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CHRONIC MIGRAINE: LIMITS AND ADVANCES IN ACUTE AND PROPHYLACTIC TREATMENT

MARIO SERGIO BRAGA DO COUTO¹
PRISCILA FRANCISCA BIANCHI²
SUELEN MUXFELDT³
FELIPE DA SILVA VALENTE⁴

1. Biomedical Scientist and Master of Science – Applied Health Sciences from the State University of Western Paraná.
2. Biomedical Scientist and Specialist in Clinical Analysis – Community University of the Chapecó Region.
3. Doctor – Southern Faculty of Passo Fundo.
4. Biologist, Biomedical Scientist, and Master of Science – Environmental Science and Technology from the University of Vale do Itajaí.

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INTRODUCTION

Migraine is one of the most prevalent and disabling neurological diseases on a global scale, affecting more than one billion individuals annually (DONG *et al.*, 2025). Historically, the understanding of migraine has evolved from strictly vascular models to a more comprehensive approach that recognizes it as a complex neurovascular disorder (TANG *et al.*, 2015).

Beyond individual suffering, this condition represents a serious public health challenge and generates a significant socioeconomic impact. This burden extends to both direct costs of treatment and healthcare and indirect costs associated with lost productivity, absenteeism, and impairment of social relationships (KARLSSON *et al.*, 2024; WHO, 2025). Clinically, it is characterized by recurrent headache episodes of moderate to severe intensity, frequently accompanied by nausea, vomiting, and hypersensitivity to light and sound (AMIRI *et al.*, 2022; LIU *et al.*, 2024).

Although it can affect both sexes and various age groups, it is considerably more prevalent among women and working-age individuals (LIU *et al.*, 2024; COPPOLA *et al.*, 2025). The condition is frequently influenced by a combination of genetic, environmental, and lifestyle factors, being commonly associated with comorbidities such as stress, sleep disorders, anxiety, and depression (AMIRI *et al.*, 2022; GARCIA *et al.*, 2024).

In the prophylactic context, the traditional management of migraine has notable limitations, particularly with respect to tolerability (GARCIA *et al.*, 2024). Despite its high incidence and severe impact on quality of life, migraine remains frequently underdiagnosed and undertreated worldwide. This highlights the importance of expanding knowledge on the sub-

ject to optimize patient management and support (COPPOLA *et al.*, 2025; WHO, 2025). In this scenario, the contemporary challenge is to integrate interventions that not only control symptoms but also interrupt the disease's chronification, balancing the limitations of conventional therapies with advances in biotechnology (MOREIRA *et al.*, 2026).

Given this context, the present study aims to analyze and synthesize scientific evidence on chronic migraine, with an emphasis on prophylactic therapeutic strategies and abortive treatments for attacks, to assess their efficacy, mechanisms of action, and clinical applicability. Furthermore, it proposes to evaluate recent advances in the management of this condition, highlighting new therapeutic approaches and their implications for contemporary clinical practice.

METHODOLOGY

This study is an integrative literature review that gathers, analyzes, and critically discusses existing knowledge on chronic migraine, thereby providing a comprehensive and up-to-date understanding of the field. It is an approach that allows exploration of concepts, identification of trends, and reflection on existing advances, which proves especially relevant in the context of new approaches and perspectives for the acute and prophylactic treatment of migraine.

The search was conducted in scientific databases, including the Latin American and Caribbean Literature in Health Sciences (LILACS), the National Center for Biotechnology Information (PubMed), and the Scientific Electronic Library Online (SciELO). The following descriptors were used: "migraine treatment"; "migraine perspectives"; "migraine", combined with the boolean operator "AND", resulting in

the following combinations: treatment AND migraine; perspectives AND migraine, in English, Portuguese, and Spanish.

The research was limited to articles published between 2015 and 2026 that addressed the topic. Relevant studies aligning with the review's objective were included, while non-systematic reviews, theses, dissertations, and studies outside the established period were excluded.

The study selection process yielded an initial set of articles. After applying the inclusion and exclusion criteria, the studies were analyzed, and their findings were synthesized to provide an analysis of new approaches and perspectives in migraine treatment.

