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Abstract

Migraine is a common disease affecting approximately 15% of the population of the developed world, where patients are predominantly women. The two main subtypes of the disease are migraine with aura and migraine without aura. The disease has a significant impact on quality of life; reducing its performance and limiting the ability and capacity to fully live. Migraine is a multifactorial neurological disease. According to recent studies, genetics plays an important role in migraine pathophysiology. Some gene mutations in populations of patients have been found and are thought to be the key underlying feature of the disease. Having a family history of migraine incidence greatly increases the likelihood of migraine and can provide some explanation to its presence. People who suffer from migraines in most cases have sensitive nervous systems and are susceptible to a number of surrounding factors precipitating migraine attacks. For patients, these factors are usually individual-specific and migraine attacks may vary in intensity, frequency and duration from patient to patient. Correct and properly selected acute treatment or prophylaxis started at the right time is a key factor for improving the lives of patients with migraine.

Today, preventive and acute therapy of migraine encompasses a wide selection of medications. To simplify the pharmacotherapy of migraine, different European and national guidelines have been established. Guidelines recommend approaches for treatment, drugs with levels of their efficacy as well as dosage. All recommendations are evidence-based and form a reliable source for physicians.

Kurzfassung

Migräne ist eine Erkrankung, die ungefähr 15 % der Bevölkerung in den Entwicklungsländern betrifft., die Mehrzahl davon sind Frauen. Die wichtigsten Subtypen sind Migräne mit und ohne Aura. Bei Migräne handelt es sich um eine multifaktorielle, neurologische Erkrankung, welche einen signifikanten Einfluss auf die Lebensqualität besitzt. In der Pathophysiologie dieser Erkrankung spielt eine genetische Prädisposition eine wichtige Rolle. In Patienten wurden einige Genmutationen gefunden, welche im Verdacht stehen Ursache für diese Erkrankung zu sein. Personen, welche an Migräne leiden, haben in den meisten Fällen ein sensitives Nervensystem und sind daher empfänglicher für die auslösenden Faktoren von Migräneattacken. Diese Faktoren sind gewöhnlich individuell verschieden und die Migäneattacken variieren von Patient zu Patient in Intensität, Frequenz und Dauer. Eine geeignete Therapie und Prophylaxe sind notwendig zur Verbesserung der Lebensqualität.

Die heutige Therapie umfasst ein breits Spektrum von Medikamenten. Zur Vereinfachung und Verbesserung der Pharmakotherapie wurden Europäische und nationale Richtlinien in Hinblick auf die Wirksamkeit und Dosierung der Pharmaka ausgearbeitet. Alle Empfehlungen sind evidenzbasiert und stellen eine wichtige Informationsquelle für die behandelnden Ärzte dar.

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1. Introduction

Definition of Migraine

According to the World Health Organization (WHO), migraine is a common disabling, neurologic condition characterized by primary recurrent headaches lasting 4 to 72 h. As stated by WHO, attacks typically include as headaches which can be unilateral, pulsating, of moderate or severe intensity, or aggravated by routine physical activity [1]. Mannix *et al.* state, that migraine attacks are often accompanied by nausea, vomiting, photophobia and phonophobia [2]. According to International Classification of Headache Disorders III (ICHD-III 2016) patients have on average one attack per month and 25% have at least two attacks per month [3].

1.1 Clinical features of migraine

According to L.P. Hudson, a migraine attack is divided into four components:

- prodrome
- aura
- headache
- resolution [4].

According to International Classification of Headache disorders III edition (ICHD-III), the prodrome phase may occur hours or days before the headache and headache resolution phase, which includes hyper- and hypoactivity as well as food-related cravings. The consequences may be frequent yawning, fatigue and neck stiffness and even depression. ICHD-III describes migraine aura as a neurological symptom that occurs in migraine with aura (MA) and can be characterized by gradually developing and recurrent attacks that last for minutes. There are also unilateral but fully reversible visual, sensory and other central nervous system symptoms, which are usually accompanied by headache and are associated with migraine symptoms. According to ICHD-III, the resolution symptoms occur hours or days before the headache. These symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain [5].

1.2 Migraine with aura and migraine without aura

According to the WHO, migraine has two major subtypes: migraine with aura (MA) and migraine without aura (MwA). However, there are some cases when a patient may have both types [6]. According to ICHD-III, MwA is a clinical syndrome characterized by recurrent headache attacks lasting 4-72 hours. Typical characteristics of the headache are:

- unilateral location
- pulsating quality
- moderate or severe intensity
- can be accompanied by nausea and/or photophobia and phonophobia [7].

As stated in ICHD-III, an aura may consist of the following symptoms: visual, sensory, speech and/or language, motor and brainstem. Aura symptoms follow one another in succession. An aura begins with visual, sensory and aphasic symptoms with a typical duration for most aura symptoms being 1 hour. Motor symptoms however, last for a significantly longer period. 90% of patients with MA experience visual aura, which is often presented as a fortification spectrum [8]. Typical aura without headache happens amongst patients who may present a history of migraine with aura [9].

