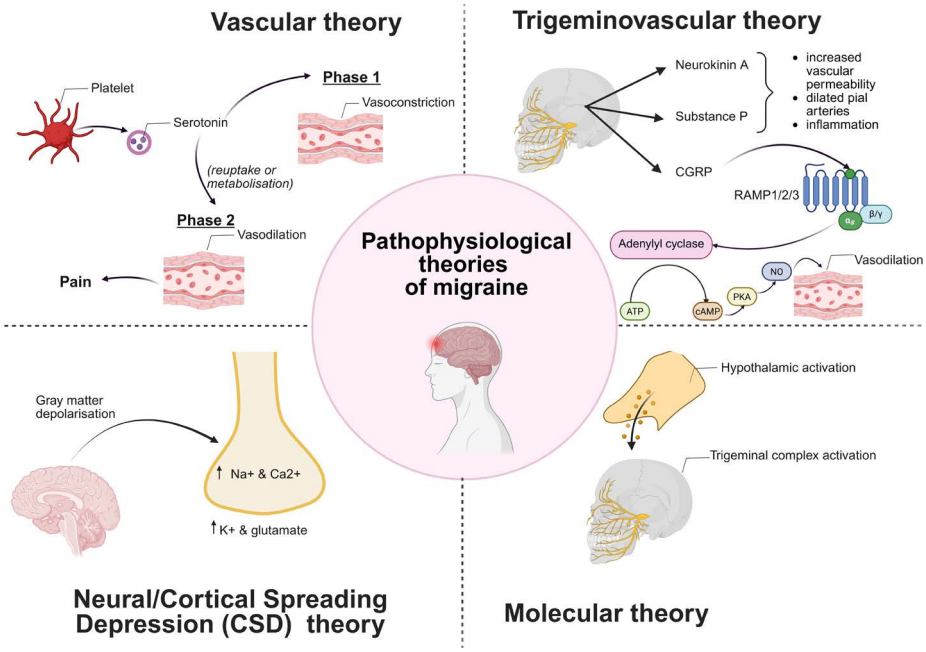

Figure 2: Theories related to the pathophysiology of migraines, including 1) the vascular theory, 2) the neural theory, 3) the trigeminovascular theory, and 4) the molecular theory (created using BioRender)

Pathophysiology of migraines

The pathophysiology of migraine involves a complex interplay between the vascular, neurological and biochemical factors and has led to the development of several theories, including 1) the vascular theory, 2) the neural theory, 3) the trigeminovascular theory, and 4) the molecular theory (Figure 2).

Vascular theory

The vascular theory was one of the earliest theories developed to explain migraine pain. This theory suggests that the pulsatile nature of migraine pain originates from haemodynamic changes in the brain's vasculature. Specifically, the vascular theory by Graham and Wolff proposes that platelet-released serotonin causes vasoconstriction, which is followed by homeostatic vasodilation when serotonin reuptake or metabolisation occurs, causing pain.[45] In support of this theory, caffeine (ergotamine tartrate), which is a known cranial vasoconstrictor, previously reduced the severity of the pain associated with migraines while reducing the amplitude of temporal artery pulsation.[46]

However, increasing evidence suggests that vasodilation is not the primary cause of migraines but rather a consequence of neuronal activation and inflammation. This counterargument is supported by evidence that the trigeminal nerve causes vascular dilatation and neurogenic inflammation, leading to the suggestion that the stimulation of the trigeminal nerve is the origin of migraines. Nevertheless, the cause of trigeminal nerve stimulation remains unexplained by this theory.

Trigeminovascular theory

The trigeminovascular system connects the brainstem to intracranial vessels and meninges. Specifically, cerebral vessels are located close to the trigeminal fibres, which contain various neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A, each playing distinct roles in inducing migraines.[47]

By releasing vasoactive neuropeptides like CGRP, the trigeminal system contributes to vascular dilatation, neurogenic inflammation, and pain pathway sensitisation. Calcitonin gene-related peptide (CGRP) activates its receptors located in the cortex and meninges, which increases glutamate activation, thereby improving signal transmission between neurons and subsequently increasing neuronal excitability, leading to pain.[48] Calcitonin gene-related peptide (CGRP) receptors are composed of an accessory protein, namely receptor activity-modifying protein (RAMP1/2/3), linked to a G-protein-coupled receptor, specifically the calcitonin receptor-like receptor (CLR). The classical CGRP receptor, CLR/RAMP1, and the amylin receptor 1 (AMY1) are both equally capable of binding and activating CGRP.[49] Downstream signalling pathways ultimately activate protein kinase A (PKA), subsequently leading to the production of nitric oxide (NO), which in turn causes vasodilation.[50]

Apart from CGRP, trigeminovascular neurons and their peripheral unmyelinated nerve fibres also emit substance P, which increases vascular permeability, dilates pial arteries, and activates cells involved in the inflammatory response.[51]

When released into the meningeal circulation, Neurokinin A induces meningeal vasodilation. However, it is hypothesised that Neurokinin A does not significantly contribute to migraine since the meningeal effects of Neurokinin A and substance P have similar molecular mechanisms. In agreement with the theory, Neurokinin A1 receptor antagonists have been shown to be ineffective in treating migraine.[52]

Neural/cortical spreading depression theory

The Cortical Spreading Depression (CSD) theory, also known as the neural theory, suggests that migraines, as well as the aura associated with them, are caused by CSD, which is defined as a wave of depolarisation of grey matter that spreads slowly over a few minutes as a result of large increases in intracellular Na^+ and Ca^{2+}, as well as extracellular K^+ and glutamate.[53] Additionally, CSD can also involve ATP, K^+, hydrogen ions, arachidonic acid and NO release locally, thereby causing sensitisation of trigeminal neurons, which contributes to neurogenic inflammation.[53] However, there is an increasing amount of criticism arising against this theory, involving 1) the inability to induce CSD in humans; 2) the fact that CSD does not affect both sides of the head, disrupts the blood-

brain-barrier, does not increase brain metabolism or cause brain cell swelling; 3) CGRP is not elevated in CSD; 4) premonitory signs or allodynia is not explained by CSD; and 5) pain mechanisms and responses are different in CSD compared to migraines.[54]

Molecular theory

A new molecular theory suggests that vascular dilation is not the primary cause of pain, but rather a result of neuronal inflammation.[46] According to Shibata's novel molecular explanation, the pathophysiology of migraines begins with functional alterations in the hypothalamus, which regulates mood and appetite, potentially causing premonitory symptoms. Following hypothalamic and/or CSD activation, the trigeminocervical complex is activated. The pain results from the activation of the nociceptive trigeminal nerve together with the trigeminal nucleus caudalis. Particularly, the sharp pain associated with migraines is the result of neurogenic inflammation and the production of CGRP from C-fibres, which stimulates CGRP receptors located in Aδ-fibres of the trigeminal nerve.