RESULTS AND DISCUSSION

Epidemiological and clinical aspects

Chronic migraine is a complex, multifactorial, and highly disabling neurological disorder, exerting a substantial impact on global public health (MOREIRA *et al.*, 2026). It is clinically defined by the occurrence of headache on 15 or more days per month for a period exceeding three months, where, on at least eight of those days, the pain must present typical characteristics of migraine, such as a pulsating quality, moderate to severe intensity, worsening with routine physical activities, and association with symptoms like nausea, photophobia, and phonophobia (GARCIA *et al.*, 2024; PRADO *et al.*, 2025). It is further classified as a primary headache, meaning it constitutes an autonomous clinical entity and is not secondary to other structural or systemic pathologies (BOZHENKO, 2025; DONG *et al.*, 2025).

According to the International Headache Society (2018), the International Classification of Headache Disorders (ICHD-3) can be subdivided into different clinical categories: “Mi-

graine without aura: Represents the most prevalent form, accounting for approximately 70% to 75% of cases, and is characterized by unilateral pain of a pulsating nature and the absence of premonitory neurological manifestations; Migraine with aura: Defined by the presence of transient neurological symptoms, predominantly visual, but also sensory or language-related, which precede or accompany the painful phase; Chronic migraine: Constitutes an evolutionary stage of the disease, characterized by a high frequency of episodes, according to the previously described diagnostic criteria”.

Besides these forms, there are less common variants, such as hemiplegic, retinal, basilar, and abdominal migraine, which present specific clinical manifestations and, in some cases, greater diagnostic complexity (MOREIRA *et al.*, 2026). Additionally, migraine can be classified according to therapeutic response. Resistant migraine is defined as that which does not respond adequately to at least three classes of prophylactic treatments, while *refractory migraine* corresponds to therapeutic failure across all available options, representing an important clinical challenge (AMIRI *et al.*, 2022).

Migraines rank among the most prevalent neurological disorders on a global scale, affecting more than one billion individuals annually. Its global prevalence is estimated at 14%-15% of the population, underscoring its significant epidemiological magnitude (BOZHENKO, 2025; COPPOLA *et al.*, 2025). A striking difference in distribution between the sexes is observed, with a higher prevalence in women (about 18% to 22%) than in men (about 6% to 9%). The incidence peaks between 30 and 45 years of age, a period that coincides with individuals' phase of highest economic productivity and social responsibilities (FITZEK *et al.*,

2025; WHO, 2025). Recent data indicate a significant increase in the global burden of the disease, with approximately 58% growth in the number of cases between 1990 and 2021, reflecting both population growth and potential changes in risk factors and diagnostic recognition (DONG *et al.*, 2025).

The impact of chronic migraine is broad and multifaceted, affecting physical, psychological, social, and economic dimensions. From a functional standpoint, the recurrence of attacks and the unpredictability of episodes impose significant limitations on daily activities, negatively affecting interpersonal relationships, family life, and engagement in social and leisure activities. Anticipatory anxiety, characterized by the constant fear of new attacks, further worsens this impairment (COPPOLA *et al.*, 2025; WHO, 2025).

From an economic perspective, migraine carries high direct and indirect costs. Direct costs include expenditures on medications, medical appointments, and hospitalizations, while indirect costs are related to lost productivity, as reflected in absenteeism and presenteeism. In Europe, annual economic losses are estimated at around €27 billion, underscoring the substantial financial impact of the disease (GARCIA *et al.*, 2024; COPPOLA *et al.*, 2025). Additionally, work disability associated with chronic migraine is high, with approximately 85% of attacks classified as disabling, reinforcing the need for effective therapeutic strategies and multidisciplinary approaches in managing the condition (MOREIRA *et al.*, 2026).

Pathophysiology and triggering factors

The pathophysiology of migraine is complex, involving the dynamic interaction between genetic, environmental, and neurobiological factors. Currently, the neurovascular theory is the most widely accepted explanation

for the disease's underlying mechanisms, highlighting the central role of activation of the trigeminovascular system as the initiating and perpetuating event of attacks (GARCIA *et al.*, 2024; MOREIRA *et al.*, 2026).

