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Chronic Migraine: Pathophysiology, Clinical Presentation, Current Management, and Emerging Translational Therapies

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Abstract

Chronic migraine is a disabling neurological disorder defined by headache occurring on at least 15 days per month for more than 3 months, with migraine features on at least 8 days per month. It represents a dynamic disease state arising from the interaction of genetic susceptibility, trigeminovascular activation, cortical and brainstem hyperexcitability, neurogenic inflammation, central sensitization, and environmental or behavioral factors. Psychiatric comorbidity, sleep disturbance, obesity, medication overuse, and social stressors can further increase disease burden and complicate treatment. Diagnosis remains clinical and depends on careful application of the International Classification of Headache Disorders, 3rd edition (ICHD-3), while targeted investigations are reserved for patients with atypical features or red flags. Contemporary management combines acute treatment, preventive pharmacotherapy, behavioral and lifestyle interventions, and, when appropriate, neuromodulation. CGRP-targeted therapies have substantially expanded preventive options, although treatment response is heterogeneous and access, cost, long-term safety, and implementation remain important barriers. Emerging translational strategies, including advanced drug-delivery systems, nano-enabled therapeutics, and CRISPR-based approaches—are scientifically intriguing but remain largely preclinical or early translational in migraine. Their future clinical relevance will depend on demonstrating disease-relevant target engagement, reproducible delivery to appropriate tissues, acceptable toxicity, scalable manufacturing, and regulatory feasibility. This review synthesizes current understanding of chronic migraine, emphasizes limitations in the evidence base, and discusses the barriers that continue to separate mechanistic discoveries from durable clinical benefit.

Keywords: Chronic migraine; trigemini vascular system; central sensitization; calcitonin gene-related peptide; medication-overuse headache; preventive therapy; neuromodulation; nanomedicine; CRISPR; clinical translation

1. Introduction

Chronic migraine ranks among the most disabling primary headache disorders, taking a heavy toll on individuals, families, and healthcare systems worldwide (Ferrari et al., 2022). The condition is defined by

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frequent headaches occurring on at least 15 days per month, often accompanied by nausea, sensitivity to light and sound, sensory hypersensitivity, difficulty concentrating, and significant functional impairment (Eigenbrodt et al., 2021). The transition from occasional migraines to chronic daily headaches does not happen through any single pathway. Instead, it reflects a complicated dance between genetic vulnerability, changes in pain processing, repeated activation of pain pathways in the head, other health conditions, and environmental factors (Puledda et al., 2023; Ferrari et al., 2022).

Recent years have brought remarkable advances in migraine treatment, especially through the development of CGRP targeting monoclonal antibodies and gepants (American Headache Society, 2024; Özge et al., 2024). However, having effective treatments does not mean we have solved the problem. Many patients still do not receive adequate care (Blumenfeld et al., 2023). Real world results vary considerably, and we lack long term comparative data to guide treatment sequencing (Oliveira et al., 2024). Access to these new therapies remains uneven, with cost and insurance coverage creating significant barriers for many patients (American Headache Society, 2024). Additionally, many exciting molecular discoveries have not translated into practical treatments that meaningfully help patients, highlighting the persistent gap between mechanistic understanding and clinical application (Puledda et al., 2023).

This review explores the pathophysiology, diagnosis, clinical features, management, and future directions for chronic migraine. We pay particular attention to treatment limitations, safety concerns, implementation challenges, nanotechnology approaches, CRISPR based strategies, regulatory considerations, and the current state of clinical development. By synthesizing current evidence and identifying persistent knowledge gaps, we aim to provide a balanced perspective on what is established, what remains uncertain, and what lies on the horizon for this disabling condition (Eigenbrodt et al., 2021; Özge et al., 2024; Ferrari et al., 2022).

2. Diagnostic Criteria and Clinical Assessment

2.1 ICHD 3 Diagnostic Criteria

Doctors diagnose chronic migraine when a patient with a history of migraine has headaches on 15 or more days per month for over three months, with migraine features on at least eight of those days. This is a clinical diagnosis, meaning it relies on careful history taking and ruling out other possible explanations. Interestingly, not every headache day has to feel like a classic migraine. Some days might resemble tension type headaches, and the pattern can shift over time.

Keeping a structured headache diary can be incredibly helpful for tracking headache frequency, symptom patterns, medication use, disability, and treatment response. Because chronic migraine often overlaps with medication overuse headache, it is important to get a detailed medication history rather than just accepting the patient's impression that they do not use medications "too often" (Robbins, 2021; Headache Classification Committee, 2018).