1.3 Migraine aura

According to Goadsby and Indian statement, migraine aura is experienced by 30% of patients and is a focal neurological disturbance manifested as visual, sensory or motor symptoms. The underlying mechanism of aura is cortical spreading depression (CSD) [10]. As stated in ICHD-III, the aura symptoms usually occur before the headache and may begin either after the pain phase has commenced or proceeds into the headache phase. The aura may be variable in its manifestation, though most often it is characterized by visual phenomena such as the fortification spectrum (zigzag), scotomata. ICHD-III describes some further sensory disturbances that may also be evident, including the appearance of pins and needles, which move slowly from the point of origin. Such disturbances affect various parts of the body, face and/or tongue

and in some cases, numbness may also occur. Speech disturbances are not reported to occur frequently [11].

1.4 Epidemiology of migraine

Migraine is highly prevalent with the WHO rating it as the most disabling chronic disorder [12]. In the Global Burden of Disease Study, updated in 2013, migraine was ranked as the sixth most prevalent disorder causing disability worldwide [13].

Stovner and Andree write that prevalence is especially high in developed countries where approximately 15% of the population suffer from migraine [14].

Various studies show that the spread of migraine prevalence has large variations, which are influenced by age, gender, and race. Wessman *et al.* report, that migraine is three times more common in women than in men [15].

1.5 Gender and age

As Davidoff states, migraine can occur at any age. According to his statement, approximately 90% of patients experience their first attack between the ages of 35-45 years. Migraine can also begin at puberty. In opposition to the trend seen in adulthood and during puberty, migraine is more prevalent in males prepubescently. The disease varies with age and gender by incidence, prevalence and frequency. It is also possible, that migraine can start in childhood or early adolescence with the first incidence in children beginning between the ages of 5 and 11 years. In comparison to adults, children tend to have a shorter duration of attack and abdominal symptoms are usually more expressive [16]. As WHO notes, the course of migraine headaches is different between boys and girls [17] with 10-year-old boys experiencing migraines more often in comparison to girls. Davidoff writes, that despite that fact, girls tend to experience a longer duration of headaches. In children and adolescents, migraine headaches are more often bilateral compared to adults. In adolescence, pain tends to be in the unilateral format and in this post pubescent phase, migraines are more manifested amongst women compared to men [18].

Reffering to the data of research performed in the United States and Europe, Mengistu and Alemayehu state, that the percentage of women who suffer from migraine is 15-18% and with the rate for men being 6-8% [19]. Kowalska *et al.* state, that women are more prone to photophobia, phonophobia and nausea and have more frequent, longer and stronger headaches, which may possess a chronic form compared to men [20]. As Maleki *et al.* write, first migraine attacks in young women mostly take place in the period when menarche occurs [21]. Davidoff states that for men the timing of initial incidence occurrence shows less dependence on age than it does for women [22]. Figure 1 proposed by Lipton *et al*. outlines the statistics on frequency of migraine attacks in a gender-specific manner and shows that women experience much often migraine attacks than men. The rate of initial onset declines after the age of 40 for both genders and the possibility of migraines developing after the age of 60 is rare [22].

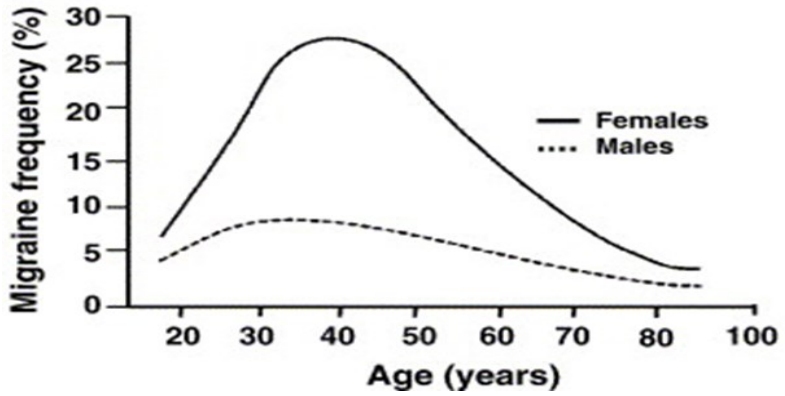

Fig.1 Age-specific prevalence of migraine by sex adjusted by Lipton *et al*. 2001 [23].

1.6 Migraine in women

Maleki *et al.* state that migraine is the fourth most disabling disease amongst women worldwide [24]. Vos *et al.* referring to some evidence, report that migraine is linked with the hormonal status of women where ovarian steroids are shown to affect the phenotypic expression of migraine [25]. Sacco *et al.* write, that migraine occurrence and its frequency may be influenced by menarche, menstruation, pregnancy, menopause, use of oral contraceptives and by hormone replacement treatment [26,27].