Activation of the trigeminal nerve constitutes one of the main initial events in the pathophysiological cascade of migraine. When stimulated, this nerve promotes the release of pro-inflammatory neuropeptides, including substance P and, more importantly, calcitonin gene-related peptide (CGRP), considered one of the primary mediators of migraine pain (**Figure 28.1**) (TANG *et al.*, 2015; XU *et al.*, 2016). The release of these mediators results in vasodilation of intracranial blood vessels, particularly in the meninges, and promotes plasma extravasation and the activation of local inflammatory processes, thereby characterizing neurogenic inflammation. This inflammatory environment amplifies nociceptive signals and maintains pain (MOREIRA *et al.*, 2026).

Therefore, a state of peripheral and central sensitization develops, characterized by a reduction in the activation threshold of nociceptive neurons and an increase in central nervous system responsiveness. This phenomenon explains the hypersensitivity to sensory stimuli (such as light, sound, and odors) and plays a fundamental role in the chronification of migraine (MOREIRA *et al.*, 2026).

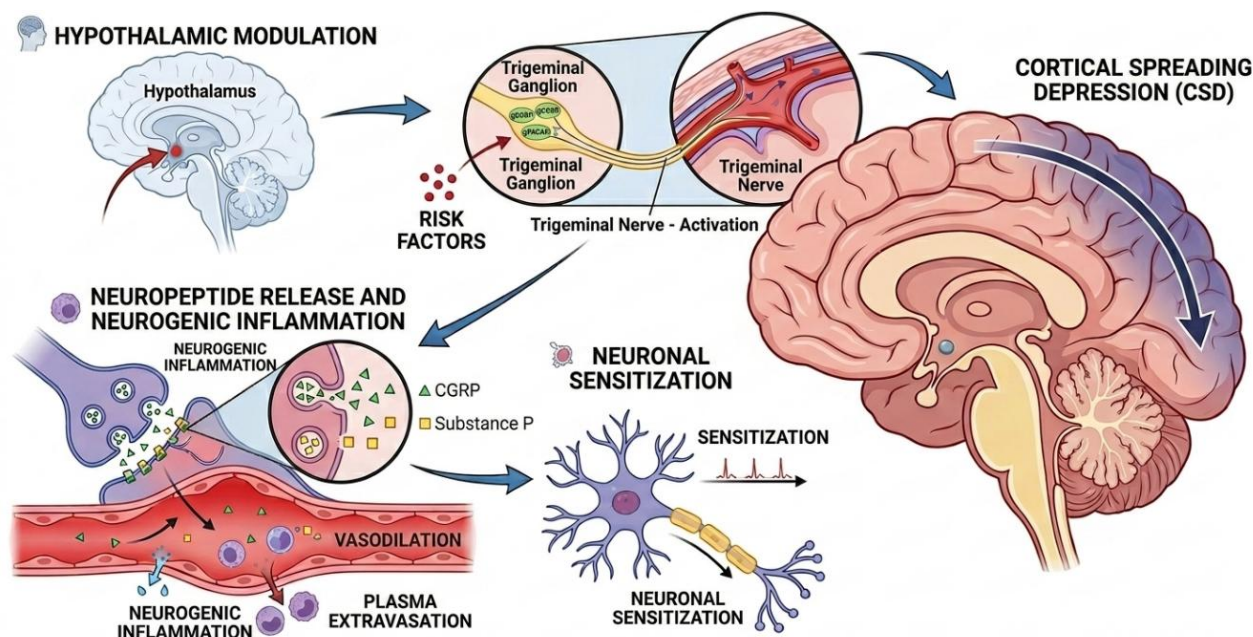
In migraine with aura, cortical spreading depression is characteristic, a wave of neuronal depolarization followed by suppression of cortical electrical activity that propagates slowly through the cerebral cortex. This phenomenon is directly related to the transient neurological symptoms that precede or accompany the painful phase (XU *et al.*, 2016; RAVI *et al.*, 2024).

