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# A REVIEW ON PHARMACOTHERAPEUTIC APPROACHES IN MIGRAINE MANAGEMENT

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## ABSTRACT

Migraine is one of the most frequent forms of primary headache disorder with the worldwide prevalence ranging between 10% and 15% of population and the disorder ranking among the main causes of years lived with disability [(1,13).] It is characterized by the trigeminovascular system activation, release of vasoactive neuropeptides, predominantly calcitonin gene-related peptide (CGRP), and disturbance in central pain modulation [(4,5).] Migraine treatment involves both acute and preventive approaches and consists of pharmacological and non-pharmacological treatments such as analgesics, NSAIDs, triptans, ditans, ergots, novel CGRP-targeting monoclonal antibodies and gepants, nutraceuticals, behavioral therapy, acupuncture, and neuromodulation [(6).] Current real-world evidence shows that triptans and NSAIDs are still the main prescribed acute treatments for the disorder, whereas non-pharmacological treatments remain underutilized in comparison with the available evidence base [(2).] Besides, migraine is accompanied with various comorbidities including depression, anxiety, stroke, epilepsy, and obesity, which makes the treatment of the disorder complicated due to the need for therapeutic independence rather than combination therapy [(3).] This paper provides the summary of the current literature on pharmacological and non-pharmacological treatment of the migraine and describes the novel therapeutic approaches for the disease based on the CGRP and PACAP targeting.

**KEYWORDS:** Migraine; Cgrp; Triptans; Gepants; Monoclonal Antibodies; Neuromodulation; Pain Management; Comorbidity.

## 1. INTRODUCTION

Migraine is a chronic neurological condition which manifests in frequent unilateral headaches, nausea, photophobia and phonophobia lasting for 4 to 72 hours if left untreated [(1).] The WHO has

listed migraine among the top twenty most disabling conditions throughout lifetime, and according to various Global Burden of Disease studies, migraine is among the main causes of years lived with disability especially among working-age adults [9,13]. The prevalence rate of the disease is estimated between 10% and 29%, and in addition, there is clear female predominance of the disease by the factor of two to three, which appears after puberty [1]. In the USA, the prevalence of the disease is estimated as 18% among women and 6% among men [2].

Despite the high prevalence rate of the disease, migraine remains underdiagnosed and undertreated, because less than half of the population suffering from the disorder has been diagnosed, and there is great discrepancy between the number of headache specialists and patients [2]. This state of affairs leads to the wide-spread practice of self-management of the disease symptoms and medication intake without prescription, as well as the popularity of complementary treatment [2,6]. This paper aims at providing the review of the existing literature on the pathophysiology of the migraine and critical summary of the evidence on the acute and preventive pharmacologic treatment, non-pharmacological management, and comorbidity-based treatment of the migraine based on the results of systematic reviews, randomized controlled trials and clinical guidelines.

## 2. Epidemiology and Burden

Prevalence rate of migraine varies depending on age, gender, and geography, but in population surveys, increasing prevalence in adolescents, peak prevalence between the third and fourth decades of life, and subsequent decrease after menopause has been established [3,11]. On average, each migraineur experiences 13 attacks per year; however, the number of attacks may vary, ranging from occasional attacks up to chronic migraine, which is the occurrence of the headache lasting for 15 or more days per month for at least three months, during which migraine attacks occur on eight days or more [1,14]. Based on the results of Global Burden of Disease Study 2016, migraine and tension-type headaches occupy the third and second places, respectively, in the list of the most prevalent disorders, and migraine is among the main causes of disability among the people younger than Impact of migraines on 50 [9,10]people is tremendous in terms of financial and psychosocial aspect. Families with the patients experiencing migraines have 70% more healthcare costs in comparison with unaffected families, this disorder is characterized with decreased work productivity, absenteeism and reduced quality of life [2,12]. Patients with chronic migraines suffer from higher disability, depression and anxiety levels as well as from lower family incomes in comparison with episodic patients in the AMPP study [12].