According to Vetvik *et al*., the first migraine attack for women often presents itself with menarche and often declines after menopause [28]. Davidoff referring to the data of recent studies indicates that between 14% and 18% of young women have their first attack during the year of or the year following menarche. This incident onset is especially associated with the migraine without aura form of headache [29].

Maleki *et al*. write, referencing to the data of prospective cohort study, The Growing Up Today Study (GUTS), that early puberty increases the risk of developing migraines. Irrespective of age and family history of migraine, each one-year delay in onset of menarche decrease the odds of migraine by 7% [30]. Sacco *et al.* state that the appearance of migraine amongst women of reproductive age is often related to menstruation, the so-called menstrual migraine [31]. Namely, as E. A. MacGregor states, two days before the onset of menstruation and during the first 3 days of menstruation, incidence of migraine without aura is the most evident [32]. Sacco *et al.* state that the falling of estrogen levels in the late luteal/early follicular phase of the menstrual cycle is the key factor in menstrual migraine occurrence [33]. According to the ICHD-III edition, there are two types of menstrual migraine: pure menstrual migraine and menstrually related migraine. They are defined as subtypes of migraine without aura [34].

As reported by Sacco *et al*., 10–20% of women report migraine exclusively during menstruation and at no other time of the month. It has been noted that patients who suffer from migraine with aura may additionally have menstrual migraine attacks without aura [35]. Vetvik *et al.* report, that the level and strength of menstrual migraine attacks and menstrual related migraine are higher, more severe and more recurrent than non-menstrual migraine attacks at other times of the cycle [36]. E. A. MacGregor states, that patients with menstrual migraine are less responsive to acute treatment [37].

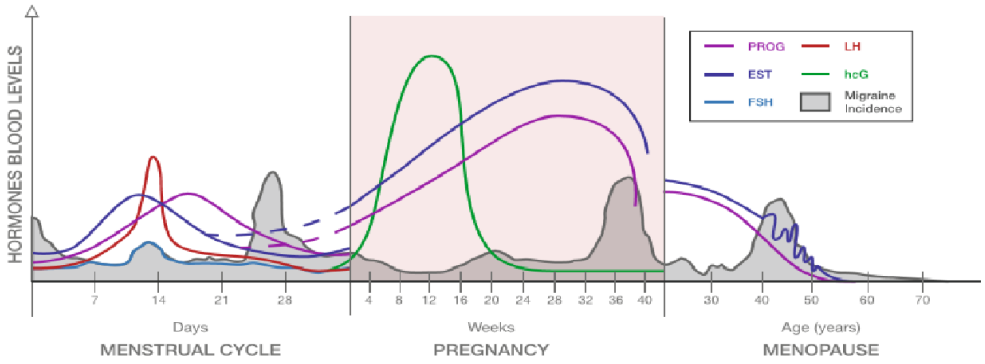

Fig.2 Hormonal changes and incidence of migraine without aura in women by Granella *et al*. [38]

Migraine during pregnancy.

Goadsby *et al.* state, that migraine shows a tendency to retreat with the onset of pregnancy in women who have previously suffered from migraine without aura and menstrual migraine [39]. According to Kvisvik *et al.,* most women report an improvement of migraine attacks during the course of pregnancy [40]. Granella *et al*. explain that this phenomenon is likely to be due to the high levels of estrogen present during pregnancy where increases by up to a hundred times relative to normal levels are observed. Granella *et al.* also assumes, that increased endorphin production may also play a role in the improvement of migraine during pregnancy [41].

Goadsby *et al*. find evidence that the frequency of migraine attacks in the first trimester may increase but is followed by a decrease later in pregnancy. It is also evidenced that attacks are usually less frequent in the second and third trimesters [42]. Sacco *et al*. report that if there is no improvement of migraine in the first trimester, the attacks will continue to occur throughout the duration of pregnancy and sometimes a worsening of migraines is possible or in some rare cases, a few pregnant women even experience new onset migraine [43]. Hutchinson *et al.* inform, that after delivery, and in almost all cases, migraine attacks will return [44].

Menopause.

Ripa *et al.* state, that when approaching the menopause, migraines without aura normally retreat whereas migraines with aura continue to occur. In some cases, worsening of attacks may occur [45].

Hormonal contraceptives and migraine.

The work of Nappi *et al*. focuses on the usage of combined oral contraceptives (COCs) in women suffering from migraine with aura, because of its probable aggravation of the condition. Nappi *et al.* remind, that migraine with aura increases the risk of ischemic stroke two-fold. The use of COCs further increases this risk. Especially at risk are women who smoke, are over the age of 35 years and those who suffer from hypertension, diabetes, hyperlipidemia or thrombophilia [46]. Edlow *et al*. stress that patients who have migraine with aura are at four times greater risk of worsening their headache attacks after initiation of COCs compared with women who have migraines without aura [47]. The World Health Organization Medical Eligibility Criteria for Contraceptive Use states that use of COCs in patients with MA at any age is absolutely contraindicated [48]. As Nappi *et al.* conclude that women with migraine should prefer an estrogen-free containing contraception. As an alternative, progestogen-only contraception could also be chosen as it is not associated with increased risk of ischemic stroke and is appropriate for women with vascular diseases or risk factor for stroke [49].

