

# MIGRAINES: UNRAVELING THE MYSTERY

Lukas Librić

University of Zagreb, School of Medicine

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## Abstract

Migraine is a prevalent and complex neurological disorder that significantly impacts the quality of life of affected individuals. This paper explores the pathophysiology, classification, and treatment options for migraine. The disorder is characterized by altered sensory processing and heightened susceptibility, with an apparent gender disparity, affecting 18% of women and 6% of men. Pathogenesis involves abnormal cortical processing and mitochondrial dysfunction, ultimately leading to the overexcitation of the trigeminovascular system, neurogenic inflammation, and vasodilation. Migraine is classified into three subtypes: migraine with aura, migraine without aura, and chronic migraine, each with distinct phases such as prodrome, aura, headache, and postdrome. The diagnosis relies on these clinical presentations and symptom patterns. Non-pharmacological treatments, including lifestyle modifications, stress management, and physical therapy, play an essential role in preventing chronic migraine development. Pharmacological therapies, such as over-the-counter medications, triptans, and newer treatments like ditans and gepants, are effective in alleviating migraine symptoms. This paper highlights the importance of a comprehensive and individualized treatment approach for managing migraine and improving patient outcomes.

**KEYWORDS:** headache, migraine, neurology, pharmacology, review literature

## INTRODUCTION

Migraine is a sophisticated genetic disorder, with altered sensory processing and heightened susceptibility, while also being prone to both environmental and behavioral conditions.<sup>1,2</sup> Migraine is the world's second factor leading to disability, as well as the first etiological factor of disability among young women.<sup>3</sup> Furthermore, primary care finds migraine to be the most common neurological factor causing disability. Migraine affects large portions of the population, with a prevalence of 15–18% annually.<sup>1</sup> Among primary care patients consulting for headaches, more than 90% can be diagnosed with migraine or probable migraine (attacks sharing similarities with migraine but missing one of the features to meet all diagnostic criteria fully).<sup>4,5</sup> Many patients tend to be undiagnosed and are not given proper medical care.<sup>6</sup> Furthermore, more than 50% of patients with migraine-like symptoms have not visited doctors' offices. Among those who have, only 25% of patients with chronic migraine and 87% of patients with episodic migraine have been adequately diagnosed.<sup>7,8</sup>

## PATHOPHYSIOLOGY OF MIGRAINE

To understand the complex pathophysiology of migraine, it is essential to start with the character of pain and the sheer sensation. The consensus is that migraine is usually a pulsating headache affecting one side of the head and, therefore, a unilateral condition. Migraine can also, relatively commonly, affect both sides of the head, with the pain located in the occipital and frontal areas. While attacks are

moderate to severe, exertion can also make pain worse.<sup>9</sup> The problem of migraine pathogenesis has not been fully solved. Nevertheless, there are two known main ways of migraine progression: abnormal processing of information in the cortex or dysfunction of mitochondria. Both pathways converge in overexciting the trigeminovascular system.<sup>10</sup> The beginning of the headache involves neuron stimulation and increased blood flow throughout the brain.<sup>11</sup> Many factors and substances are involved in the process of neurogenic inflammation and blood vessel widening, with the most important one being calcitonin gene-related peptide (CGRP), and others such as nitric oxide (NO) and substance P (SP). Due to the increased permeability of the blood vessels, these factors are washed away towards the thalamic and cortical regions of the brain, where they cause a sensation of pain.<sup>12</sup> The amino acid glutamate levels also tend to be higher in cerebral and peripheral circulation compared to the population unaffected by migraine attacks.<sup>13</sup> Contrary to the rise in the levels of glutamate, a drop in serotonin levels plays a role in the stimulation of meninges via the trigeminal nerves' neuropeptides.<sup>14</sup> Central sensitization is a process in which activation and linking of the trigeminal vascular neurons to the areas of the brainstem and regions of the subcortex leads to the final stages of migraine attacks.<sup>15,16</sup> The triad of central sensitization, vasodilatation in the meninges, and neurogenic inflammation is ultimately perceived as a pain sensation.<sup>17</sup>

## CLASSIFICATION OF MIGRAINE

Migraine can be classified as migraine with aura and migraine without aura, as well as chronic migraine.<sup>5</sup> Furthermore,