In addition, recent evidence points to the involvement of the hypothalamus in the patho-

physiology of migraine, especially in the prodromal phase. This structure seems to modulate early symptoms, such as mood changes, yawning, fatigue, and changes in appetite, suggesting its participation in regulating the initiation cycles of attacks (GARCIA *et al.*, 2024).

Among the main triggers, hormonal factors stand out, especially in women, for whom fluctuations in estrogen levels, particularly during the menstrual period, are among the most frequent triggers (RAVI *et al.*, 2024; COPPOLA *et al.*, 2025).

Figure 28.1 Pathophysiological cycle of migraine



Legend: The process begins with the activation of the trigeminovascular system, leading to the release of neuropeptides (CGRP) and triggering neurogenic inflammation and meningeal vasodilation. The perpetuation of these stimuli generates peripheral and central sensitization, progressively worsening the clinical picture and culminating in the chronification of pain, with the hypothalamus and cortical spreading depression (CSD) acting in specific phases of the cycle.

Psychological factors (stress and anxiety) also play a relevant role, acting both as precipitants and as modulators of attack intensity (AMIRI *et al.*, 2022; COLLINGS *et al.*, 2026). Changes in sleep patterns, prolonged fasting, dehydration, and intense physical exertion are frequently associated with triggering episodes (GARCIA *et al.*, 2024; COLLINGS *et al.*, 2026). This is in addition to environmental and sensory factors, including exposure to bright light, loud noises, strong odors, and abrupt changes in weather (DONG *et al.*, 2025; MOREIRA *et al.*, 2026).

Clinical criteria and diagnosis of chronic migraine

The diagnosis of chronic migraine is eminently clinical, based on a detailed medical history and thorough characterization of the attack pattern, since, to date, there are no specific biomarkers or imaging exams capable of objectively confirming the disease. In this context, excluding secondary causes of headache and carefully applying classification systems are essential steps in the diagnostic process (TANG *et al.*, 2015). The gold standard for diagnosis is established by the ICHD-3, which provides standardized operational criteria widely used in

clinical practice and research (FITZEK *et al.*, 2025).

For diagnosis, there must be headache on 15 or more days per month for more than three months. Additionally, on at least eight of these monthly days, the headache must present typical characteristics of migraine, with or without aura, or respond to the use of specific therapies, such as triptans or ergot derivatives. These criteria reflect not only the high frequency of attacks but also the maintenance of the migraine phenotype over time (IHS, 2018; GARCIA *et al.*, 2024; PRADO *et al.*, 2025).

To be classified as chronic migraine, it must present a well-defined set of clinical characteristics. Attacks generally last between 4 and 72 hours when untreated or when treatment is ineffective. Pain is typically unilateral, though it can be bilateral in some patients (MOREIRA *et al.*, 2026). Regarding quality, the pain has a pulsating or throbbing character, with intensity varying from moderate to severe, frequently resulting in significant functional disability. A relevant aspect is the worsening of pain with routine physical activities, such as walking or climbing stairs, which differentiates migraine from other forms of headache (PRADO *et al.*, 2025). Furthermore, associated symptoms are common, such as nausea and/or vomiting, as well as sensory hypersensitivity manifested by photophobia and phonophobia. These clinical elements are fundamental for diagnostic differentiation and proper classification of the disease (PRADO *et al.*, 2025; MOREIRA *et al.*, 2026).

According to Garcia *et al.* (2024), the clinical diagnosis of migraine also involves understanding its cyclic nature, which can be divided into distinct phases: “Prodromal or premonitory phase: Generally occurs 24 to 48 hours before the onset of pain and is characterized by non-

specific symptoms such as mood changes, fatigue, frequent yawning, and food cravings, suggesting the participation of central structures such as the hypothalamus; Aura phase: Consists of transient neurological symptoms, predominantly visual, but which can include sensory or language manifestations. These symptoms usually last between 5 and 60 minutes and precede or accompany the following phase; Headache phase (pain phase): The period of actual pain and the most disabling stage of the cycle; Postdromal phase: Occurs after the pain resolves and is characterized by symptoms such as exhaustion, difficulty concentrating, apathy, and, occasionally, diffuse residual cephalic discomfort”.