Management and treatment of migraine

Effective management of migraines and their complications requires a multifaceted approach. This includes preventive therapies to reduce attack frequency and severity, and lifestyle modifications to identify and avoid individual migraine triggers and the use of acute medications to relieve symptoms during attacks.

Pharmacological management for acute migraine

Migraine treatment can include acute therapy, used to halt migraine attacks, as well as preventative treatment, used to reduce the frequency and severity of migraine attacks.[55] A variety of medications are recommended for the treatment of acute migraines, allowing for individualised management based on the severity of the patient's symptoms and preferences (Table I).[56] The main objective of acute management of migraines is the reduction of the attack duration and severity.[57] The pharmacological treatment options for acute migraine treatment can be divided into migraine non-specific and specific treatments.[55,57]

Nonsteroidal anti-inflammatory drugs

The first-line non-specific treatment of mild to moderate migraine attacks consists of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, diclofenac, ibuprofen, or naproxen, likely due to their wide availability as over-the-counter drugs.[55,58-62] NSAIDs are a class of drugs widely used for the treatment of pain, fever, and inflammation by inhibiting the activity of cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes, which are responsible for the synthesis of prostaglandins and thromboxanes from arachidonic acid.[63] Prostaglandins are particularly relevant in migraine pathophysiology because their receptors are distributed throughout the trigeminovascular system, a key player in generating migraine pain. Prostaglandins contribute to the development of pain by sensitising nociceptors associated with tissue damage and inflammation. Aspirin, ibuprofen and naproxen are non-selective inhibitors that inhibit neurogenic inflammation and reverse central sensitivity by inhibiting COX-2. However, COX-1 inhibition increases the risk for gastrointestinal bleeding and ulcers.[61] Diclofenac, a COX-2 selective inhibitor, has improved gastrointestinal safety, however, it leads to more cardiovascular adverse effects.[57]

Analgesics

Unlike NSAIDs, acetaminophen primarily inhibits central prostaglandin synthesis through the inhibition of COX-3 enzymes located in the CNS, without affecting the expression of COX-1 and COX-2.[64] Although opioids, such as butorphanol, modulate nociception in the trigeminovascular complex and combination therapies of codeine/acetaminophen and tramadol/acetaminophen are effective for severe migraine attacks, they are not recommended for regular use due to medication-overuse.[55,65]

Triptans and ergot derivatives

For moderate to severe migraine attacks, migraine-specific treatments consisting of triptans i.e. almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan or ergot alkaloid, dihydroergotamine and ergotamine, are the preferred treatment strategy.[55,57] Triptan compounds are analogues of the neurotransmitter serotonin and 5-hydroxytryptamine$_1$ (5HT$_1$) receptor agonists that were specifically designed for the acute treatment of migraines.[57] Triptans centrally disrupt the afferent return of nociceptive signals to the trigeminal nucleus caudalis by activating the 5HT$_{1B}$ receptor and subsequently reducing the release of sensory neurotransmitters from neurons.[66] Similarly, ergot alkaloids act as an agonist with low specificity at various receptors, including the 5HT$_1$, dopamine and α_2-adrenergic receptors.[67] Dihydroergotamine also blocks the release of prostaglandins from glia and blocks adenosine triphosphate-mediated sensitisation of the trigeminal nucleus caudalis.[57,68] However, triptans and, more notably, ergot alkaloids are contraindicated in patients with cardiovascular diseases due to the activation of 5HT$_{1B}$ receptors in the blood vessels, leading to vasoconstriction.[69] The frequent use of triptans in patients with chronic migraine episodes results in a decrease in treatment efficacy and tolerability that predominantly cannot be overcome by switching to another oral triptan.[70] For patients who are triptan resistant or refractory, or present with comorbidities that are contraindicated in triptan treatment, alternative treatment agents that have recently been approved for acute therapy include ditans or gepants.[71,72]

Ditans or gepants

The only ditan currently approved is lasmiditan, an 5HT$_{1F}$ receptor agonist that decreases the release of excitatory transmitters such as CGRP, pituitary adenylate cyclase-activating polypeptide

Table I: Pharmacological management for acute migraine

Drug class	Drug	Mechanism of action	Special notes
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aspirin	Inhibits cyclooxygenase enzymes, decreasing the synthesis of prostaglandins.[63]	Non-specific NSAIDs may cause medication overuse headache and may also lead to gastrointestinal side-effects such as gastric bleeding and ulcers.
	Diclofenac Naproxen Ibuprofen Celecoxib		
Analgesics	Acetaminophen	Central inhibition of prostaglandin synthesis.[57]	Using acetaminophen or NSAIDs on 15 or more days per month or taking combination analgesics, opioids, ergotamines, or triptans on 10 or more days per month is associated with an increased risk of developing medication-overuse headache.[57]
Triptans	Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan	Bind to neurogenic and central 5-hydroxytryptamine (5-HT) receptors and suppress trigeminal nerve activation, thereby inhibiting the release of vasoactive neuropeptides and blocking the transmission of nociceptive signals to the central nervous system.[77]	Contraindications: renal impairment, hepatic impairment, pregnancy, cardiovascular disease.[77]
Ditans	Lasmiditan	5HT1F receptor agonist that decreases the release of excitatory transmitters (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP) and nitric oxide (NO).[78]	Side-effects: dizziness, fatigue, nausea, and paraesthesia.[79]
Gepants[70,75]	Ubrogepant	CGRP receptor antagonists.[70,75,80]	Contraindications: concomitant use with strong CYP3A4 inhibitors.[80] Side-effects: nausea, somnolence and dry mouth.[81]
	Atogepant		Contraindications: None Side-effects: nausea, constipation, somnolence, elevated AST/ALT.[81]
	Rimegepant		Contraindications: concomitant administration with potent CYP3A4 inhibitors.[80] History of hypersensitivity.[80,81] For triptan contraindications or intolerance.[1] Side-effects: nausea.[82]
Ergot derivatives [55,57]	Ergotamine[82]	Activates 5HT-1B and 5HT-1D receptors.[82,83]	Contraindications: peripheral vascular diseases, hepatic/renal impairment, sepsis, pregnancy, uncontrolled hypertension, cardiovascular disease.[82] Avoid using with CYP3A4 inhibitors and other ergot-like agents.[82]
	Dihydroergotamine[1]		Contraindications: hepatic/renal impairment, pregnancy and cardiovascular disease.[1] Avoid with CYP3A4 inhibitors and other ergot-like agents.[1]
Antiemetics [55,76]	Prochlorperazine	Antagonises the D2 receptor.[84]	Contraindications: hypersensitivity reactions and extrapyramidal side effects.[84]
	Metoclopramide	Antagonises the D2 receptor (lower doses), antagonises the 5HT-3 (higher doses).[84]	Known hypersensitivity reactions and extrapyramidal symptom reactions.[8]

(PACAP) and nitric oxide (NO) without inducing blood vessel constriction as seen with triptan treatment.[66,73] The neuropeptide CGRP causes vasodilation, neurogenic inflammation and pain signal transmission.[74] Gepants, such as ubrogepant, telcagepant, atogepant, vazegepant and rimegepant, are CGRP receptor antagonists that are an effective treatment of acute migraine in patients with a history of triptan resistance.[70,75]

Antiemetic drugs

Oral antiemetics, such as promethazine, prochlorperazine and metoclopramide, can be used in conjunction with analgesics to treat disabling nausea and may contribute to headache pain relief due to their dopamine antagonist properties.[57,76]

Preventative pharmacological therapies for migraine attacks

Preventive migraine treatment is useful in patients with frequent migraine attacks and reduces the frequency and severity of migraine attacks by at least 50% compared to the preceding three-month period.[85] The majority of preventative treatments were repurposed for episodic and chronic migraine prevention after initial development for arterial hypertension, epilepsy, and depression (Table II).