**Figure 1.** Foods connected with migraine occurrence. Based on reference<sup>27</sup>  
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migraine consists of four phases: prodromal, aura, headache, and postdrome, which may follow each other or show signs of overlapping.<sup>18</sup> The prodromal phase is characterized by relatively unnoticeable symptoms that are often overlooked. Most of them appear around three days before the start of the typical headache phase. The most important ones include agitation, mood fluctuations, exhaustion, appetite surges, sound sensitivity, and cervical rigidity.<sup>19</sup> Furthermore, these symptoms are connected with heightened hypothalamic blood flow, thus pointing out the role of the hypothalamus in the prodromal phase. Prodromal phase sensations can span throughout the aura and the headache phase.<sup>20</sup> Trigger factors vary among study participants, while some, such as food deprivation, insomnia, or bright light, are well-known and recognized.<sup>21</sup> Metabolic abnormalities are the most common trigger factors, including sleep pattern disruptions, alcoholic beverages, weather changes, strenuous exercise, and ovarian endocrine function changes.<sup>22</sup> Both physiological and psychological stress can be the inducers

of migraine, especially with their links to oxidative stress.<sup>23</sup> Interestingly, many foods, such as milk products, fried food, coffee, beverages with caffeine, tea, chocolate, citrus fruits, and high-fat foods, are connected to migraines (Fig. 1).<sup>18</sup> It is important to note that more than 10% of migraineurs have higher levels of insulin as well as insulin resistance.<sup>24</sup> There are many parallels between hypoglycemia and migraine, as patients often present similarly, with shakiness, paleness, dysarthria, peripheral coldness, and hypotension. Therefore, this strongly indicates a linkage between these conditions.<sup>25</sup> The aura phase, which occurs in up to 33% of patients, is propagated by cortical spreading depression, a mechanism of cortical depolarization and transient wave formation.<sup>26</sup> These events are further connected through the retinotropic propagation.<sup>27</sup> Throbbing pain of moderate to extreme intensity is felt on one side of the head during the headache phase.<sup>5</sup> With the aforementioned trigemino-vascular activation and activation of the dura's pain-sensing fibers, as well as their sensitization and release of inflammation factors, pain signals are initiated. Upper neck pain is moderated by the afferent fibers of the skin and neck muscles and the trigeminal ganglia afferent nerves.<sup>27</sup> The postdromal phase is mostly unreported and ignored, and because of that, it is also the least researched phase of the migraine. Typical symptoms are linked with diencephalic and brainstem activation, including exhaustion, mental and muscular fatigue, mood swings, and loss of appetite.<sup>22</sup>

**DIAGNOSIS AND CLINICAL PICTURE**

The division of migraine into the subtypes—migraine with aura, migraine without aura, and chronic migraine—helps with the diagnosis.<sup>28</sup> Migraine without aura is characterized by at least four-hour-long attacks lasting up to three days. It is a throbbing pain of medium to severe intensity, marked by the fear of light and sound, and vomiting sensations that worsen with exertion.<sup>28</sup>

Migraine without aura is characterized by unilateral, repeating attacks with steadily progressing symptoms of central nervous system involvement, such as sensory and optical impairment. These attacks usually last for a few minutes and are precursors to migraine-like symptoms and headaches. Migraine without aura is generally bilateral in children, while unilaterality is more often associated with early adulthood. It is important to note that prodromal symptoms start from hours to a day or two before other symptoms, such as lack of concentration, tiredness, neck stiffness, hyperacusis, photophobia, nausea, pallor, and impaired vision.<sup>28</sup> Postdromal

**Table 1.** Migraine without aura diagnostic guidelines, postulated by the International Headache Society<sup>28</sup>

At least five attacks ranging from 4 – 72h
Moderate to intense pain
Routine physical activity exacerbates headache intensity
Unilateral localization
Throbbing pain
Symptoms accompanied by photophobia/phonophobia and nausea/vomiting

**Table 2.** Migraine with aura diagnostic guidelines, postulated by the International Headache Society<sup>28</sup>

At least five headaches, with a minimum of two episodes characterized by aura
Headache occurrence within 60 minutes of the aura, or starting with an aura
Aura must include: <ul style="list-style-type: none"> <li>• Temporary difficulties with language and/or speech</li> <li>• One-sided sensory disturbance</li> <li>• Same-sized visual symptoms</li> </ul>

symptoms may persist up to two days after headache resolution. These include difficulty concentrating, fatigue, and neck stiffness. While migraine without aura follows a typical pattern of frontotemporal headache, some patients have “facial migraine,” characterized by facial pain. Interestingly, a small fraction (less than 10%) of female patients show the link between migraine attacks and their menstrual cycles. These attacks have heavier symptoms of nausea and are longer-lasting.<sup>28</sup>