1.7 Pathophysiology of migraine

The exact pathophysiological mechanism of migraine is still unresolved. Hansen *et al.* explain that a whole series of mechanisms are involved in the development of migraine attack. There is evidence supporting that migraine with aura (MA) and migraine without aura (MwA) have a somewhat similar etiology but possess some specific differences [50].

Mauskop states, that the pathophysiological origins of migraine are in the brainstem center. As he explains, activation of this center leads to cascade of neuronal and neurochemical events. These events cause neurogenic inflammation followed by sensitization of trigeminal nucleus caudalis, what in turn

leads to transmission of signals to the thalamus and cortex where pain is perceived [51].

Bernstein *et al.* explain that central nervous system of migraine sufferers is genetically hyperexcitable, making them susceptible to different environmental factors precipitating migraine. He called this phenomena "central sensitization" [52].

The following mechanisms outlined by Gasparini *et al*. are considered to be the main components in migraine pathophysiology:

- neural (hyperexcitability and cortical spreading depression-like neural events)
- vascular (intracranial constriction and vasodilation)
- nociceptive (activation of trigeminal structures and release of several neuromediators) [53].

As Burstein *et al*. state, the mechanism of action underlying migraine with aura is more researched and better understood. For instance, it is known that cortical spreading depression (CSD) forms an underlying basis of activation of migraine aura [54], which proceeds the appearance of a migraine attack [55].

1.7.1 Cortical spreading depression

Diener describes cortical spreading depression as a wave of cortical neuronal excitation in the cortical gray matter that is followed by a wave of long-lasting depression [56], which propagates across the cortex at a velocity 2-6 mm/min according to Hauge *et al*. statement [57]. In the third edition of ICHD, it is stated that the triggers initiating CSD still remain unknown. A vast array of literature suggests that CSD does not occur in migraine without aura, however, some recent studies disagree. [58] As stated in the ICHD-III there is a suggestion that glial waves or other cortical phenomena may be involved in migraine without aura [59]. M. Green describes "silent" CSD as a phenomena that is supposed to present in migraine attacks without aura. He hypothesizes that cognitive changes surrounding migraine attack in migraine

patients may be due to unrecognized cortical spreading depression encompassing the "silent brain regions" [60]. Wessman *et al.* describe CSD as a primary mechanism of migraine aura [61]. Noseda and Burstein proclaimed that CSD promotes the release of a variety of neuromediators [62] into the meninges, a process that is considered to activate the trigeminovascular system and to trigger a migraine attack [63].

1.7.2 Trigeminovascular system

According to Burstein *et al.* and Gasparini *et al.*, activation and sensitization of trigeminovascular system, which is characterized by decrease of response threshold and increase of response magnitude respectively [64, 65],causes dilatation of meningeal blood vessels and thus local release of various neuropeptides as explained by Gasparini *et al.* and Samsam *et al.* [66,67]. According to Gallagher *et al.* statement, substances involved in the migraine process are calcitonin gene−related peptide (CGRP), substance P, neurokinin A, [68] serotonin, nitric oxide and many others [69]. Each of these neuropeptides play an important role in the cascade of processes involved in migraine pathophysiology. Gupta *et al.* describe CGRP as a main sensory vasoactive neuropeptide, which exerts vasodilative, immunomodulative, and inflammatory effects. CGRP, together with substance P and neurokinin A [70] mediate neurogenic inflammation as well as vasodilation of cerebral and dura blood vessels [71]. Referring to evidence obtained in the field of migraine research, Malhotra states that the changes in blood vessels and muscle tone that occur during chronic headaches are preceeded by changes in serotonin levels [72]. Durham explains that serotonin acts as vasoconstrictor of nerve endings and blood vessels and in this way affects nociceptive pain. Contextually, normal serotonin levels in the brain prevent migraine headache and in support of this, a study by Coming states that low serotonin levels dilate blood vessels and initiate migraine [73]. Aggarwa *et al*. note that the influence of serotonin on headache may also explain the effectiveness of medications used to treat migraine. 5-HT1B and 5-HT1D receptor agonists are known to be effective in treating migraine [74].

M. W. Green describes another neuropeptide implicated in migraine pathogenesis, nitric oxide [75]. Gupta *et al.* highlight that the full mechanism of nitric oxide action in this process still remains unclear but it is known that nitric oxide leads to vasodilation and the consequent development of headache. According to some studies conducted in rats, nitric oxide may also contribute to the release of CGRP from dural afferents [76,77]. Pardutz and Schoenen highlight, that many experimental data have also shown cyclooxygenases to be implicated in the peripheral activation of the trigeminovascular system. COX 1 and COX 2 are present in the dura mater and are a key factor in the inflammatory process. This explains the efficacy of NSAIDs in migraine acute treatment [78].