Antihypertensive drugs

Antihypertensive agents that have been repurposed for the prevention of episodic migraines include beta-blockers, calcium

Table II: Preventative pharmacological therapies for migraine attacks

Drug class	Drug	Mechanism of action	Special notes
Anti-hypertensive drugs	beta-blockers (BBs) - propranolol	Non-selective beta-blocker.[100]	Contraindications: asthma and chronic obstructive pulmonary disease.[84]
	calcium channel blockers (CCBs) - flunarizine	Sodium and calcium channel blocker.[101]	
	calcium channel blockers (CCBs) - verapamil	Inhibits the influx of calcium ions by selectively binding to L-type voltage-gated calcium channels located in cardiac tissue, vascular smooth muscle, and pancreatic cells.[102]	
	angiotensin-converting enzyme inhibitors (ACE-I) - lisinopril	Prevents the conversion of angiotensin I to angiotensin II.[103]	
	angiotensin receptor blockers (ARBs) - candesartan	Antagonises type 1 angiotensin II receptor.[104]	
Anti-epileptic drugs	valproate/valproic acid	Enhances inhibitory neurotransmission and the modulation of voltage-gated ion channels.[105]	Contraindications: hepatic dysfunction, mitochondrial disorders, hypersensitivity, urea cycle disorders, and pregnancy.[84]
	topiramate	Blocks voltage-dependent sodium and calcium channels.[106] Inhibits the excitatory glutamate pathway.[106] Inhibits carbonic anhydrase activity.[106]	Contraindications: hypersensitivity reactions.[84]
	lamotrigine	Binds and inhibits voltage-gated sodium channels, stabilising presynaptic neuronal membranes.[107] Inhibits presynaptic glutamate and aspartate release.[107]	Contraindications: hypersensitivity reactions.[108]
Antidepressant drugs	fluoxetine	Inhibition of serotonin reuptake in presynaptic neuron.[109]	
	amitriptyline	Increases noradrenergic or serotonergic neurotransmission by blocking the norepinephrine or serotonin transporter at the presynaptic neuron.[110]	Somnolence.[1]
CGRP monoclonal antibodies	galcanezumab	Blocks the CGRP pathway by targeting the CGRP.[111]	Contraindications: hypersensitivity reactions Injection site reactions, vertigo, pruritus, constipation.[1]
	fremanezumab	CGRP antagonist.[112]	
	eptinezumab	Binds to α- and β-CGRP ligands, blocking it from binding to CGRP receptors.[113]	Contraindications: hypersensitivity reactions Side-effects: Injection site reactions, muscle spasms, and hypersensitivity reactions.[1]
Botulinum toxin	onabotulinumtoxinA	Primarily acts upon trigeminal and cervical nerve endings, inhibiting the release of inflammatory mediators including CGRP.[114]	Side-effects: headache, neck pain, injection site irritation, drooping eyelids.[1]

channel blockers, and angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB). Beta-blockers, metoprolol and propranolol, inhibit β_1 receptors, which reduces the rate of noradrenaline release and neuronal firing, and interferes with transmission in the trigeminocervical complex.[86] Some beta-blockers have a high affinity for $5HT_{1A}$ receptors and inhibit the $5HT_{1A}$-mediated synthesis of serotonin.[87] However, the use of beta-blockers is contraindicated in patients with asthma or cardiovascular failure.[85] Alternatively, calcium channel blockers (CCB) such as flunarizine and verapamil have shown some efficacy in preventing migraines by modulating serotonin release and inhibiting neurovascular inflammation.[88] Flunarizine is a non-selective voltage-gated sodium channel antagonist, which leads to reduced neuronal excitability, and acts as a dopamine receptor antagonist.[89] ACE-I/ARB compounds, lisinopril and candesartan, might prevent migraine through decreasing the renin-angiotensin system activity and delaying nociceptive signals.[90]

Anti-epileptic drugs

Several anti-epileptic compounds that act at different pre- and post-synaptic sites of neurons have been proven effective in the prevention of migraine, including valproic acid, topiramate and lamotrigine.[85] Valproic acid is a gamma-aminobutyric acid (GABA)-mimetic agent which decreases the excitability of serotonergic neurons and prevents vasodilation during migraine attacks.[91] Similarly, topiramate enhances the inhibitory activity of GABA neurotransmitters as well as inhibiting voltage-gated sodium channels, and carbonic anhydrase activity.[92] Lamotrigine inhibits neuronal release of glutamate, an excitatory neurotransmitter implicated in central sensitisation, by inhibiting voltage-sensitive sodium channels and thus reducing the frequency of migraine attacks.[85,93]

Antidepressant drugs

For patients with anxiety or mood disorders, antidepressants could be useful for migraine prevention because they interfere

with noradrenaline and serotonin reuptake and inhibit $5HT_2$ receptors. Although its mechanism of migraine prevention is unclear, amitriptyline is a serotonin-norepinephrine reuptake pump inhibitor, α_2-adrenergic receptor agonist, and sodium channel blocker. Fluoxetine is a more selective compound that inhibits serotonin reuptake in the synaptic cleft, leading to increased serotonin levels and analgesia.[94]

Calcitonin gene-related peptide monoclonal antibodies

Recently, CGRP monoclonal antibodies, which have been developed against the CGRP ligand (galcanezumab, fremanezumab and eptine-zumab) and the CGRP receptor (erenumab), have been approved for the preventative treatment of migraine.[95] The monoclonal antibodies bind to and neutralise excessive CGRP release or target the CGRP receptors at the trigeminal sensory nerve with high specificity, and their prolonged half-life allows for monthly or quarterly dosing.[74]