Migraine with aura is characterized by persistent attacks that last minutes and are accompanied by one-sided central nervous system symptoms of slow development. A headache usually follows. Many patients suffering from migraine with aura also have migraine without aura. The aura, a cluster of neurological symptoms, typically precedes the headache but may continue or even occur after it. The three often described types of auras are visual, sensory, and speech aura.<sup>28</sup>

Visual aura, the most common type, manifests in over 90% of patients. It resembles a figure of a snaking pattern around the point of fixation with a steady leftwards or rightwards spread with an angulated edge and lateral convexity. Degrees of scotoma are left in its path. Adolescents and younger patients show less common symptoms with a bilateral nature.<sup>28</sup>

The second most common are sensory disturbances slowly spreading from the starting point and affecting the face, body unilaterally, and/or tongue in a needles and pins sensation.<sup>28</sup>

Speech disturbances are of the lowest-occurring frequency.<sup>28</sup> It is important to note that almost all patients with speech or sensory disturbances experience visual aura. In contrast, claims in the opposite direction cannot be said with the same guaranteed level.

When multiple symptoms characterize an aura, they usually appear sequentially, from visual to sensory and finally

aphasic. While motor symptoms typically last longer, most aura symptoms last for an hour. It is of the utmost importance for patients to note the time and record their symptoms because they are difficult to describe for the general population. Patients often wrongly report monocular visual disturbances and lateralization of rapid onset. Sensory loss is also commonly mistaken for muscular weakness.<sup>28</sup> Before or following the symptoms of an aura, cerebral perfusion is decreased in the brain’s cortical regions with posteroanterior progression of ischemia. A few hours later, the pattern is reversed with hyperperfusion developing in the same areas. Prodromal symptoms usually start a few hours or a few days before other symptoms of a migraine, and they do not include aura. These include photophobia, nausea, hyperacusis, fatigue, nuchal rigidity, skin paleness, and yawning. Postdromal symptoms can persist for up to two days from headache resolution, usually including problems with concentration, tiredness, and nuchal rigidity.<sup>28</sup>

Chronic migraine is characterized by migraine attacks occurring at least 15 times per month, for more than 3 months, with attacks having features of the migraine headache for at least 8 days per month.<sup>28</sup>

**NON-PHARMACOLOGICAL TREATMENT**

Migraine is an intermittent and sporadic disease, and although there is no cure for now, treatment allows for a high quality of life. If treated inadequately, migraine can transition into chronic migraine.<sup>29</sup>

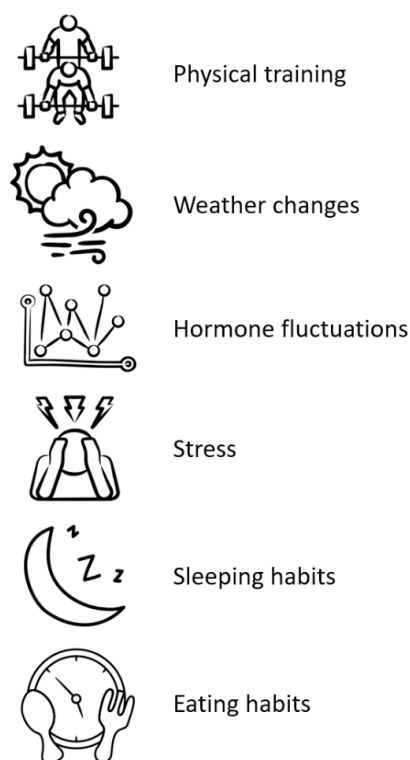
Lifestyle plays a significant role in pathophysiology, and factors such as stress, sleeping and eating habits, as well as physical training, are well intertwined in the development of migraine. Chronic migraine patients tend to have higher levels of stress compared to the control group, as well as lower regularity in their lifestyle patterns. The most

**Table 3.** Six ways of non-pharmacological treatment for migraine<sup>30</sup>

Structured daily plans and consistent routines
Adequate fluid intake
Regular meal consumption
Aerobic training
Relaxation therapies
Minimizing stress exposure

common triggers are stress, weather changes, sleep-associated triggers, and fluctuations in the level of hormones in the female population. Interestingly, sleep can be described as a two-way street, with lack of sleep worsening migraine occurrence, as well as migraines causing a fall in the quality of sleep. It is essential to keep track of migraine occurrence, with tracking changes in the number of migraines monthly.<sup>30</sup>

It is also important to note that caffeine consumption changes can worsen headaches. Withdrawal headaches are minimized by keeping caffeine intake under 200 mg daily and consumption consistent. Forward posture of the head, aspartame, and disorders of the temporomandibular joint have been linked with the advancement into chronic migraine. At the same time, physical therapy proves to be a factor in migraine management (Fig. 2).<sup>30</sup>



