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MIGRAINE TREATMENT BEYOND TRADITIONAL THERAPIES: CURRENT TRENDS AND FUTURE DIRECTIONS

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ABSTRACT

Migraine is a highly prevalent neurological disease associated with considerable personal, social, and economic burden. The disease represents a major contributor to disability and reduced quality of life. Over the years migraine pharmacotherapy has evolved from non-specific vasoconstrictive agents such as ergot alkaloids to mechanism-based therapies targeting serotonin and CGRP pathways, including triptans, gepants, ditans, and monoclonal antibodies. This review analyzes modern treatment approaches on migraine and evaluates their clinical relevance.

KEYWORDS

Migraine Treatment, CGRP-Targeted Therapies, CGRP Monoclonal Antibodies, Gepants, Lasmiditan, Neuromodulation and Nerve Blocks, PACAP-Targeted Therapies

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1. Introduction

Migraine is a common neurological condition that places a significant burden on healthcare resources and costs. Usually asocciated with symptoms such as a severe throbbing head pain of the one side of the head with vomiting, nausea and hypersensitivity to light and sound, it is recognized as one of the most widespread disorders and a major cause of disability worldwide [1]. In recent years, extensive research has been dedicated to developing new treatments for both acute and chronic migraine management. Scientists are focused on exploring non-pharmacological interventions, investigating lifestyle factors that affect the severity of the condition, and creating predictive models for migraine attacks. New targeted therapies may also play a key role in improving efficiency in management outcomes [2].

Pathophysiology of migraine is complex and multifactorial. It is associated with a complex interaction between genetic predisposition, behavioral factors, and environmental influences that disrupt normal sensory processing in the brain. Individuals with migraine develop increased sensory sensitivity. As a result ordinary sensory inputs are percieved as unpleasant or overwhelming [3,4].

2. Methodology

The present review was conducted through a narrative search of PubMed and Google Scholar databases. Publications related to new developments in migraine management from 2020–2025 were considered.

3. Early development of migraine pharmacological treatment - historical outline

Pharmacological treatment has developed significantly over time. In the 19th century early therapies included ergot alkaloids such as ergotamine and dihydroergotamine, later combined with caffeine. Although effective, these drugs acted on multiple receptor systems and were associated with numerous adverse effects, including gastrointestinal, cardiovascular, and neurological complications [1,5]. The discovery of their action on serotonin 5-HT1B and 5-HT1D receptors led to the development of triptans, which became the standard treatment for acute migraine. Triptans reduce migraine symptoms through cranial vasoconstriction and inhibition of trigeminovascular activation. However, their vasoconstrictive properties limit their use in patients with cardiovascular disease. Vast group of patients also experiences incomplete relief or recurrence of symptoms [5,6]. The identification of calcitonin gene-related peptide (CGRP) as a key factor in the complex pathophysiology of migraine has significantly advanced the development of novel therapeutic strategies for both acute and preventive treatment. This discovery contributed to the introduction of small-molecule CGRP

receptor antagonists, known as gepants, as well as monoclonal antibodies targeting either CGRP itself or its receptor [7,8,9]. More recently, therapies such as lasmiditan, a selective 5-HT1F receptor agonist without vasoconstrictive effects, have been introduced. Preventive migraine treatment has also evolved from traditional medications, including antiepileptics, antidepressants, and beta-blockers, to targeted therapies such as onabotulinumtoxin A [1,3].

4. Modern trends in migrane therapy

Migraine treatment commonly begins with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, and triptans. However, the effectiveness of these therapies may be limited by insufficient symptom control, side effects, and contraindications in individual groups, including pregnant and breastfeeding women [6].

4.1. CGRP-targeted therapies

Calcitonin gene-related peptide (CGRP) is a neurotransmitter that plays a key role in the development of migraine. In a migraine attack CGRP concentrations rise causing blood vessels dilation, inflammatory processes activation and pain transmission within the trigeminovascular pathway. CGRP-targeted therapies were designed to suppress this mechanism and decrease migraine activity. Drugs targeting the CGRP pathway can be classified into two major groups: monoclonal antibodies and gepants [7,8,9].

4.2. CGRP monoclonal antibodies

The mechanism of action of these drugs is based on blocking calcitonin gene-related peptide (CGRP) or its receptor, which play a crutial role in migraine pathophysiology. Currently there are four available CGRP monoclonal antibodies. Erenumab, Fremanezumab and Galcanezumab block the CGRP receptor. Eptinezumab binds directly to the CGRP ligand [10]. The administeration of drugs is executed by subcutaneous or intravenous injection, once

a month or every three months. Among patients with inadequate response to traditional preventive medications treatment they are used for the prevention of episodic and chronic migraine with very convincing outcomes [11]. Use of CGRP monoclonal antibodies has proven effectivness in lowering the number of monthly migraine days, following reduction the need for acute migraine medications and improvement of daily functioning and quality of life [12]. Frequently reported side effects include reactions at the injection site, fatigue, constipation and mild allergic reactions. While long-term research is still in progress, available evidence suggests that these therapies are generally safe and well tolerated [13,14].