Botulinum toxin

Botulinum toxin, a neurotoxin produced by the bacterium *Clostridium botulinum*, has emerged as an effective treatment for chronic migraines.[96] The most commonly used formulation for migraine prevention is onabotulinumtoxin A, marketed under the brand name Botox.[96] The mechanism of action involves the toxin's ability to inhibit the release of neurotransmitters, acetylcholine into the synaptic cleft at nerve endings.[97] Furthermore, BTX-A influences the release of several neurotransmitters and neuropeptides associated with pain transmission, including substance P, CGRP, and glutamate.[98] This inhibition reduces peripheral and central sensitisation, leading to a decrease in the frequency and severity of migraine attacks. Administered through a series of injections into specific head and neck muscles, botulinum toxin treatment typically provides relief for up to three months, making it a valuable option for patients with chronic migraines who have not responded adequately to conventional preventive therapies.[99]

Non-pharmacotherapy management for migraine

Migraine is the most common and incapacitating neurological disorder. However, pharmacological treatments are often ineffective and may be poorly tolerated by patients. There is a significant need in clinical practice for alternative approaches for both acute and preventive treatment of migraine episodes. This section highlights a spectrum of non-pharmacological treatment options from widely used and readily available nutraceuticals such as magnesium and riboflavin, to well-established psychological interventions like cognitive-behavioural therapy (CBT). It also highlights the emerging field of neuromodulation as a promising area of interest.

Nutraceuticals

Nutraceuticals are food-based or dietary supplements that provide medicinal or health benefits. Although evidence of the efficacy of many products remains debatable, their use is becoming increasingly popular in the general population, particularly those with chronic diseases.[115] The most commonly used nutraceuticals which have shown some evidence in migraine prevention are riboflavin (vitamin B2), coenzyme Q10 (CoQ10), magnesium, butterbur root extract (*Petasites hybridus*), and feverfew (*Tanacetum parthenium*).[116] Riboflavin is a precursor of coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) which are key actors in the electron transport chain and antioxidative function in the cell.[115] Although, there is no clear evidence of riboflavin deficiency in migraine patients, several studies have suggested its potential benefits in migraine prophylaxis, probably by reducing oxidative stress. Like riboflavin, coenzyme Q10 plays a crucial role in the mitochondrial electron transport chain and overall energy metabolism.[117] A randomised controlled trial involving 42 patients demonstrated the efficacy of coenzyme Q10, with participants receiving either a placebo or a daily dose of 300 magnesium.[115,118] Magnesium is a key regulator of cellular metabolism, primarily due to its function as a cofactor in all phosphoryl transfer reactions. Some studies have reported reduced serum magnesium levels in individuals with migraines and tension-type headaches, suggesting that supplementation may offer therapeutic benefits. The commonly recommended dosage is 400–600 mg of oral magnesium per day.[115,119]

Petasites hybridus or butterbur root is a herbal extract that has shown some efficacy in migraine prevention. A study by Diener et al. demonstrated a significant reduction in migraine attack frequency with a 75 mg dose, while lower doses showed no benefit.[120] Despite butterbur's apparent effectiveness, safety concerns currently prevent it from being recommended as a preventive treatment.[121]

Tanacetum parthenium or feverfew, has been used for centuries in folk medicine as treatment for fevers, headaches, toothaches and other conditions. Feverfew has been investigated for migraine prevention. However, the evidence remains limited and of low quality. A large randomised controlled trial involving 170 migraine patients reported good overall tolerability and a reduction in migraine attacks with a 6.25 mg dose of feverfew extract.[122]

Behavioural techniques and acupuncture

Migraine is commonly regarded as a bio-behavioural disorder resulting from a combination of behavioural and biological central nervous system (CNS) dysfunction factors. Behavioural therapies focus on modifying specific actions by employing techniques that reduce or eliminate behaviours that create discomfort while encouraging the development of behaviours that enhance overall quality of life.[115] Behavioural techniques include various strategies such as relaxation training, thermal, electromyographic biofeedback, and cognitive behavioural therapy that are primarily used in migraine treatment to help patients better manage their symptoms and recognise potential headache triggers.[123] Relaxation techniques can be learned and practised to help regulate the body's response to stress and pain, lower sympathetic nervous

system arousal, and reduce muscle tension. There is a wide range of methods that can be used to induce relaxation, ranging from traditional practices like yoga and meditation to contemporary approaches such as breathing exercises and mindfulness. Evidence-based methods include progressive muscle relaxation, autogenic training, and meditation. Biofeedback training uses electronic devices to help the patient understand and monitor certain physiological processes associated with the experience of pain, such as muscle tension, blood pressure and heart rate changes.[116]

Cognitive behavioural therapy (CBT) is a psychotherapeutic approach grounded in the biopsychosocial model. It incorporates a range of cognitive and behavioural techniques, which can be used to improve headache management and quality of life.[115,123] Another related technique commonly used in traditional Chinese medicine is acupuncture, which has been widely applied in headache treatment. Its proposed mechanisms of action include stimulating endogenous analgesic pathways, inhibiting pain processing, and reducing neuroinflammation through both peripheral and central mechanisms.[115]

Non-invasive neuromodulation

Non-invasive neuromodulation has become a prominent non-pharmacological approach for migraine management due to its demonstrated efficacy and non-invasive characteristics. These methods involve the use of electrical or magnetic stimulation to modulate the activity of the brain, cranial and peripheral nerves, with the aim of influencing the pathways for the transmission and perception of pain. This category includes techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcutaneous electrical nerve stimulation (TENS).[115]

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses electromagnetic induction to cause depolarisation or hyperpolarisation in the neurons of the brain. It is commonly used in the diagnosis and therapy of various diseases, including multiple sclerosis, Parkinson's disease, dystonia, and depression.[124] Single-pulse transcranial magnetic stimulation (sTMS) functions by interrupting cortical spreading depression, a wave of increased cortical excitability followed by reduced neural activity which is thought to trigger migraine aura, pain, and sensory disturbances by activating the trigeminovascular and trigeminocervical systems.[125] Lipton et al.,[121] suggested that that treating migraine with aura early using sTMS leads increased and sustained freedom from pain in acute attacks.[121] Moreover, activating the sensorimotor cortex with rTMS was also able to increase the interictal low thalamo-cortical drive-in migraines.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) may help prevent migraine attacks by altering cortical excitability and addressing underlying pathophysiological triggers. Several pilot randomised controlled trials (RCTs) have evaluated the efficacy of tDCS for migraine prevention and compared with TMS, it is better tolerated, easier to use, and more portable. The use of tDCS offers a safe and effective technological approach for both the prevention and treatment of chronic migraine.[115]

Transcutaneous electrical nerve stimulation

Although its exact mechanism remains unclear, transcutaneous supraorbital neurostimulation (tSNS) is a primary technique for electrical trigeminal nerve stimulation (eTNS) in migraine treatment. Experimental evidence has suggested that the mechanism of action of eTNS is both peripheral and central. As a non-invasive neurostimulation method, TENS has increasingly attracted significant research attention for the treatment of headache disorders. Cefaly® is the first Food and Drug Administration (FDA)-approved medical device for the prevention of episodic migraine, targeting stimulation of the supratrochlear and supraorbital nerves.[115,126] TENS therapy is an effective and economical treatment with few side-effects and may be used in the emergency department for treatment of acute migraine episodes.