2.2 Clinical Assessment and Red Flags

A thorough evaluation should explore when headaches started, how often they occur, how long they last, associated symptoms, triggers, disability, medications used, other health conditions, and neurological examination findings. For typical, stable cases with a normal neurological exam, brain imaging is not routinely necessary.

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Doctors should consider imaging or other tests when they suspect a secondary cause. This includes sudden or abrupt onset, progressive changes in headache pattern, signs of systemic illness, neurological deficits, papilledema, headaches triggered by position or exertion, or other concerning features.

The real diagnostic challenge is not simply recognizing migraine. It is identifying when a patient's headache pattern has changed, ruling out secondary causes, and distinguishing chronic migraine from overlapping conditions like medication overuse headache, new daily persistent headache, tension type headache, cluster headache, and other trigeminal autonomic cephalalgias (Eigenbrodt et al., 2021; Robbins, 2021).

3. Epidemiology, Risk Factors, and Comorbidity

Migraine is a leading cause of disability worldwide, with the heaviest burden often falling during people's most economically and socially productive years. Chronic migraine represents a particularly challenging subgroup, with greater headache frequency, disability, comorbidity, and treatment complexity than episodic migraine.

Several factors influence the risk of transitioning from episodic to chronic migraine. Some, like genetic susceptibility, cannot be changed. Migraine has a complex genetic architecture, and while genetics contribute to risk, they do not provide a simple prediction model for clinical use. More importantly, several potentially modifiable factors can increase risk. These include medication overuse, sleep problems, obesity, mental health conditions, stress, and inadequate treatment of the underlying migraine disorder.

Depression, anxiety, sleep disorders, and other chronic pain conditions frequently accompany chronic migraine. These comorbidities can amplify disability while complicating treatment decisions. Rather than pointing to a single shared mechanism in every patient, these associations support a biopsychosocial model where biological vulnerability and environmental context interact over time (Amiri et al., 2022; Yin et al., 2021).

4. Pathophysiology of Chronic Migraine

Chronic migraine is fundamentally a disorder of abnormal sensory processing rather than simply a vascular condition. The trigeminovascular system, which includes pain sensing nerves in the meninges and their connections to the brain, plays a central role in generating headache pain. When these pathways become activated, they release neuropeptides like CGRP and amplify pain signals.

Cortical spreading depression, a wave of neuronal depolarization, is strongly linked to migraine with aura and may help activate downstream pain pathways. However, the fact that many migraines occur without aura shows that cortical spreading depression is not required for every attack. This distinction matters because findings from aura models should not automatically be generalized to all chronic migraine cases.

Repeated pain pathway activation can produce peripheral and central sensitization. Essentially, the nervous system becomes increasingly responsive to pain signals. Clinically, this may show up as cutaneous allodynia, where normally non painful stimuli like touching the skin or brushing hair become painful, along with heightened sensory sensitivity. Brainstem and hypothalamic networks also contribute to attack

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timing and expression, including premonitory symptoms and changes in basic bodily regulation. Neuroimaging studies have identified functional and structural differences in several pain processing networks. However, establishing causality is challenging because most studies are cross sectional and may be confounded by illness duration, medication exposure, and other conditions (Gollion et al., 2022; Ferrari et al., 2022; Mínguez Olaondo et al., 2022).

Inflammatory and immune related mechanisms are increasingly studied, including interactions between neurons, glial cells, blood vessels, and meningeal immune cells. While biologically plausible, these findings need cautious interpretation. Detecting an inflammatory signal does not necessarily mean it is a therapeutically actionable driver of chronic migraine.