Pardutz and Schoenen also focuse on an interesting observation, that migraine patients tend to have magnesium deficiencies. Low magnesium levels are being observed not only in the brain area but also in the whole body. Therefore there is an assumption that migraine and low magnesium levels are associated [79].

Migraine is a disorder with a complicated and still unresolved pathophysiology involving a cascade of many different mechanisms. To understand a migraine, it is important to consider the factors that influence its development and trigger its attack. Chiu *et al*. accentuate the importance of a genetic component could be underlying a patient's migraine pathophysiology [80].

1.8 The genetic component of migraine pathophysiology

Goadsby states that one of the most important aspects of migraine pathophysiology is inheritence of the disease [81]. Gasparini *et al.* report that there is reliable evidence from epidemiological twin studies, family case studies and unrelated cases of migraine confirming that there is a genetic component underlying migraine [82]. According to Kowalska *et al.*, migraine is most likely a polygenic/oligogenic disease with a wide genetic heterogeneity [83]. It was found that at least 50 % of patients have a first-degree relative with a history of migraine [84]. Hansen *et al.* report that heritability of migraine with typical aura that affects approximately one third of migraineurs is higher than

for migraine without aura [85]. Wessman *et al.* provide a summary of data from a Danish population-based study devoted to the heredity of migraine. It was found that the first-degree relatives of probands with migraine without aura had 1.9 times greater risk of this disorder and a reduced 1.4 times greater risk of MA compared with the general population. First-degree relatives of probands with MA had nearly four times greater risk of MA but no increased risk of MwA. Here, it was importantly identified that although there are specific environmental triggers causing the development of MwA, genetics plays a pivotal role [86]. ICHD-III describes the familial hemiplegic migraine, a rare and well-studied subtype of migraine with aura. It is genetically heterogeneous and autosomal dominant. According to ICHD-III, there are three subtypes of familial hemiplegic migraine: FHM1, FHM2, FHM3 [87]. Gasparini *et al.* explain that each subtype is caused by mutations in a different gene and according to data from the genetic studies, three specific genes are responsible. CACNA1A, ATP1A2 and SCN1A for FHM1, FHM2 and FHM3 respectively. All three genes are responsible for ion transport, namely CACNA1A for – voltage-gated calcium channels, ATP1A2 for – neuronal sodium-potassium pump, and SCN1A for - voltage-gated sodium channels. Similarly, genetic studies have produced a large list of other genes implicated in migraine, but how they actually participate in the migraine processes still remains unknown [88].

Consequently, the discovery of genes that are implicated in migraine disease may lead to new insights of migraine pathogenesis, as Gasparini *et al.* write. [89]. Kowalska *et al.* state that new advances in genetic research will help to identify different migraine subtypes and may help to develop new antimigraine treatments [90].

1.9 Migraine triggers

Migraine attack can be elicited by different environmental factors called "triggers". Hoffmann and Recober explain , that common triggers have been identified through analysis of different studies from large populations of patients. For each patient, the trigger can be different [91]. Stephen J. Peroutka has provided a systematic review of 25 scientific publications devoted to pre-

cipitating factors of migraine. He concluded that common factors most associated with the onset of a migraine attack are stress, fatigue, food consumption or fasting, hormonal fluctuations, lack of sleep or oversleeping, weather changes, alcohol consumption and also visual, olfactory and auditory stimuli.

Table [1]. The most common triggers in women by S. Peroutka [92].

Precipitating factor	% of migraineurs
Stress	58
Auditory	56
Fatigue	43
Fasting	44
Hormonala	44
Sleep	43
Weather	39
Visual	38
Olfactory	38
Alcohol	27

According to Holm *et al.* between 50 % and 70 % of migraineurs show correlations between having stress and migraine activity [93]. Referring to the evidence obtained in migraine research, Sauro *et al*. state that the first migraine occurrence can be precipitated by stress in a person who is predisposed to migraine but who has not previously experienced an attack. Stress also may promote the development of chronic migraine [94].

As Sacco *et al*. write there is evidence suggesting that migraine activity is influenced by hormonal factors. The fluctuations of estrogen levels in women during the menstrual cycle is one of the most common known precipitating factors [95]. In the analysis of migraine triggers provided by Andress-Rothrock *et al.,* most women reported that menstruation was a trigger [96].

In the lives of people suffering from migraine, sleep plays an important role. Wöber and Wöber-Bingöl note that 80% of migraine patients identified sleep disturbances as triggers [97]. Ahn *et al.* explain that lack of sleep, oversleeping, staying up too late, getting up earlier than usual, changes in activity pattern due to shift work and jet lag can all cause a migraine attack [98].

Peroutka reported different visual, olfactory and audio factors that can be precipitating factors to a migraine attack. Bright or flickering lights and glare as well as contrasting patterns may provoke migraine in many patients [99]. According to Mollaogˇlu statement, perfumes, nail polish, paint, gasoline, and other odors may be also correlated to migraine onset [100]. Different sounds, especially those at a loud volume may also elicit migraine attack [101]. Silva-Neto *et al*. report that 70% of patients who suffer from migraine have had at least one attack in their lifetime that has been triggered by odor [102].