Lifestyle modifications

Lifestyle modifications play an increasingly important role in migraine management. Physical activity, management of obesity, a healthy diet, and a better lifestyle, such as adequate sleep and avoidance of drug abuse, significantly contribute to reducing the frequency and severity of attacks. It is important to consider these factors in the overall management strategies for migraine.[127]

Conclusion

Migraine treatment continues to face several challenges globally. Therapeutic barriers that limit the optimal treatment of headache vary greatly between the global north and global south especially where access to advanced therapies remains limited due to cost, availability, and healthcare infrastructure. The implementation of personalised medicine, especially through pharmacogenomics, holds promise in tailoring treatments based on an individual's genetic profile, potentially improving efficacy and reducing side-effects. However, the integration of such approaches is still in its early stages and requires greater investment and awareness. Emerging therapies, including novel neuromodulation techniques and monoclonal antibodies targeting migraine-specific pathways, are under active investigation in ongoing clinical trials. These innovations offer hope for more effective and targeted interventions. In conclusion, while significant progress has been made, future efforts must focus on improving access, advancing personalised treatment strategies, and supporting research to ensure better outcomes for all migraine patients.

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References

1. Karunarathna I, Aluthge P, Perera N, Gunathilake S. Pharmacological innovations in migraine therapy: A review [Internet]. Uva Clinical Anaesthesia and Intensive Care; 2025. Available from: https://www.researchgate.net/publication/387736140_Pharmacological_Innovations_in_Migraine_Therapy_A_Review. Accessed 13 May 2025.
2. Pescador Ruschel MA, De Jesus O. Migraine Headache [Internet]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560787/. Accessed 19 May 2025.
3. Amiri P, Kazeminasab S, Nejadghaderi SA, et al. Migraine: A review on its history, global epidemiology, risk factors, and comorbidities. Front Neurol. 2022;23(12):800605. https://doi.org/10.3389/fneur.2021.800605.
4. Khan J, Al Asoom LI, Al Sunni A, et al. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. Biomed Pharmacother. 2021;139:111557. https://doi.org/10.1016/j.biopha.2021.111557.
5. Kikkeri NS, Nagalli S. Migraine with aura. [Internet]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [updated 2024 Feb 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554611/.
6. Begasse de Dhaem O, Sakai F. Migraine in the workplace. eNeurologicalSci. 2022;27:100408. https://doi.org/10.1016/j.ensci.2022.100408.
7. Shimizu T, Sakai F, Miyake H, et al. Disability, quality of life, productivity impairment and employer costs of migraine in the workplace. J Headache Pain. 2021;22(1):29. https://doi.org/10.1186/s10194-021-01243-5.
8. World Health Organization. Headache disorders [Internet]. Geneva: World Health Organization; 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/headache-disorders. Accessed 19 May 2025.
9. Ding C, Wu Y, Chen X, et al. Global, regional, and national burden and attributable risk factors of neurological disorders: The Global Burden of Disease study 1990-2019. Front Public Health. 2022;10:952161. https://doi.org/10.3389/fpubh.2022.952161.
10. Ye S, Wei L, Jiang Y, et al. Mechanism of NO2-induced migraine in rats: The exploration of the role of miR-653-3p/IGF1 axis. J Hazard Mater. 2024;465:133362. https://doi.org/10.1016/j.jhazmat.2023.133362.
11. Pleș H, Florian IA, Timis TL, et al. Migraine: Advances in the pathogenesis and treatment. Neurol Int. 2023;15(3):1052-1105. https://doi.org/10.3390/neurolint15030067.
12. Satapathy P, Chauhan S, Gaidhane S, et al. Trends in migraine and tension-type headaches in South Asia: findings from the Global Burden of Disease Study 2021 (1990-2021). Front Neurol. 2025;16:1514712. https://doi.org/10.3389/fneur.2025.1514712.
13. Dueland AN, Leira R, Burke TA, Hillyer EV, Bolge S. The impact of migraine on work, family, and leisure among young women - a multinational study. Curr Med Res Opin. 2004;20(10):1595-1604. https://doi.org/10.1185/030079904X3357.
14. Kesserwani H. Migraine triggers: An overview of the pharmacology, biochemistry, atmospherics, and their effects on neural networks. Cureus. 2021;13(4):e14243. https://doi.org/10.7759/cureus.14243.
15. Tu YH, Chang CM, Yang CC, et al. Dietary patterns and migraine: Insights and impact. Nutrients. 2025;17(4):669. https://doi.org/10.3390/nu17040669.
16. Hindiyeh NA, Zhang N, Farrar M, et al. The role of diet and nutrition in migraine triggers and treatment: A systematic literature review. Headache. 2020;60(7):1300-1316. https://doi.org/10.1111/head.13836.
17. Friedman DI, De Ver Dye T. Migraine and the environment. Headache. 2009;49(6):941-952. https://doi.org/10.1111/j.1526-4610.2009.01443.x.
18. Haghdoost F, Togha M. Migraine management: Non-pharmacological points for patients and health care professionals. Open Med (Wars). 2022;17(1):1869-1882. https://doi.org/10.1515/med-2022-0598.
19. Amin FM, Aristeidou S, Baraldi C, et al. The association between migraine and physical exercise. J Headache Pain. 2018;19(1):83. https://doi.org/10.1186/s10194-018-0902-y.
20. Al-Shimmery EK. Precipitating and relieving factors of migraine headache in 200 Iraqi Kurdish patients. Oman Med J. 2010;25(3):212-217. https://doi.org/10.5001/omj.2010.59.
21. Negro A, Seidel JL, Houben T, et al. Acute sleep deprivation enhances susceptibility to the migraine substrate cortical spreading depolarization. J Headache Pain. 2020;21(1):86. https://doi.org/10.1186/s10194-020-01155-w.
22. Waliszewska-Prosół M, Nowakowska-Kotas M, Chojdak-Łukasiewicz J, Budrewicz S. Migraine and sleep-an unexplained association? Int J Mol Sci. 2021;22(11):5539. https://doi.org/10.3390/ijms22115539.