## 3. Pathophysiology

Three overlapping hypotheses existed to explain pathophysiology of migraines – vascular, platelet and CNS. According to the vascular theory, proposed by Wolff in 1938, aura was caused by intracranial vasoconstriction followed by extracranial vasodilatation. In the platelet hypothesis abnormal platelet

aggregation and serotonin release were supposed to cause migraines, and CNS theory assumed changes in cortical excitability and subsequent vasomotor changes [1]. However, modern scientists tend to consider trigeminovascular system as an anatomical substrate for migraines [5,7].

Trigeminal ganglion afferents innervate meningeal blood vessels and make connections with second-order neurons in the trigeminocervical complex, at the same time projecting to the thalamus and the cortex through the quintothalamic pathway. The descending modulatory system originates from the periaqueductal grey, rostral ventromedial medulla, hypothalamus and locus coeruleus [5]. Descending system releases vasodilator neuropeptides such as CGRP, substance P, neurokinin A and PACAP, which provoke vasodilation, neurogenic ("sterile") inflammation and sensitization of trigeminal nociceptors [1,4,5]. CGRP being a primary mediator, it became a target for development of monoclonal antibodies and gepants described in section 5 [4,18,19].

FHM genetic studies proved the mutations in CACNA1A and SCN1A genes encoding calcium and sodium channels respectively, which proves the role of changes in neuronal excitability in the susceptibility to migraines [1]. Meningeal mast cells, which are located near trigeminal nerve endings, are considered as participants in positive feedback loop because histamine release provokes activation of nociceptors, which further provokes degranulation of mast cells and increased neurogenic inflammation [4]. Sensitization may be both peripheral and central and manifests as cutaneous allodynia. Delay in treatment results in reduction of treatment response [5].

**4. Classification and Diagnosis**

According to the classification of International Classification of Headache Disorders (ICHD), migraines without aura are different from migraines with aura and consist of several subtypes including familial and sporadic hemiplegic migraines, chronic migraine and probable migraine [1,8]. Migraine without aura, also known as common migraine, should occur more than five times with each attack lasts between 4 and 72 hours, having at least two out of four features such as unilateral localization, pulsating character, moderate-to-severe pain intensity, aggravation with routine physical activity, nausea/vomiting or photophobia and phonophobia [1]. Migraine with aura implies the presence of additional criteria of reversible visual, sensory or speech disturbance, developing within 5-60 minutes before or during the headache [1].

The clinical basis of migraines' diagnosis is defined by the frequency of attacks and accompanying symptoms, while neuroimaging and laboratory investigations are performed only to exclude secondary factors [1]. It is crucial to differentiate between migraine and tension-type headache, cluster headache, and medication-overuse headache (MOH) because of the different treatment strategies for the above conditions [1, 23].

## 5. Pharmacological Management

### 5.1 Acute (Abortive) Treatment

Acute therapy of migraines consists of the provision of rapid and prolonged pain relief, prevention, restoration of the patients' ability to conduct daily activities, and minimizing adverse effects [4, 5]. In accordance with the DISC study data, the strategy is stratified and not step-wise [5].

Simple analgesics and nonsteroidal anti-inflammatory agents (NSAIDs) are used as the first-line drugs in mild to moderate attacks. Drugs like ibuprofen, naproxen, diclofenac potassium, and aspirin provide a therapeutic gain of approximately 8-14% in pain relief for 2 hours after administration compared to placebo, having as their mechanism of action the blockage of neurogenic inflammation by inhibition of cyclooxygenase [4, 5]. Paracetamol (acetaminophen) is less effective but can be utilized in patients sensitive to NSAIDs [4].