**Figure 2.** Common migraine triggers. Based on reference <sup>30</sup>  
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## PHARMACOLOGICAL TREATMENT

When discussing the acute treatment, it is divided into migraine-specific treatment such as triptans and ergot with its derivatives<sup>31</sup> and gepants<sup>32</sup> as well as non-specific treatment including NSAIDs, antiemetics and narcotic-opiates. Valproic acid (intravenous) and steroids can also be used in the context of miscellaneous drugs.<sup>31</sup> Over-the-counter medications, such

as paracetamol, naproxen, ibuprofen, and acetylsalicylic acid, are considered the first treatment line.<sup>33</sup> They are highly effective and cheap, with minimal side effects.<sup>33, 34</sup> The primary focus of the therapy is to reduce both the duration and the intensity of the attack.<sup>33</sup> Other concerns are treatment with minimal side effects, reducing the number of drugs used, and rebuilding the patient's functional capabilities.<sup>35</sup> The most commonly used therapies include aspirin, ibuprofen, naproxen, paracetamol, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, caffeine, and melatonin.<sup>27</sup>

### Aspirin

Aspirin is primarily used for the treatment of chronic migraines, and it can be either swallowed or injected, while its antiplatelet effects heighten the risk of hemorrhage.<sup>36</sup> It is important to note that in terms of acute migraine, aspirin is considered a first-line treatment regarding NSAIDs.<sup>37</sup> Aspirin has also shown properties of reducing pain from severe or moderate to mild or painless, while also easing the symptoms of photophobia and phonophobia.<sup>38</sup>

### Ibuprofen

Ibuprofen's mechanism of action is COX inhibition and stopping prostaglandin synthesis. The highest concentration is achieved one or two hours after ingestion.<sup>39</sup> Ibuprofen is used to treat acute migraine, with pain reduction to mild or painless in doses of both 200 mg and 400 mg. In contrast, only the 400 mg dose proved to be effective against phonophobia and photophobia.<sup>40</sup> Its side effects include dizziness, gastrointestinal (GI) discomfort, ulcerations, and reflux.<sup>41</sup>

### Naproxen

The primary use of naproxen is the treatment of moderate to severe migraines. Naproxen's effects are similar to those of ibuprofen or frovatriptan.<sup>37</sup> Naproxen is quickly absorbed in the GI tract. Its effects can begin an hour after consumption and last eight to twelve hours. The drug's half-life is fifteen hours, and side effects include ulcerations, GI bleeding, nausea, and acid reflux.<sup>42</sup> It is considered an early therapy for pyrexia, aches, and headaches while being contraindicated in patients with ulcers or NSAID allergies.<sup>27</sup>

### Paracetamol

Paracetamol's mechanism of action is probably related to COX inhibition and lowering levels of prostaglandins, specifically in the nervous system.<sup>43</sup> It is used as a treatment for non-severe migraines, acting as a temperature-lowering agent and painkiller. The side effects are sleep difficulties, dizziness, lack of bowel movement, and headache.<sup>33</sup> It is important to note that a combination of paracetamol, caffeine, and aspirin is used to treat migraine and tension headaches with higher efficiency than each of these drugs individually.<sup>33</sup>

### Triptans

Triptans are regarded as a second line of therapy while providing choice (e.g., change between seven triptans if one is ineffective with another one).<sup>44</sup> Triptans work through the triple mechanism of action: blocking nociceptive signals, binding to the 5-HT<sub>1D</sub> receptors, leading to antagonization of the CGRP and substance P, and binding to the 5-HT<sub>1B</sub> receptors, combating vasodilatation of the cranial blood

vessels.<sup>27</sup> Oral sumatriptan is usually the first method of administration, while the subcutaneous route, as the most efficient, can be used when the patient doesn't respond adequately to the oral route. The change between triptans is used if treatment wasn't adequate for three attacks or if a combination of non-steroidal anti-inflammatory drugs and triptan could be used.<sup>45</sup>

#### *Ditans and gepants*

Ditans such as lasmiditan are 5-hydroxytryptamine type 1F receptor agonists, and gepants such as rimegepant and ubrogepant are CGRP-receptor antagonists. Currently, the cost and the lack of accessibility of these molecules prevent broader use for patients where other drugs have not proven effective.<sup>45</sup>