23. Fischer MA, Jan A. Medication-overuse headache. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2023 Aug 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538150/.
24. Arca KN, Halker Singh RB. Dehydration and headache. Curr Pain Headache Rep. 2021;25(8):56. https://doi.org/10.1007/s11916-021-00966-z.
25. National Institute of Neurological Disorders and Stroke. Migraine [Internet]. Bethesda (MD): National Institutes of Health; 2025. Available from: https://www.ninds.nih.gov/health-information/disorders/migraine. Accessed 19 May 2025.
26. Lisicki M, Schoenen J. Old habits die hard: Dietary habits of migraine patients challenge our understanding of dietary triggers. Front Neurol. 2021;12:748419. https://doi.org/10.3389/fneur.2021.748419.
27. Lampl C, Rudolph M, Deligianni CI, Mitsikostas DD. Neck pain in episodic migraine: Premonitory symptom or part of the attack? J Headache Pain. 2015;16:566. https://doi.org/10.1186/s10194-015-0566-9.
28. Güven B, Güven H, Çomoğlu SS. Migraine and yawning. Headache. 2018;58(2):210-216. https://doi.org/10.1111/head.13195.
29. Barbanti P, Fofi L, Aurilia C, et al. Dopaminergic symptoms in migraine. Neurol Sci. 2013;34(Suppl 1):67-70. https://doi.org/10.1007/s10072-013-1415-8.
30. Grodzka O, Dzagoevi K, Rees T, et al. Migraine with and without aura-two distinct entities? A narrative review. J Headache Pain. 2025;26(1):77. https://doi.org/10.1186/s10194-025-01998-1.
31. Ashina M. Migraine. N Engl J Med. 2020;383(19):1866-1876. https://doi.org/10.1056/NEJMra1915327.
32. Paemeleire K, Vandenbussche N, Stark R. Chapter 11 - Migraine without aura. Handbook of Clinical Neurology. 2023. p. 151-67. https://doi.org/10.1016/B978-0-12-823356-6.00007-X.
33. He Y, Li Y, Nie Z. Typical aura without headache: a case report and review of the literature. J Med Case Rep. 2015;9:40. https://doi.org/10.1186/s13256-014-0510-7.
34. Mungoven TJ, Henderson LA, Meylakh N. Chronic migraine pathophysiology and treatment: A review of current perspectives. Front Pain Res (Lausanne). 2021;2:705276. https://doi.org/10.3389/fpain.2021.705276.
35. The Migraine Trust. Chronic migraine [Internet]. London: The Migraine Trust; 2025. Available from: https://migrainetrust.org/understand-migraine/types-of-migraine/chronic-migraine/. Accessed 19 May 2025.
36. Kim SJ, Lee HJ, Lee SH, et al. Most bothersome symptom in migraine and probable migraine: A population-based study. PLoS One. 2023;18(11):e0289729. https://doi.org/10.1371/journal.pone.0289729.
37. Lenglar T, Caula C, Moulding T, et al. Brain to belly: Abdominal variants of migraine and functional abdominal pain disorders associated with migraine. J Neurogastroenterol Motil. 2021;27(4):482-494. https://doi.org/10.5056/jnm20290.
38. Gelfand AA. Episodic syndromes that may be associated with migraine: A.K.A. "the childhood periodic syndromes". Headache. 2015;55(10):1358-1364. https://doi.org/10.1111/head.12624.
39. Iljazi A, Chua A, Rich-Fiondella R, et al. Unrecognized challenges of treating status migrainosus: An observational study. Cephalalgia. 2020;40(8):818-827. https://doi.org/10.1177/0333102420911461.
40. Prakash S, Prakash A, Lodha D. Bilateral persistent ophthalmoplegia in a patient with migraine: persistent migraine aura without infarction? BMJ Case Rep. 2021;14(4):e242099. https://doi.org/10.1136/bcr-2021-242099.
41. Lebedeva ER, Gurary NM, Olesen J. Diagnosis of migrainous infarction: A case report and analysis of previously published cases. Diagnostics (Basel). 2023;13(15):2502. https://doi.org/10.3390/diagnostics13152502.
42. Davies PT, Panayiotopoulos CP. Migraine triggered seizures and epilepsy triggered headache and migraine attacks: a need for re-assessment. J Headache Pain. 2011;12(3):287-288. https://doi.org/10.1007/s10194-011-0344-2.
43. Kwon MJ, Choi HG, Kim YH, et al. A higher probability of subsequent stroke and ischemic heart disease in migraine patients: a longitudinal follow-up study in Korea. J Headache Pain. 2023;24(1):98. https://doi.org/10.1186/s10194-023-01632-y.
44. Duan S, Ren Z, Xia H, et al. Associations between anxiety, depression with migraine, and migraine-related burdens. Front Neurol. 2023;14:1090878. https://doi.org/10.3389/fneur.2023.1090878.
45. Graham JR, Wolff HG. Mechanism of migraine headache and action of ergotamine tartrate. Arch Neurol Psychiatry. 1938;39(4):737-63. https://doi.org/10.1001/archneurpsyc.1938.02270040093005.
46. Shibata Y. Migraine pathophysiology revisited: proposal of a new molecular theory of migraine pathophysiology and headache diagnostic criteria. Int J Mol Sci. 2022;23(21):13002. https://doi.org/10.3390/ijms232113002.
47. Terrier LM, Hadjikhani N, Velut S, et al. The trigeminal system: the meningovascular complex-a review. J Anat. 2021;239(1):1-11. https://doi.org/10.1111/joa.13413.
48. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev Pharmacol Toxicol. 2015; 55:533-52. https://doi.org/10.1146/annurev-pharmtox-010814-124701.
49. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets. 2020; 24(2):91-100. https://doi.org/10.1080/14728222.2020.1724285.
50. Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017; 158(4):543-59. https://doi.org/10.1097/j.pain.0000000000000831.
51. Moskowitz MA. The neurobiology of vascular head pain. Ann Neurol. 1984;16(2):157-68. https://doi.org/10.1002/ana.410160202.
52. Hoffmann J, Baca SM, Akerman S. Neurovascular mechanisms of migraine and cluster headache. J Cereb Blood Flow Metab. 2019; 39(4):573-94. https://doi.org/10.1177/0271678X17733655.
53. Costa C, Tozzi A, Rainero I, et al. Cortical spreading depression as a target for anti-migraine agents. J Headache Pain. 2013;14(1):62. https://doi.org/10.1186/1129-2377-14-62.
54. Borgdorff P. Arguments against the role of cortical spreading depression in migraine. Neurol Res. 2018;40(3):173-81. https://doi.org/10.1080/01616412.2018.1428406.
55. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Head-