Kelman reports that every fourth migraineur has expirienced an acute migraine attack that has been provoked by some foodstuff [103]. M. Green outlines a list of products that contain tyramine, nitrites, monosodium glutamate and aspartame as migraine triggers [104]. Kelman states, that food such as chocolate, cheese, nuts, citrus fruits, processed meats, food with high fat content and coffee are also noted to aggravate migraine attacks in predisposed patients [105]. According to Andress-Rothrock *et al.* statement, missing or delaying a meal can also be a causal factor for migraine onset [106].

Panconesi writes, that many studies have shown that alcoholic drinks, especially red wine are key at triggering migraine. Alcoholic drinks form a frequent trigger in about 10% of patients and as an occasional, trigger in about one-third of migraine patients [107].

Identification and avoidance of such triggers can be an extremely effective addition to migraine prevention [108]. Khalid *et al.* state, that keeping a migraine diary is recommended to patients whose attacks are often triggered by different precipitating factors. Patients usually record characteristics of the

migraine attacks and what could have initiated it. This approach helps to recognize triggers so that they can be avoided and thus reducing the frequency of attacks [109].

1.10 Migraine Classification

The new improved third edition of International Classification of Headache Disorders is currently recommended as the gold standard for classification of headache disorders [110]. The National Institute for Health and Clinical Excellence (NICE) notes that ICHD III is more evidence-based compared to the previous two editions, which were mostly based on the opinions of experts [111].

This classification includes many types and subtypes of migraine. It allows a better diagnosis of migraine and enables a more accurate identificatıon of its subtype, thus enhancing the chances of appropriate therapy. Antonaci *et al*. write that the diagnosis of migraine is recommended to be based on medical and family history, symptoms, and a physical and neurological examination [112].

According to ICHD-III, migraine is classified into:

- migraine with aura;
- migraine without aura;
- retinal migraine;
- probable migraine;
- migraine complications;
- chronic migraine.

As stated in the ICHD-III, migraine with aura and migraine without aura remain two main migraine types. MA identifies hemiplegic migraine, familial hemiplegic migraine and its subtypes, sporadic migraine. MwA is often related to menstruation in women so it also includes such criteria as pure menstrual migraine and menstrually related migraine.

According to the ICHD-III, appearance of headaches less than 15 days per month is classed as episodic migraine but if the headaches are continuing for

15 or more days per month for more than 3 months, it should be defined as a chronic migraine [113].

Table [2]. Diagnostic criteria of migraine without and with aura according to International Classification of Headache Disorders III Edition [113].

Migraine without aura	**Migraine with aura**
A. At least five attacks1 fulfilling criteria B–D	A. At least two attacks fulfilling criteria B and C
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal
C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoid-ance of routine physical activity (e.g. walking or climbing stairs)	C. At least two of the following four characteristics: 1. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession 2. Each individual aura symptom lasts 5-60minutes 3. At least one aura symptom is unilateral

D. During headache at least one of the following: 1. nausea and/or vomiting 2.photophobia and phonophobia	
E. Not better accounted for by another ICHD-III diagnosis.	

2. Migraine treatment

As Antonaci *et al.* state, the pharmaceutical industry has seen few advances in recent years for acute migraine treatment and migraine prevention. Some potential new approaches are being developed. The range of potential anti-migraine drugs has increased over the last years and more data about their efficacy is available, thus enabling the improvement of acute treatment and prevention of migraine [114].

According to Antonaci *et al.*, the treatment of migraine is divided into acute and preventive treatment. Acute treatment is used to eliminate migraine attacks whereas preventive is aimed at reducing the frequency of attacks [115].

Cady and Farmer report, that 97% of migraine sufferers are treated with acute therapy and only 8-13% receive preventive treatment [116] As Antonaci *et al.* state, an important factor in migraine treatment is early therapeutic intervention when pain is still mild and which in turn can help to accelerate the pain-free response [117]. Steiner *et al*. stress that a very important aspect of migraine treatment is the nature of the chosen medication together with its duration and frequency of use in order to receive the maximal effective therapy and to avoid development of medication overuse headache (MOH) [118].

Antonaci reports, that different evidence-based guidelines for migraine management have been developed to aid the improvement of migraine management. The guidelines encompass evidence-based recommendations and effective medications for acute treatment of migraine attacks and for migraine prophylaxis [119].

2.1 Acute treatment

Effective acute treatment forms the basis of successful migraine management. Today, migraine management is more qualitative and allows an individual approach to each patient depending on the course of the disease, comorbidities and response to therapy [120]. EFHS defines migraine treatment as successful when the following criteria are observed: pain free after 2

hours, improvement of headache from moderate or severe to mild or none after 2 hours, consistent efficacy in two of three attacks or no headache recurrence and no further drug intake within 24 hours after treatment [121,122].