Selective 5-HT1B/1D receptor agonists-triptans are second-line medications, and they can affect peripheral processes (vasoconstriction, neuropeptide release inhibition) and central (nociceptive transmission inhibition in trigeminal nucleus caudalis) processes [5]. The minimum number needed to treat is in subcutaneous sumatriptan 6 mg providing the greatest therapeutic gain in pain relief at 2 hours (44%) compared to others among triptans, while the maximum pain-free rate among oral triptans is provided by rizatriptan and eletriptan [4, 5]. Therapy with a combination of sumatriptan and naproxen sodium is more effective compared to monotherapy [4]. Triptans are contraindicated in patients with cardiovascular and cerebrovascular disorders, uncontrolled hypertension, and hemiplegic and brainstem-aura migraines due to triptans' effect of vasoconstriction [5].

Ditans, 5-HT1F receptors agonists without vasoconstriction effect, and gepants, small molecule CGRP-receptor antagonists, are third-line medications for acute therapy in patients contraindicated for triptans' use because of vascular pathology [4]. Though, the therapeutic gain of the above agents is usually smaller compared to triptans, the use of gepants does not lead to MOH in animal models [4].

Antiemetics (metoclopramide and domperidone) are the drugs belonging to the group which is often prescribed in order to relieve nausea; however, these medications increase the absorption of oral analgesics in the stomach [2,5,28]. Ergot alkaloids, opioids, and barbiturates are not recommended as first-line prophylactic drugs because of the undesirable side effects and the possibility of becoming addicted, which leads to medication-overuse headache [5,23,28].

### 5.2 Preventive Treatment

It is necessary to start the prevention when a patient has frequent and strong attacks (more than 4 migraine days in a month); it is recommended to decrease their frequency or severity up to 50% [4]. The first-line preventive drugs are beta-blockers (propranolol, metoprolol), anticonvulsant (topiramate), and angiotensin II receptor blocker (candesartan); the second line consists of amitriptyline, flunarizine, and sodium valproate (the last one is contraindicated for women of reproductive age) [3,4]. The use of onabotulinumtoxin A proved to be effective in case of chronic

migraine, as it was demonstrated during the clinical trials within the framework of the PREEMPT study [4].

The main breakthrough in the area of preventive pharmacotherapy during the recent years is the development of the drugs affecting the CGRP pathway. The monoclonal antibodies targeting CGRP (fremanezumab, galcanezumab, eptinezumab) and its receptor (erenumab) demonstrated their efficacy in case of both episodic and chronic migraine, including patients who did not respond to other preventive treatment, and these drugs became the first-line preventive ones according to certain guidelines [4]. According to the data from the head-to-head study (HER-MES trial), erenumab demonstrates better tolerance and the biggest percentage of patients with more than 50% reduction of monthly migraine days in comparison with topiramate [4]. There are some orally administrated gepants (rimegepant, atogepant) which have already been approved for preventive purpose; in addition, atogepant was proved to be efficacious in case of patients' prevention failure in the ELEVATE trial [4].

As far as the currently studied targets are concerned, it is possible to mention the following: the monoclonal antibodies to PACAP (Lu AG09222, LY3451838), the histamine receptor modulators (AGX-201), oxytocin agonists, neurosteroid modulators (sepranolone in case of menstrual migraine), ketogenic agents (tricaprilin), the cannabinoid-based therapy, and the new formulations of botulinum toxin [4].

**6. Comorbidities and Special Populations**

Migraine can be combined with some comorbidities: depression, anxiety, stroke, epilepsy, obesity, and gastrointestinal diseases [3]. There is a possibility that the relation between migraine and any of these diseases is bidirectional or unidirectional; therefore, the monotherapy ("two-for-one" strategy) is dangerous as far as under-treatment of both conditions is concerned. For that reason, the therapeutic-independence strategy is preferable nowadays [3].

Specifically, an independent synergic association between migraine with aura in women younger than 45 years old and stroke risk exists, being significantly amplified by the concomitant presence of smoking and oral contraception use [3]. Obesity is not associated with episodic migraines but is a risk factor for development of chronic daily headaches. Bidirectional connection between epilepsy and migraines can be attributed to both genetic and injury-based common factors [3]. Changes in hormonal levels during menstrual periods, pregnancy, and perimenopause play a role in migraine frequency and should be considered while developing treatment strategy regarding peri-menstrual prophylaxis, medications safe during pregnancy such as acetaminophen and triptans during later pregnancy trimesters [3,5].