ache. 2015;55(1):3-20. https://doi.org/10.1111/head.12499.
56. Mayans L, Walling A. Acute migraine headache: treatment strategies. Am Fam Physician. 2018;97(4):243-51.
57. Ong JJY, De Felice M. Migraine treatment: current acute medications and their potential mechanisms of action. Neurotherapeutics. 2018;15(2):274-90. https://doi.org/10.1007/s13311-017-0592-1.
58. Becker WJ, Findlay T, Moga C, et al P. Guideline for primary care management of headache in adults. Can Fam Physician. 2015;61(8):670-9.
59. Diener HC, Montagna P, Gacs G, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalalgia. 2006; 26(5):537-47. https://doi.org/10.1111/j.1468-2982.2005.01064.x.
60. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. Cephalalgia. 2000;20(4):233-43. https://doi.org/10.1046/j.1468-2982.2000.00055.x.
61. Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. Ann Pharmacother. 2007;41(11):1782-91. https://doi.org/10.1345/aph.1K121.
62. Lampl C, Voelker M, Diener HC. Efficacy and safety of 1,000 mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine headache and migraine accompanying symptoms. J Neurol. 2007;254(6):705-12. https://doi.org/10.1007/s00415-007-0547-2.
63. Pardutz A, Schoenen J. NSAIDs in the acute treatment of migraine: A review of clinical and experimental data. Pharmaceuticals (Basel). 2010;3(6):1966-87. https://doi.org/10.3390/ph3061966.
64. Graham GG, Scott KF. Mechanisms of action of paracetamol and related analgesics. Inflammopharmacology. 2003;11(4):401-13. https://doi.org/10.1163/156856003322699573.
65. Barbanti P, Aurilia C, Egeo G, et al. Dopaminergic symptoms in migraine: A cross-sectional study on 1148 consecutive headache center-based patients. Cephalalgia. 2020;40(11):1168-76. https://doi.org/10.1177/0333102420929023.
66. Vila-Pueyo M. Targeted 5-HT(1F) therapies for migraine. Neurotherapeutics. 2018;15(2):291-303. https://doi.org/10.1007/s13311-018-0615-6.
67. Tfelt-Hansen P, Saxena PR, Dahlof C, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. Brain. 2000;123(Pt 1):9-18. https://doi.org/10.1093/brain/123.1.9.
68. Masterson CG, Durham PL. DHE repression of ATP-mediated sensitization of trigeminal ganglion neurons. Headache. 2010;50(9):1424-39. https://doi.org/10.1111/j.1526-4610.2010.01714.x.
69. MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation. 1998;98(1):25-30. https://doi.org/10.1161/01.CIR.98.1.25.
70. Lipton RB, Blumenfeld A, Jensen CM, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: Pooled results from three phase 3 randomized clinical trials. Cephalalgia. 2023; 43(2):3331024221141686. https://doi.org/10.1177/03331024221141686.
71. Sacco S, Lampl C, Amin FM, et al. European Headache Federation (EHF) consensus on the definition of effective treatment of a migraine attack and of triptan failure. J Headache Pain. 2022;23(1):133. https://doi.org/10.1186/s10194-022-01502-z.
72. Bentivegna E, Galastri S, Onan D, Martelletti P. Unmet needs in the acute treatment of migraine. Adv Ther. 2024;41(1):1-13. https://doi.org/10.1007/s12325-023-02650-7.
73. Labastida-Ramirez A, Rubio-Beltran E, Haanes KA, et al. Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. Pain. 2020;161(5):1092-9. https://doi.org/10.1097/j.pain.0000000000001801.
74. Giamberardino MA, Affaitati G, Curto M, et al. Anti-CGRP monoclonal antibodies in migraine: current perspectives. Intern Emerg Med. 2016;11(8):1045-57. https://doi.org/10.1007/s11739-016-1489-4.
75. Goadsby PJ, Friedman DI, Holle-Lee D, et al. Efficacy of atogepant in chronic migraine with and without acute medication overuse in the randomized, double-blind, phase 3 PROGRESS Trial. Neurology. 2024;103(2):e209584. https://doi.org/10.1212/WNL.0000000000209584.
76. Cooper W, Doty EG, Hochstetler H, Hake A, Martin V. The current state of acute treatment for migraine in adults in the United States. Postgrad Med. 2020;132(7):581-9. https://doi.org/10.1080/00325481.2020.1767402.
77. Nicolas S, Nicolas D. Triptans [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554507/. Accessed 20 May 2025.
78. Clemow DB, Johnson KW, Hochstetler HM, et al. Lasmiditan mechanism of action - review of a selective 5-HT1F agonist. J Headache Pain. 2020;21(1):71. https://doi.org/10.1186/s10194-020-01132-3.
79. Berger AA, Winnick A, Popovsky D, Kaneb A, Berardino K, Kaye AM, et al. Lasmiditan for the treatment of migraines with or without aura in adults. Psychopharmacol Bull. 2020;50(4 Suppl 1):163-88.
80. Rashid A, Manghi A. Calcitonin gene-related peptide receptor. [updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560648.
81. Rissardo JP, Caprara ALF. Gepants for acute and preventive migraine treatment: a narrative review. Brain Sci. 2022;12(12):1612. https://doi.org/10.3390/brainsci12121612.
82. Ngo M, Tadi P. Ergotamine/caffeine. [updated 2023 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555953/.
83. Tepper SJ, Albrecht D, Kellerman D. Dihydroergotamine for migraine: evidence for multiple modes of action: the single molecule 'combination' product-a narrative review. Cephalalgia Rep. 2024;7. https://doi.org/10.1177/25158163241292297.
84. Lew C, Punnapuzha S. Migraine medications. [updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553159/.
85. Ranganathan LN, Ramamurthy G, Kanthimathinathan S. Preventive oral treatment of episodic migraine: An overview. Neurol India. 2021;69(Supplement):S51-S8. https://doi.org/10.4103/0028-3886.315985.
86. Boyer N, Signoret-Genest J, Artola A, Dallel R, Monconduit L. Propranolol treatment prevents chronic central sensitization induced by repeated dural stimulation. Pain. 2017;158(10):2025-2034. https://doi.org/10.1097/j.pain.0000000000001007.
87. Chugani DC, Niimura K, Chaturvedi S, et al. Increased brain serotonin synthesis in migraine. Neurology. 1999;53(7):1473-1479. https://doi.org/10.1212/WNL.53.7.1473.
88. Kumar A, Kadian R. Migraine Prophylaxis. [Updated 2025]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan- Available from: https://www.ncbi.nlm.nih.gov/books/NBK507873/.
89. Bisol LW, Brunstein MG, Ottoni GL, et al. Is flunarizine a long-acting oral atypical antipsychotic? A randomized clinical trial versus haloperidol for the treatment of schizophrenia. J Clin Psychiatry. 2008;69(10):1572-9. https://doi.org/10.4088/JCP.v69n1007.
90. Ripa P, Ornello R, Pistoia F, Carolei A, Sacco S. The renin-angiotensin system: a possible contributor to migraine pathogenesis and prophylaxis. Expert Rev Neurother. 2014;14(9):1043-55. https://doi.org/10.1586/14737175.2014.946408.
91. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology. 1994;44(4):647-51. https://doi.org/10.1212/WNL.44.4.647.
92. Shank RP, Doose DR, Streeter AJ, Bialer M. Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase. Epilepsy Res. 2005;63(2-3):103-12. https://doi.org/10.1016/j.eplepsyres.2005.01.001.
93. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia. 1997;17(2):109-12. https://doi.org/10.1046/j.1468-2982.1997.1702109.x.
94. Sprenger T, Viana M, Tassorelli C. Current prophylactic medications for migraine and their potential mechanisms of action. Neurotherapeutics. 2018;15(2):313-23. https://doi.org/10.1007/s13311-018-0621-8.
95. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022;23(1):67. https://doi.org/10.1186/s10194-022-01431-x.
96. Escher CM, Paracka L, Dressler D, Kollewe K. Botulinum toxin in the management of chronic migraine: clinical evidence and experience. Ther Adv Neurol Disord. 2017;10(2):127-135. https://doi.org/10.1177/1756285616677005.
97. Nestor MS, Arnold D, Fischer DL. The mechanisms of action and use of botulinum neurotoxin type A in aesthetics: Key Clinical Postulates II. J Cosmet Dermatol. 2020;19(11):2785-2804. doi:10.1111/jocd.13702. Epub 2020 Sep 16. Erratum in: J Cosmet Dermatol. 2021;20(6):1954. https://doi.org/10.1111/jocd.14108.
98. Rahmatipour H, Shabestari SM, Benisi SZ, Samadikhah H. Pioneering pain management with botulinum toxin type A: From anti-inflammation to regenerative therapies. Heliyon. 2025;11(4):e42350. https://doi.org/10.1016/j.heliyon.2025.e42350.
99. Nigam PK, Nigam A. Botulinum toxin. Indian J Dermatol. 2010;55(1):8-14. https://doi.org/10.4103/0019-5154.60343.
100. Danesh A, Gottschalk PCH. Beta-blockers for migraine prevention: a review article. Curr Treat Options Neurol. 2019;21(4):20. https://doi.org/10.1007/s11940-019-0556-3.
101. Deligianni CI, Sacco S, Ekizoglu E, et al. European Headache Federation (EHF) critical reappraisal and meta-analysis of oral drugs in migraine prevention-part 2: flunarizine. J Headache Pain. 2023;24(1):128. https://doi.org/10.1186/s10194-023-01657-3.
102. McKeever RG, Patel P, Hamilton RJ. Calcium channel blockers. [updated 2024 Feb 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482473/.
103. Olvera Lopez E, Parmar M, Pendela VS, et al. Lisinopril. [updated 2024 Oct 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482230/.
104. Bulsara KG, Patel P, Makaryus AN. Candesartan. [updated 2024 Feb 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519501/.
105. Rahman M, Awosika AO, Nguyen H. Valproic acid. [updated 2024 Mar 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559112/.
106. Naegel S, Obermann M. Topiramate in the prevention and treatment of migraine: efficacy, safety and patient preference. Neuropsychiatr Dis Treat. 2010;6:17-28. https://doi.org/10.2147/NDT.S6459.
107. Belete TM. Recent progress in the development of new antiepileptic drugs with novel targets. Annals of Neurosciences. 2023;30(4):262-276. https://doi.org/10.1177/09727531231185991.
108. Betchel NT, Fariba KA, Saadabadi A. Lamotrigine [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan- [updated 2023 Feb 13; cited 2025 Jun 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470442/.
109. Sohel AJ, Shutter MC, Patel P, et al. Fluoxetine [Internet]. Treasure Island (FL): StatPearls