Identifying these phases significantly contributes to an accurate diagnosis and enables more targeted and individualized therapeutic interventions throughout the course of the disease (GARCIA *et al.*, 2024; PRADO *et al.*, 2025).

Abortive treatment of migraine

Abortive treatment, or acute migraine treatment, primarily aims to rapidly interrupt the painful attack and control associated symptoms, such as nausea, vomiting, and sensory hypersensitivity, aiming for the patient's functional restoration with minimal adverse effects. The therapeutic choice must be individualized, considering the intensity of the attack, previous response to medications, and the presence of comorbidities (XU *et al.*, 2016; KARLSSON *et al.*, 2024).

Generally, pharmacological strategies for acute migraine management are divided into non-specific therapies, such as common analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), and specific therapies, including triptans, CGRP antagonists (gepants), and selective serotonin receptor agonists (ditans) (XU

et al., 2016). Simple analgesics and NSAIDs constitute the first line of treatment for attacks of mild to moderate intensity. Drugs such as ibuprofen, acetylsalicylic acid, diclofenac, and naproxen have well-established efficacy in reducing pain and associated inflammation (KARLSSON *et al.*, 2024; PULEDDA *et al.*, 2024).

Triptans represent the gold standard in the treatment of moderate to severe attacks, or those refractory to conventional analgesics. These drugs act as selective agonists of 5-HT_{1B/1D} serotonin receptors, promoting cranial vasoconstriction, inhibiting neuropeptide release, and modulating nociceptive transmission (YANG *et al.*, 2021; KARLSSON *et al.*,

2024; Liu *et al.*, 2024). In a study conducted by Collings *et al.* (2026), the authors examined the prescription rates of various medications used to treat attacks in patients with chronic migraine within a total cohort of 62.205 newly diagnosed migraine patients in England (**Table 28.1**). Triptans are the most widely used by patients undergoing active treatment. Common medications like ibuprofen or naproxen (NSAIDs) and combinations with paracetamol appear next as frequent treatment options. Opiates and codeine have much lower prescription rates, which typically reflects current clinical guidelines that avoid using opioids for migraine due to the risk of dependence and the risk of causing a rebound effect (worsening headaches in the long term).

Table 28.1 Prescription rate of medications used for migraine attacks

Drug class	General	Acute only	Acute and preventive
Triptans	16.5 ± 0.25	76.2 ± 1.55	67.2 ± 1.60
NSAIDs / Anti-inflammatories	8.3 ± 0.15	20.9 ± 0.60	29.0 ± 0.85
Paracetamol Regimens	7.2 ± 0.15	16.9 ± 0.55	26.6 ± 0.80
Paracetamol + Codeine	6.0 ± 0.15	13.8 ± 0.45	20.3 ± 0.70
Opiates	4.5 ± 0.10	8.6 ± 0.35	16.7 ± 0.55
Antiemetics	3.9 ± 0.15	8.6 ± 0.35	12.3 ± 0.50
Codeine	2.3 ± 0.10	4.5 ± 0.25	7.4 ± 0.35

Source: COLLINGS *et al.*, 2026.

In recent years, new therapeutic classes have been incorporated into migraine management. Gepants act as CGRP receptor antagonists, directly blocking one of the main mediators of migraine pathophysiology. These drugs are particularly useful in patients who do not respond to triptans or who have cardiovascular contraindications, since they do not induce vasoconstriction (YANG *et al.*, 2021; KARLSSON *et al.*, 2024).

Ditans, represented by lasmiditan, are selective 5-HT_{1F} receptor agonists that act on cen-

tral pain modulation without promoting vasoconstrictive effects. Despite its efficacy, its use may be associated with adverse effects, including dizziness and sedation, and caution is recommended during activities that require attention, such as driving. Ergot derivatives, such as ergotamine, currently occupy a secondary role in migraine treatment, being reserved for specific or refractory cases due to their less favorable safety profile and greater risk of adverse effects (PULEDDA *et al.*, 2024).