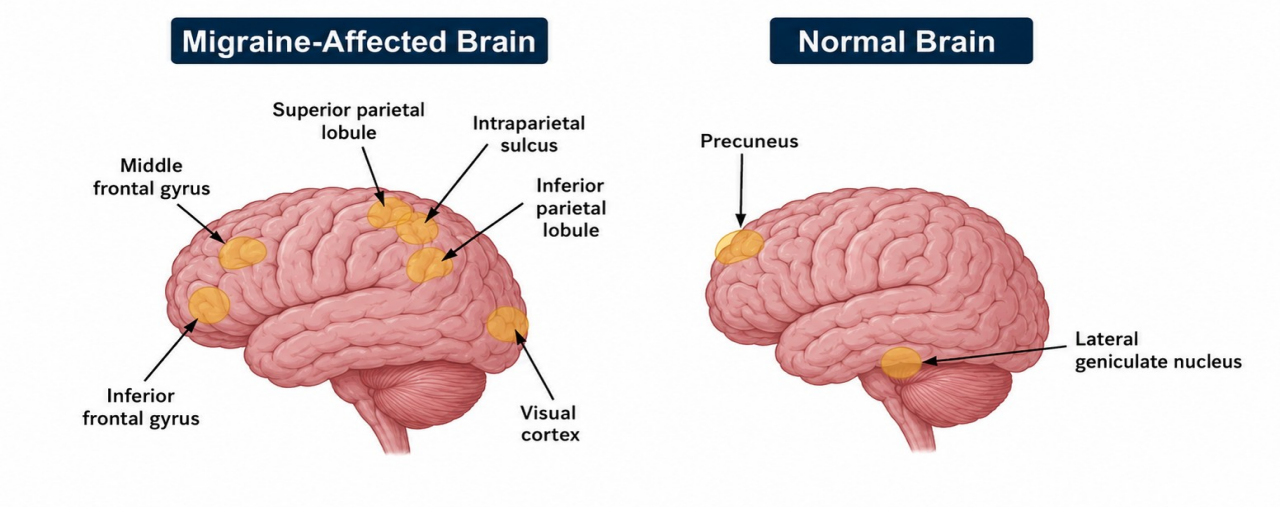


Figure 1: The Complexity of Medication Overuse

Medication overuse can reinforce headache frequency and complicate treatment response interpretation. However, this relationship is not simply linear. Medication overuse may be both a cause and a consequence of severe, poorly controlled migraine. This bidirectional relationship has important clinical implications, as withdrawal strategies and preventive treatment often need to be individualized (Diener et al., 2022; Koonalintip et al., 2024).

5. Clinical Presentation and Associated Symptoms

Chronic migraine typically presents with frequent moderate to severe headache, though the experience can vary substantially between patients and even from day to day. Pain may be one sided or both sided, pulsating or pressure like. Many people experience nausea, vomiting, sensitivity to light, sound, and smells, and sensitivity to movement.

Cutaneous allodynia, where things that should not hurt like wearing glasses or touching your scalp become painful, can be particularly disabling. Cognitive symptoms like trouble concentrating or "brain fog" are also common and can significantly impact daily functioning.

Many patients experience premonitory symptoms before the headache starts. These can include fatigue, mood changes, difficulty concentrating, changes in appetite, or altered urination patterns. Aura occurs in

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some patients and typically involves fully reversible neurological symptoms that develop gradually and resolve within the expected timeframe.

Clinical burden is determined not just by headache frequency but by cumulative disability, sleep disruption, mental health conditions, medication use, work demands, and access to care. For this reason, treatment success should ideally be measured not only by headache day reduction but also by patient centered outcomes like function, quality of life, and treatment satisfaction (Fernandes et al., 2024; Eigenbrodt et al., 2021).

6. Differential Diagnosis and Diagnostic Work up

The differential diagnosis includes medication overuse headache, tension type headache, new daily persistent headache, cluster headache and other trigeminal autonomic cephalalgias, cervicogenic headache, idiopathic intracranial hypertension, vascular disorders, inflammatory disease, infection, and intracranial structural problems. The workup should be guided by the clinical presentation rather than by ordering tests indiscriminately.

A major limitation in current diagnosis is the lack of validated, widely available biomarkers that can independently establish chronic migraine or predict treatment response. While molecular, imaging, and digital biomarkers show promise, most have not been sufficiently validated for routine clinical use (Robbins, 2021; Eigenbrodt et al., 2021).

7. Current Management

7.1 Acute Treatment

Acute treatment aims to restore function, reduce pain and associated symptoms, and minimize medication overuse. Treatment selection should consider attack severity, presence of nausea or vomiting, other health conditions, contraindications, prior response, and patient preference. Non steroidal anti-inflammatory drugs, acetaminophen where appropriate, triptans, gepants, and selected antiemetics may all be used according to clinical context and current guidelines.

The main limitation of acute treatment is that frequent use can contribute to medication overuse headache. Therefore, acute therapy should be integrated with a preventive strategy when headache frequency or disability is high (Clemow et al., 2020; Blumenfeld et al., 2023).

7.2 Preventive Treatment

Preventive therapy should be individualized based on headache frequency, disability, other health conditions, prior treatment response, tolerability, reproductive considerations, access, and patient preference. Traditional options include topiramate and several other preventive agents, while onabotulinumtoxinA and CGRP targeted therapies have become important options specifically for chronic migraine.