4.3. Gepants

Gepants function as CGRP receptor antagonists, they act directly at the receptor level to inhibit the activity of CGRP what is benefitial in both acute migraine attacks as and preventive migraine therapy [15]. In contrast to triptans, gepants do not constrict blood vessels, which makes them a safer option for many patients with cardiovascular conditions, although inhibition of CGRP may still negatively affect ischemic disorders or blood pressure regulation [16]. Three generations of gepants have been developed. First generation has limited clinical use due to poor absorption and significant liver toxicity. Second generation demonstrated better effectiveness and improved safety profiles without major hepatotoxic effects. Among group representatives Rimegepant is additionally approved for both migraine prevention and acute treatment. Third-generation was designed to provide non-oral treatment options, for patients with severe nausea or vomiting. Zavegepant was approved in the USA in 2023 as a nasal spray for the acute treatment of migraine. This method of drug administration avoids limitations related to gastrointestinal absorption and first-pass liver metabolism. Hence may contribute to reducing of gastrointestinal side effects [17,18]. Currently there are four available gepants on the market: Rimegepant, Ubrogepant, Zavegepant and Atogepant. Advances in their chemical structure over time have improved drug stability, absorption, and overall safety, making gepants play a significant role in modern-day migraine management [19].

4.4. Combination therapy

A modern approach to migraine treatment is also based on combining different forms of the therapy. The study of evaluation of the long-term efficacy and safety of bridging CGRP mAbs with gepants to manage the wearing-off phenomenon of mAbs has shown very promising results. Significant decrease in headache severity has occured among 41.54 % patients. [20]

4.5. Ditans

Ditans represent a novel class of drugs in acute migrane management, especially among patients with increased cardiovascular risk, who have contraindications to triptans treatment. The mechanism of action of these drugs involves selectively activating 5-HT1F receptors, resulting in inhibition of nociceptive transmission and suppression of the release of proinflammatory neuropeptides without causing vasoconstriction effect [21]. Lasmiditan is the only currently approved ditan indicated for the acute treatment of migraine attacks. The medicament is administrated orally and it is characterized by low risk of drug interactions. In the third phase of clinical trials have been conducted two pivotal double-blinded, placebo controlled, randomized studies SAMURAI and SPARTAN. Both showed significant relief from migraine pain and associated symptoms (including nausea, phonophobia and photophobia) in individuals treated with lasmiditan. However use of this drug is limited by central nervous system side effects (such as fatigue, paresthesia, dizziness, and sedation), which result from the ability to cross the blood–brain barrier. Ongoing research continues to investigate new selective 5-HT1F receptor agonists with their potential influence in migraine management [22].

4.6. Neuromodulation and nerve blocks

Interventional techniques have been constantly developed since the 1960 s. They use have significant impact particularly among individuals with chronic migraine, refractory migraine, or insufficient response to pharmacological treatment. One of the most widely used interventional strategies is peripheral nerve blockade, especially greater occipital nerve block. This procedure involves the injection of local anesthetics, often combined with corticosteroids, around the greater occipital nerve to reduce nociceptive transmission within the trigeminocervical complex. Greater occipital nerve blocks have been shown to effectively decrease the frequency, severity, and duration of migraine attacks, particularly in patients with chronic migraine. Evidence indicates that ultrasound guidance allows for more accurate identification of the targeted nerve structures, which may improve both the precision and safety of interventional procedure [23]. Sphenopalatine ganglion blockade represents another interventional approach used in selected patients with migraine. Administration of local anesthetics via intranasal or other minimally invasive techniques may offer short-term migraine relief and has demonstrated potential efficacy in patients with refractory headache conditions. Another therapeutic strategy used in migraine treatment is Onabotulinumtoxin A, commonly known as botulinum toxin type A. This therapy is approved for chronic migraine prophylaxis and is administered following the PREEMPT protocol, which consists of repeated injections into designated muscles of the head and neck every 12 weeks. Its mechanism of action is linked to the suppression of neurotransmitters and neuropeptides involved in pain signaling. Clinical studies have shown that this therapy significantly decreases the number of monthly headache days and improves quality of life in patients with chronic migraine [24].

4.7. PACAP-targeted therapies

Pituitary adenylate cyclase-activating polypeptide (PACAP)-targeted therapies might offer

a potential new avenue for migraine management. This agent is a neuropeptide widely distributed in the central and peripheral nervous systems and has been implicated in the pathophysiology of migraine due to its role in vasodilation, nociceptive transmission, and neurogenic inflammation. Elevated levels of PACAP have been observed during migraine attacks and experimental studies have shown that PACAP administration can induce migraine-like headaches in susceptible individuals. Therapeutic strategies involve monoclonal antibodies directed either against the PACAP ligand itself or its receptor. Inhibition of PACAP signaling should reduce trigeminovascular activation and prevent the cascade of events associated with migraine generation. Several investigational agents are currently undergoing clinical evaluation. Early studies suggest potential efficacy in reducing migraine frequency and severity. However further research is necessary to evaluate the efficacy of this migraine therapy [25].

5. Discussion

Recent advances in migraine treatment have focused primarily on CGRP-targeted therapies, including monoclonal antibodies and gepants, which have significantly improved both acute and preventive management strategies [26,27]. Ditans represent an important advancement in migraine pharmacotherapy by providing effective acute treatment reducing the cardiovascular risks associated with traditional vasoconstrictive agents such as triptans [28]. Interventional techniques represent an important component of multidisciplinary migraine management. They are particularly valuable in patients with chronic or treatment-resistant migraine, offering alternatives to conventional pharmacotherapy while potentially reducing medication burden and improving patient quality of life [29]. Although PACAP-targeted therapies are still under development, they are considered promising alternatives for patients who do not respond adequately to existing preventive treatments, including CGRP-targeted therapies. Further clinical trials are required to establish their long-term safety, efficacy, and role in migraine management. Individualizing therapies among patients should become a stanadard in a modern migrane therapy. New therapies present better effectivness and less treatments side effects. Despite these advances, there still remain a vast space for the ongoing research for safer and more effective migraine therapies [30].

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