Prophylactic treatment: pharmacological and non-pharmacological therapies

Prophylactic or preventive migraine treatment primarily aims to reduce the frequency, intensity, and duration of attacks, minimize the need for abortive therapies, and promote significant improvement in patients' functioning and quality of life. This approach is especially indicated for individuals with frequent attacks, highly intense or disabling episodes, or failure/contraindication to acute treatment (BOZHENKO, 2025; COLLINGS *et al.*, 2026).

Preventive pharmacological management is based on the use of conventional oral drugs, biological agents, and injectables, highlighting beta-blockers (such as propranolol and metoprolol) as first-line options, along with anticonvulsants (such as topiramate and sodium valproate) and tricyclic antidepressants (such as amitriptyline), which have shown efficacy in reducing attack frequency and supporting associated comorbidities. However, adherence to these treatments may be limited by adverse effects, including fatigue, cognitive changes, sleep disorders, and weight gain (GARCIA *et al.*, 2024).

Advances in understanding the pathophysiology of migraine have enabled the development of target-specific therapies, such as anti-CGRP monoclonal antibodies. These agents represent the state of the art in preventive treatment, acting directly on the CGRP pathway, one of the main mediators of migraine pain. In general, they present a better tolerability profile and greater treatment adherence, although their high cost still limits their widespread use (FILGUEIRA *et al.*, 2023).

Botulinum toxin type A constitutes the gold standard for chronic migraine prophylaxis, particularly in patients with a high frequency of attacks. According to PREEMPT 1 and 2 (Phase III Research Evaluating Migraine Prophylaxis

Therapy), pivotal clinical trials that proved the efficacy of onabotulinumtoxinA (Botox®) in chronic migraine prevention, the protocol involves multiple injections at specific points in the head and neck every 12 weeks, demonstrating a significant reduction in the number of headache days (between 40% and 50%) (MOREIRA *et al.*, 2026). Gepants, initially developed for acute treatment, have emerged as a promising alternative for prevention as well, with drugs like rimegepant demonstrating efficacy in both episodic and chronic migraine (COLLINGS *et al.*, 2026).

Non-pharmacological approaches should be recommended to all patients, preferably as part of a multidisciplinary strategy. Regular aerobic physical activity has consistently been associated with reduced attack frequency and has been shown to potentiate the effects of pharmacological treatments (GARCIA *et al.*, 2024). The use of migraine diaries is a relevant clinical tool, allowing the identification of individual triggers, the monitoring of the frequency and intensity of attacks, and the evaluation of therapeutic response over time (PULEDDA *et al.*, 2024).

Non-invasive neuromodulation therapies have gained prominence as therapeutic alternatives, modulating cerebral electrical activity and regulating pain pathways. Among these techniques, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and occipital nerve stimulation stand out (PRADO *et al.*, 2025). Integrative practices, such as acupuncture, present moderate evidence of efficacy and are recommended by clinical guidelines, acting as important adjuvants in disease control (RAVI *et al.*, 2024).

The ideal therapeutic approach for migraine involves combining pharmacological and non-pharmacological interventions, individualizing

treatment according to the patient's clinical profile. This integrated strategy is critical to preventing disease progression, reducing functional impact, and significantly improving the quality of life of affected individuals (GARCIA *et al.*, 2024).

Therapeutic limitations and perspectives

Despite the therapeutic advances observed in recent decades and the expansion of pharmacological options for migraine management, several barriers still compromise adequate disease control and the achievement of satisfactory clinical outcomes in a significant proportion of patients (MOREIRA *et al.*, 2026).

One of the main limitations relates to the insufficient efficacy of acute treatments. Although triptans are considered the therapeutic standard for treating moderate to severe attacks, approximately one-third of patients do not show an adequate clinical response to this class of medications. Furthermore, only about 27% to 30% of treated individuals achieve complete pain freedom two hours post-administration, highlighting the need for more effective and individualized therapeutic alternatives (YANG *et al.*, 2021; COLLINGS *et al.*, 2026).