CGRP targeted monoclonal antibodies and gepants represent a major therapeutic advance. They were developed based on understanding of migraine biology and often have better tolerability than some older preventive drugs. However, treatment response varies considerably, and the evidence base still has limitations regarding long term comparative effectiveness, treatment sequencing, discontinuation

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strategies, cost, access, and representation of medically complex populations (Oliveira et al., 2024; American Headache Society, 2024).

OnabotulinumtoxinA remains an established preventive option for chronic migraine and may be particularly useful in patients who prefer injection-based treatment or have not responded adequately to oral therapies. Real world data are valuable, but observational studies remain vulnerable to selection bias, treatment persistence bias, and confounding by indication (Blumenfeld et al., 2023; Szok et al., 2023).

7.3 Behavioral, Lifestyle, and Neuromodulation Strategies

Behavioral interventions, regular sleep, physical activity, stress management, and treatment of other health conditions should be considered core components of comprehensive care rather than optional add ons. Their effects may be difficult to quantify using headache frequency alone, but they can improve coping, function, and treatment adherence.

Neuromodulation is an expanding field with varying evidence quality among different devices and stimulation approaches. Patient selection, treatment parameters, adherence, and comparative effectiveness remain important unknowns. Recent evidence syntheses support a role for selected neuromodulation approaches but also emphasize the need for higher quality trials and clearer implementation pathways (Tana et al., 2025; Szok et al., 2023).

8. Emerging Translational Therapies and Advanced Delivery Platforms

8.1 Nano enabled Drug Delivery

Nanotechnology based drug delivery offers a potentially useful platform for improving solubility, stability, tissue distribution, and controlled release of therapeutic molecules. In migraine, its most plausible near term application is not as a standalone treatment but as a delivery strategy for molecules whose pharmacokinetics, tolerability, or tissue exposure could be improved. Possible approaches include lipid nanoparticles, polymeric nanoparticles, nanostructured lipid carriers, and other engineered systems designed to alter absorption or distribution.

For chronic migraine, the translational rationale is strongest where delivery limitations are clearly defined. Examples include poor oral bioavailability, rapid metabolism, inadequate exposure, or need for targeted delivery. However, claims of brain targeting should be treated cautiously. Crossing the blood brain barrier is not the same as achieving meaningful, cell specific delivery. Nanoparticle biodistribution, protein corona formation, immune activation, organ accumulation, and long term clearance all require rigorous evaluation (Wattiez et al., 2020; Puledda et al., 2023).

8.2 CRISPR and Gene Editing Delivery Systems

CRISPR based technologies may contribute to migraine research by enabling functional investigation of disease associated genes and regulatory pathways. Genetic studies have identified numerous migraine associated loci, but translating association signals into causal mechanisms remains a major challenge. CRISPR interference, CRISPR activation, base editing, and prime editing could help define the biological function of candidate genes in relevant neuronal, glial, vascular, or meningeal systems.

The main translational barrier is delivery. Viral vectors can provide efficient gene transfer but may introduce immunogenicity, cargo constraints, manufacturing complexity, and concerns about persistence.

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Non viral systems, including lipid nanoparticles and other nanocarriers, offer potentially flexible delivery but still face challenges related to tissue specificity, endosomal escape, dose control, and off target exposure. For migraine, the target cell populations and anatomical compartments requiring modification are not yet sufficiently defined to support clinical gene editing.

At present, CRISPR should be regarded primarily as a research and target validation platform in migraine rather than a clinical therapy. Any future therapeutic application would require strong evidence of target causality, a favorable risk benefit profile, precise delivery, durable but controllable effects, and extensive long term safety monitoring (Kampmann, 2020; Miao et al., 2026).

8.3 Toxicity and Safety Considerations

Toxicity is a central translational issue for advanced therapeutics. For nanoparticles, relevant concerns include acute innate immune activation, complement activation, oxidative stress, organ accumulation, neuroinflammation, and unpredictable interactions with biological barriers. For gene editing systems, risks include off target editing, unintended genomic alterations, immune responses to delivery components or editing proteins, and the possibility of effects that are difficult to reverse.

The safety standard for chronic migraine is particularly demanding because the disease is disabling but not usually immediately life threatening. A therapy with irreversible or poorly characterized risks would require a substantially higher evidentiary threshold than a therapy used for a rapidly fatal disease. Long term follow up and transparent reporting of adverse events are essential (Miao et al., 2026; Kampmann, 2020).