Cady and Farmer state, that an important factor for the efficiency of acute treatment is timing of early intervention. Clinical data support that the earlier the therapy is initiated, the better the outcome is that is achieved. According to their statement, acute treatment should therefore be started at the very onset of attack while the headache is still mild [123].

Fuman and Schoenen summarize key features for the successful use of acute anti-migraine drugs:

- the drug should be administrated at the very onset of migraine;
- the dosage must be sufficient for full efficiency in migraine treatment
- The co-administration of anti-emetic or pro-kinetic drugs may improve the absorption of the primary drug and thus ameliorates speed of action and efficacy;
- the chronification of headache or development of MOH can be provoked by overuse of acute medications and thus, their intake should be restricted. It is recommended to use triptans, ergotamine or combination analgesics for no more than one day per week and no more than two days per week of simple analgesics or non-steroidal anti-inflammatory drugs;
- severity and response to treatment can be different between attacks and should be accounted for during acute treatment [124].

As Kalra and Elliott write, acute treatment is divided into non-specific treatment and specific treatment. Non-specific treatment includes NSAIDs, opioids and combinations of analgesics and anti-emetics as symptomatic treatment. Drugs used for specific treatment are triptans and ergot derivatives [125].

The choice of migraine specific drugs for acute therapy of migraine depends on the type of headache attacks such as their intensity and severity. Table 3 presents medications recommended for acute treatment of migraine attack depending on its severity.

Table [3]. Type of medication prescribed for treatment of migraine attack, depending on its severity by Gallagher and Cutrer, 2002 and Aukerman *et al.*, 2002 [126,127].

Severity of the migraine attack	Type of medication
Mild-to-moderate migraine	Nonspecific agents (NSAIDs, combined medications)
Moderate or severe migraine	Specific agents (triptans, ergotamine, dihydroergotamine)
Migraine associated with severe nausea or vomiting	Non-oral route of administration or co-administration of anti-emetics
Severe migraine that fails to respond to other treatments	Self-administered rescue medication

2.2 Non-specific treatment

Non-specific medications proposed for acute treatment of migraine can be used to treat mild to moderate pain intensity, if there is no need for stronger migraine specific agents and response to therapy is satisfactory.

2.2.1 Non-steroidal anti-inflammatory drugs

Kelley and Tepper describe NSAIDs as an appropriate and effective decision for migraine treatment. Their efficacy is explained by their ability to affect many mechanisms that are involved in the initiation of migraine; the neuro-inflammatory processes, prostaglandin synthesis and release of vasoactive substances [128]. As Pardutz and Schoenen write, efficacy of NSAIDs

in migraine therapy is proven by many controlled trials. NSAIDs exert their anti-inflammatory, analgesic and anti-pyretic effects [129] by blocking COX 1 and COX 2, the predecessors of prostaglandins. According to Cady and Farmer, prostaglandins are reported to play an essential role in the vascular changes after CSD [130].

Ong *et al.* referring to data from several studies, state, that NSAIDs can reduce the risk of migraine chronification related to other medications for acute migraine treatment. They should however be taken carefully in patients suffering from diseases of the gastrointestinal tract and the cardiovascular system and additionally in cases when they are frequently used, because of their potential side effects [131].

Referring to the data of several studies, Rothrock states that efficiency of NSAIDs is almost equal to triptans in migraine therapy. Another advance in favor of NSAIDs is that they are more accessible to the patient due to their cheaper cost. Rothrock states also, that NSAIDs also show lower risk of development of MOH compared to other acute antimigraine drugs [132].

As Cady and Farmer write, when comparing selective COX 2 inhibitors to the non-selective COX 1/COX 2 type, it still remains unclear which is more effective. It is known, however that the former carries high potential cardiovascular risks with usage [133].

The European Federation of Neurological Associations (EFNS) task force recommends the following NSAIDs for mild/moderate migraine attack: naproxen, ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and tolfenamic acid. NSAIDs can be used as monotherapy, but in combination with triptans their efficacy increases [134].

Naproxen and ibuprofen

Khalid *et al.* write, that naproxen or ibuprofen are good treatment decisions for migraine management in young people who have no contraindications to usage of these drugs in relation to their gastrointestinal side effects, which are notably more common for naproxen compared to ibuprofen. Khalid *et al*. also state, that ibuprofen additionally is safe for use in children [135,136]. As

Suthisisang *et al.* state, ibuprofen doses of 200 and 400 mg show short-term efficacy in reducing migraine headache with a dosage of 400 mg being more likely to provide relief from photophobia and phonopobia [137]

Diclofenac

According to Xu *et al.* statement, diclofenac potassium and diclofenac sodium have shown to be effective and well tolerated in migraine patients [138]. As Pardutz and Schoenen state, diclofenac sodium has shown to be as effective as oral sumatriptan 100 mg in one study and showed to have less adverse effects [139]. The efficacy of K-diclofenac has been proven in two multicenter trials, one European and the other one American. Referring to the data of both studies, Kahn reported, that the oral solution and tablets of K-diclofenac also showed to be superior to placebo for the reduction of migraine-associated symptoms. Kahn writes, that nausea was reported as the most common side effect for oral diclofenac. As Kahn notes, it is also important to remember that fact is that patients who frequently use diclofenac as well as the elderly are at the greatest risk for cardiovascular events, including myocardial infarction and death [140].