### PROPHYLAXIS OF MIGRAINE

Different medication options are available for the prophylaxis of migraine. Almost sixty trials show the effectiveness of propranolol.<sup>46,47</sup> Valproate shows efficiency,<sup>48</sup> while topiramate is twice more potent than a placebo in reducing migraine occurrence by fifty percent.<sup>49</sup> Amitriptyline is the only tricyclic antidepressant that shows its potency in migraine prophylaxis.<sup>50</sup> Among angiotensin receptor blockers and ACE inhibitors, candesartan and lisinopril show possible effectiveness.<sup>51</sup> Erenumab, being the first CGRP monoclonal antibody used for prophylaxis, also showcases adverse effects

of constipation and pain at the site of injection.<sup>52</sup> Complementary therapy exists in the form of an extract of *Petasites hybridus*, known as Petasites, but only a commercially prepared extract should be used.<sup>53</sup>

### LIMITATIONS IN THE TREATMENT OF MIGRAINE

Proper diagnosis is severely lacking in patients with migraine, where, for example, in a study by Ertas et al., it was found that 22.8% of the patients with migraine were wrongly diagnosed with tension headache.<sup>54</sup> The occurrence of these mistakes can be attributed to the multiple natures of the migraine, tension headache and migraine alternating or that the symptoms have not met the diagnostic criteria.<sup>55</sup> Furthermore, only around 40% of the patients were supervised while using medication, and less than 3% used specific treatment options for acute attacks.<sup>54</sup> Further limitations stem from a rather insufficient usage of preventive treatment, with only 10% of patients receiving the treatment itself, whereas around 40% of the patients would find it useful.<sup>56</sup> It is also important to mention that the CGRP antagonists are not commonly used, due to their high price as well as possible adversary effects on the functions of the immune system, reducing density of the bones as well as having a negative impact overall on the cardiovascular function.<sup>57</sup> Social factors combined with cultural and economic challenges as well as overloaded healthcare providers contribute to the ineffectiveness of migraine treatment.<sup>58,59</sup>

## CONCLUSION

In conclusion, migraine is a complex and multifactorial neurological disorder that significantly affects quality of life. Its pathophysiology involves abnormal sensory processing, neurogenic inflammation, and trigeminovascular system overactivity. Recognizing the different subtypes and symptom phases is essential for accurate diagnosis and effective management. Both non-pharmacological strategies, such as lifestyle modification and stress reduction, and pharmacological treatments, including triptans,

ditans, and gepants, play important roles in reducing the frequency and severity of attacks. A personalized and comprehensive approach is key to improving patient outcomes and preventing progression to chronic migraine. Thanks to the advancements in the field of neurology and a higher interest in the problem of migraines, it is safe to assume that in the next 10 or 20 years, migraine will be more researched, classified and more effectively cured.

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## MIGRENE: RAZOTKRIVANJE MISTERIJA

### Sažetak

Migrena je čest i složen neurološki poremećaj koji značajno narušava kvalitetu života oboljelih osoba. Ovaj rad istražuje patofiziologiju, klasifikaciju i mogućnosti liječenja migrene. Poremećaj se odlikuje poremećenom obradom osjetljivih podražaja i pojačanom osjetljivošću, uz izraženu spolnu razliku – pogađa 18 % žena i 6 % muškaraca. Patogeneza uključuje abnormalnu kortikalnu aktivnost i mitohondrijsku disfunkciju, što naposljetku dovodi do pretjerane aktivacije trigeminovaskularnog sustava, neurogene upale i vazodilatacije. Migrena se dijeli na podtipove – migrena s aurom, migrena bez aure i kronična migrena – od kojih svaki ima različite faze poput prodroma, aure, glavobolje i postdroma. Dijagnoza se temelji na kliničkoj slici i obrascima simptoma. Ne-farmakološki pristupi, uključujući promjene životnog stila, upravljanje stresom i fizikalnu terapiju, imaju važnu ulogu u prevenciji razvoja kronične migrene. Farmakološke terapije, poput lijekova koji se izdaju bez recepta, triptana te novijih lijekova kao što su ditani i gepanti, učinkovite su u ublažavanju simptoma migrene. Ovaj rad naglašava važnost sveobuhvatnog i individualiziranog pristupa u liječenju migrene s ciljem poboljšanja ishoda za pacijente. Zahvaljujući napretku u neurologiji i sve većem interesu za problem migrena, može se očekivati da će u idućih 10 do 20 godina migrene biti detaljnije istražene, preciznije klasificirane i učinkovitije liječene.

**KLJUČNE RIJEČI:** glavobolja, migrena, neurologija, farmakologija, pregled literature