**7. Non-Pharmacological Management**

Non-pharmacologic therapies can be used as alternative treatment or treatment in case of contraindication to pharmacological therapies, drug overuse, or preference to low-risk treatment [6].

Several major classes of non-pharmacologic therapies exist: nutraceuticals, behavioral therapy, acupuncture, and neuromodulation.

### 7.1 Nutraceuticals

High dose riboflavin (400 mg/day), coenzyme Q10, magnesium, butterbur root extract, and feverfew were tested in RCTs as preventive treatment for migraine having heterogeneous and modest evidence base [6]. Riboflavin and magnesium are considered safe and cheap medications, and can be used in patients with concomitant diseases or tolerance issues, while butterbur is used rarely because of the potential to cause liver toxicity although it is efficacious [6].

### 7.2 Behavioural Therapy and Acupuncture

CBT, relaxation techniques, and biofeedback are based on the hypothesis of the effect of stress and maladaptive behavior on development of migraine and were proven by several RCTs, and it is considered an adjuvant therapy to pharmacological treatment including pediatrics' chronic migraines [1,6]. Effectiveness of acupuncture was proven by several large RCTs, although the difference between verum and sham acupuncture was insignificant, which speaks for its non-specific effect [6].

### 7.3 Neuromodulation

Devices for non-invasive neuromodulation (single pulse transcranial magnetic stimulation, sTMS; transcutaneous supraorbital stimulation, Cefaly; non-invasive vagus nerve stimulation, gammaCore; and transcranial direct current stimulation, tDCS) have proved good tolerability, safety, and effectiveness in RCTs, although they are rather small and blinding is difficult to achieve [6]. Occipital nerve stimulation, sphenopalatine ganglion stimulation, and high cervical spinal cord stimulation are invasive procedures and are used in refractory chronic migraines patients [6].

### 7.4 Real-World Use Patterns

Based on a systematic review of twenty studies in twelve countries, triptans (which were utilized by 9-73%) and NSAIDs (13-85%) were found to be the main pharmacological means for the management of migraines with opioids being used quite rarely (1-37%). At the same time, the usage of pharmacological measures was consistent with the recommendations of available guidelines [2]. In contrast to that, the non-pharmacological means of management seemed to be used much less frequently, with consultation with a physician (14-79%) and heat/cold application (35%) being the most common methods used, while other methods based on different kinds of class I-II evidence, including yoga, acupuncture, dietary supplements, and others, are applied unevenly [2]. Therefore, this discrepancy of the evidence base and current practices suggests an important issue which needs to be taken into account when educating and counselling patients by pharmacists or physicians [2].

## 8. Future Directions

While pharmacotherapy for migraines continues to develop towards the mechanistic approach, CGRP antagonists represent one more example of the latter [4]. However, at the moment, there is a number of people who cannot be effectively treated with currently available medications and costs can serve as a

significant barrier to the access to monoclonal antibodies and gepants [4]. With the help of individualized treatment which becomes possible because of the advances in genomics and discovery of new molecular biomarkers, other targets such as PACAP, histamine receptors, and oxytocin signaling system may be considered in case the existing treatments fail to help [4]. The research into neuromodulation devices, comparative effectiveness of non-pharmacological treatments, and the influence of the COVID-19 pandemic on the burden caused by headaches also requires further investigation [2,6].

## 9. CONCLUSION

The treatment of migraines is gradually becoming more and more mechanistic as a result of the development of CGRP-targeting monoclonal antibodies and gepants together with analgesics and triptans as well as evidence-based non-pharmacological approaches. At the same time, it is necessary to individualize the process taking into account the severity of attacks, co-morbidities, reproductive status of a person, personal preferences and risks of medication overuse. The further advances in the field will be made due to the discovery of new treatment targets in trigeminovascular, hormonal, and neuromodulatory systems.

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