8.4 Regulatory and Manufacturing Considerations

Regulatory approval of advanced therapies requires more than demonstration of biological activity. Product identity, purity, potency, batch to batch consistency, stability, delivery characteristics, and manufacturing controls must be defined. For combination products, regulators may need to evaluate both the therapeutic payload and the delivery system. Gene editing products also raise additional questions regarding off target assessment, vector shedding where applicable, immunogenicity, persistence, and long term surveillance.

A recurrent translational barrier is the gap between laboratory formulations and scalable clinical manufacturing. A formulation that performs well in a small animal study may be difficult to produce consistently at clinical scale. Regulatory uncertainty, high development costs, specialized manufacturing infrastructure, and the need for long term follow up can further slow clinical adoption (Puledda et al., 2023; Miao et al., 2026).

8.5 Clinical Trial Progress and Translational Gaps

Clinical development in migraine is currently most advanced for CGRP targeted therapies, gepants, neuromodulation, and selected non CGRP targets. By contrast, nano enabled and CRISPR based interventions remain substantially earlier in the translational pathway. Their clinical progress should not be overstated based on preclinical proof of concept studies or advances in other neurological diseases.

Future trials should prioritize clinically meaningful outcomes, including sustained reduction in monthly migraine days, disability, quality of life, acute medication use, and patient defined treatment success. Trials should also improve representation of patients with medication overuse headache, psychiatric

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comorbidity, obesity, cardiovascular disease, older age, and diverse socioeconomic backgrounds. Longer follow up and pragmatic real world evidence will be necessary to establish durability, safety, adherence, and cost effectiveness (Oliveira et al., 2024; Szok et al., 2023; Blumenfeld et al., 2023).

9. Critical Limitations and Challenges in the Current Evidence Base

Several limitations constrain interpretation of the chronic migraine literature. First, diagnostic heterogeneity and variable definitions of treatment response complicate comparisons across studies. Second, randomized trials often exclude patients with substantial comorbidity or medication overuse, limiting generalizability. Third, short follow up periods may underestimate delayed adverse effects or fail to capture durability of benefit.

Fourth, real world treatment effectiveness is influenced by access, adherence, insurance coverage, clinician expertise, and patient preference. These factors are often underrepresented in efficacy trials. Fifth, mechanistic biomarkers have not yet achieved sufficient validation for routine treatment selection. Finally, emerging technologies may appear promising because of strong mechanistic rationale while still lacking evidence of meaningful patient benefit.

A clinically useful translational framework should require convergence of mechanistic plausibility, reproducible preclinical efficacy, validated biomarkers or target engagement, scalable manufacturing, acceptable safety, and patient centered clinical benefit. Without this convergence, technological novelty should not be confused with therapeutic progress (Puledda et al., 2023; Ferrari et al., 2022; Özge et al., 2024).

10. Future Directions

Progress in chronic migraine is likely to depend on better patient stratification and integration of multiple data types, including clinical phenotyping, genetics, neuroimaging, digital monitoring, and treatment response data. The goal should not be to replace clinical judgment with a single biomarker, but to improve prediction of disease trajectory and treatment response.

The most credible near term advances are likely to come from optimizing existing mechanism based treatments, improving combination strategies, expanding access, and developing validated neuromodulation approaches and non CGRP targets. Nano enabled delivery and CRISPR based technologies may become important longer term platforms, but their development should be guided by clear disease biology and rigorous safety standards rather than technological enthusiasm alone (Grangeon et al., 2023; Ferrari et al., 2022).

11. Conclusion

Chronic migraine is a heterogeneous neurological disorder driven by interacting biological, behavioral, and environmental factors. Diagnosis remains clinical, and management is most effective when preventive therapy, acute treatment, behavioral strategies, comorbidity management, and patient preferences are considered together. CGRP directed therapies and other targeted approaches have expanded treatment

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options, but important gaps remain in long term evidence, access, treatment personalization, and implementation.

Emerging platforms like nanomedicine and CRISPR may eventually improve target validation or therapeutic delivery, but they remain investigational in migraine and face substantial barriers related to delivery, toxicity, manufacturing, regulation, and clinical proof of benefit. The central challenge for the field is therefore not simply discovering new molecular targets, but converting biological insight into safe, durable, accessible, and clinically meaningful improvements for patients with chronic migraine (American Headache Society, 2024; Ferrari et al., 2022; Puledda et al., 2023).

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