Another relevant challenge concerns the adverse effects of traditional preventive medications. Beta-blockers, antidepressants, and anti-convulsants incorporated into the prophylactic treatment of migraine bring undesirable systemic effects, including fatigue, weight gain, cognitive impairment, memory changes, and sexual dysfunction, factors that limit their acceptability and retention in treatment (FILGUEIRA *et al.*, 2023; FITZEK *et al.*, 2025).

Cardiovascular contraindications also represent a significant therapeutic restriction. Triptans and ergot derivatives exert their effects through mechanisms involving vasocon-

striction, making their use unsuitable for patients with a history of cardiovascular diseases (YANG *et al.*, 2021; PULEDDA *et al.*, 2024). Furthermore, frequent use of symptomatic medications can lead to the development of Medication-Overuse Headache (MOH), a condition characterized by pain chronification due to the repeated use of analgesics, anti-inflammatories, or triptans. This phenomenon creates a cycle of therapeutic dependence and progressive worsening of symptoms, making clinical management even more complex (GARCIA *et al.*, 2024; COLLINGS *et al.*, 2026).

Adherence to prophylactic therapy represents one of the greatest challenges in clinical practice. High dropout and treatment interruption rates are generally associated with perceptions of low clinical efficacy, delayed onset of therapeutic benefits, or intolerable adverse effects (YANG *et al.*, 2021). Additionally, it is estimated that approximately half of individuals with migraine use medications without proper professional guidance. The practice of self-medication can result in inadequate therapeutic regimens, delay accurate diagnosis, favor medication overuse, and increase the risk of disease chronification (GARCIA *et al.*, 2024; WHO, 2025).

Current trends indicate a transition toward increasingly specific therapeutic strategies, such as the use of gepants and ditans. Unlike triptans, these medications do not induce vasoconstriction, making them particularly relevant options for patients with cardiovascular contraindications (KARLSSON *et al.*, 2024; COLLINGS *et al.*, 2026).

The incorporation of Artificial Intelligence tools and precision-medicine approaches also emerges as one of the most promising areas for the future of migraine management. Predictive models capable of identifying individual pat-

terns of attack occurrence, combined with biomarker development and imaging-based diagnostic methods, such as retinal analysis, may enable earlier, personalized interventions (TANG *et al.*, 2015; BETTS *et al.*, 2025). Furthermore, the expected increase in the burden of migraine among men and adolescents by 2050 reinforces the need for new public policies, prevention programs, and research lines targeted at these specific groups, aiming to reduce the social, economic, and healthcare impact associated with the disease (DONG *et al.*, 2025; FITZEK *et al.*, 2025).

CONCLUSION

In summary, this review reaffirms that chronic migraine transcends the concept of a simple headache, establishing itself as a complex and highly disabling neurovascular disorder with a profound global socioeconomic impact. Advances in understanding its pathophysiology are a fundamental driver in moving past old vascular models and paving the way for modern medicine. Since the diagnosis remains strictly clinical and guided by ICHD-3 criteria, detailed mapping of attack phases and recognition of biological and environmental triggers

are mandatory steps for early and assertive intervention.

Regarding therapeutic management, while traditional prophylaxis encounters limitations in tolerability and treatment abandonment, biotechnology has consolidated disruptive advances, such as botulinum toxin type A and monoclonal antibodies. At the same time, abortive treatment gains new horizons with gepants and ditans, offering safe alternatives for patients with cardiovascular contraindications to triptans. However, several barriers persist in contemporary clinical practice, represented by high rates of self-medication and the imminent risk of MOH, as well as inequality in access to these innovative, high-cost therapies, especially in public health systems.

Finally, the outlook for the coming decades underscores the urgency of precision medicine, which can predict crises and personalize treatments before disease becomes chronic. Sustainable control of chronic migraine should not depend on a single approach, but on the synergistic integration of cutting-edge pharmacological therapies and multidisciplinary non-pharmacological strategies, such as neuromodulation and lifestyle regularity.

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