Publishing; 2025 Jan- [updated 2024 Feb 28; cited 2025 Jun 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459223/.
110. Thour A, Marwaha R. Amitriptyline [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan- [updated 2023 Jul 18; cited 2025 Jun 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537225/.
111. Gklinos P, Mitsikostas DD. The role of galcanezumab in migraine prevention: existing data and future directions. Pharmaceuticals (Basel). 2021;14(3):245. https://doi.org/10.3390/ph14030245.
112. Hoy SM. Fremanezumab: first global approval. Drugs. 2018;78(17):1829-34. https://doi.org/10.1007/s40265-018-1004-5.
113. Datta A, Maryala S, John R. A review of eptinezumab use in migraine. Cureus. 2021 Sep 16;13(9):e18032. https://doi.org/10.7759/cureus.18032.
114. Baraldi C, Lo Castro F, Ornello R, et al. OnabotulinumtoxinA: still the present for chronic migraine. Toxins (Basel). 2023;15(1):59. https://doi.org/10.3390/toxins15010059.
115. Puledda F, Shields K. Non-pharmacological approaches for migraine. Neurotherapeutics. 2018;15(2):336-45. https://doi.org/10.1007/s13311-018-0623-6.
116. Han X, Yu S. Non-pharmacological treatment for chronic migraine. Curr Pain Headache Rep. 2023;27:663-72. https://doi.org/10.1007/s11916-023-01162-x.
117. Licina E, Radojicic A, Jeremic M, Tomic A, Mijajlovic M. Non-pharmacological treatment of primary headaches-a focused review. Brain Sci. 2023;13(10):1432. https://doi.org/10.3390/brainsci13101432.
118. Sândor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology. 2005;64(4):713-5. https://doi.org/10.1212/01.WNL.0000151975.03598.ED.
119. Slater SK, Nelson TD, Kabbouche MA, et al. A randomized, double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of pediatric and adolescent migraine. Cephalalgia. 2011;31(8):897-905. https://doi.org/10.1177/0333102411406755.
120. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol. 2004;51(2):89-97. https://doi.org/10.1159/000076535.
121. Lipton RB, Göbel H, Einhäupl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology. 2004;63(12):2240-4. https://doi.org/10.1212/01.WNL.0000147290.68260.11.
122. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-Von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract (MIG-99) in migraine prevention - a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia. 2005;25(11):1031-41. https://doi.org/10.1111/j.1468-2982.2005.00950.x.
123. Penzien DB, Irby MB, Smitherman TA, Rains JC, Houle TT. Well-established and empirically supported behavioral treatments for migraine. Curr Pain Headache Rep. 2015;19(7);34. https://doi.org/10.1007/s11916-015-0500-5.
124. Somaa FA, de Graaf TA, Sack AT. Transcranial magnetic stimulation in the treatment of neurological diseases. Front Neurol. 2022;13:793253. https://doi.org/10.3389/fneur.2022.793253.
125. Bhola R, Kinsella E, Giffin N, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. J Headache Pain. 2015;16:535. https://doi.org/10.1186/s10194-015-0535-3.
126. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative lifetime migraine incidence in women and men. Cephalalgia. 2008;28(11):1170-8. https://doi.org/10.1111/j.1468-2982.2008.01666.x.
127. Abo-Elghiet F, Elosaily H, Hussein DK, et al. Bridging gaps in migraine management: a comprehensive review of conventional treatments, natural supplements, complementary therapies, and lifestyle modifications. Pharmaceuticals (Basel). 2025;18(2):139. https://doi.org/10.3390/ph18020139.