Paracetamol

Khalid *et al.* report, that paracetamol has limited evidence of efficacy in migraine treatment and is not usually first-line treatment [141]. As Pardutz and Schoenen write, paracetamol is efficient at a dose of 1000 mg [142] Derry and Moore summarize that paracetamol 1000 mg plus metoclopramide 10 mg provide similar levels of headache relief to oral sumatriptan 100 mg for acute migraine in patients with contraindications to non-steroidal anti-inflammatory drugs or aspirin. [143].

Acetylsalicylic acid

As Pardutz and Schoenen write, acetylsalicylic acid (ASA) is effective in treatment of mild pain, through to migraine headache pain. ASA doses of 500 to 1000 mg have been shown to be significantly superior to placebo for migraine therapy in 13 trials [144]. Kirthi *et al*. concluded that a single 1000 mg dose of ASA produces headache relief at 2 hours in 52% of attacks. Freedom

of pain at 2 hours is achieved in 24% of attacks. As Kirthi *et al.* state, a combination of metoclopramide with ASA significantly reduces nausea and vomiting, but has minimal additional effect on treatment of the headache. According to Kirthi *et al.* statement, aspirin alone is comparable to sumatriptan 100 and 50 mg only the adverse-effects are more prominent for sumatriptan [145]

Goadsby and Sprenger concluded that paracetamol and ASA are cost-effective, cheap drugs making them more affordable and therefore accessible compared to other drugs [146].

Tolfenamic acid

Pardutz *et al.* report, that efficacy of tolfenamic acid in acute treatment of migraine attack has been proven in three trials. It was found that the rapid release form has equal efficacy to oral sumatriptan, ASA 500 mg and ergotamine 1 mg [147].

2.2.2 Combined analgesics

Straube *et al.* write that combination of ASA with paracetamol and caffeine is considered to be effective in acute migraine treatment and is also more effective than the single substance or combinations without caffeine [148]. EFNS equate effectiveness of this combination to oral sumatriptan at a 50 mg dose [149].

2.2.3 Anti-emetics

According to Goadsby and Sprenger statement, anti-emetics should be used for patients suffering from nausea and vomiting. The addition of anti-emetics to NSAID or analgesic-based therapy helps to treat migraine-associated nausea. It is also possible, that anti-emetics may improve efficacy of the other drugs through improvement of their absorption [150], but there is no evidence supporting this assumption. As stated in EFNS guideline 2009, metoclopramide 20 mg is recommended for both adults and adolescents however, it must be noted that the drug may exert extrapyramidal side effects in children. In such cases domperidon 10 mg is the recommended line of treatment [151]

2.2.4 Opioids

Gupta *et al.* write, that opioids are less effective in acute migraine treatment compared with non-steroidal anti-inflammatory drugs or dyhidroergotamine [152]. Cady and Farmer state, that neither opioids nor butalbital are recommended as medications of first-choice for migraine treatment as they are reported to have low levels of efficacy in acute migraine therapy [153]. Nancy *et al*. stress that opioids have no impact on the inflammatory processes and neurovascular changes during migraine [154]

The American migraine foundation insists on limiting opioid analgesics prescription for acute management of migraine or suggests to avoid them completely due to the nature of their side effects [155]. Levin reports that common adverse events are dizziness, sedation, nausea, gastroparesis, constipation and vomiting [156]. Kelley and Tepper stress, that opiods can also easily lead to addiction [157] and often result in narcotic-induced hypersensitivity. The latter can occur after a single high-dose and leads to MOH according to American migraine foundation [158]. Opiates should be used as a reserve medication for patients who do not respond to migraine specific treatments. The American Academy of Neurology Practice Parameter: Evidence-based Guidelines for Migraine Headache emphasizes that opioids and butalbital combinations should be used adequately. Silberstein recommends to only use opioids as a treatment for a maximum of two headache days per week [159].

Butorphanol

Lee *et al.* describe butorphanol as an opioid analgesic exerting morphine like effects [160]. The intranasal formulation of butorphanol tartrate is advised as a fast-acting and easy method for relief of acute pain. Loder reports, that efficacy of butorphanol for acute migraine treatment has been approved in two double-blind placebo-controlled clinical trials [161]. The American National Headache Foundation evaluates butorphanol tartrate as a fast-acting drug. It takes effect within 15 minutes and maximal efficiency can usually be achieved within 1 to 2 hours. The efficacy lasts from 4 to 5 hours [162].

Butalbital

As Cady and Farmer write, butalbital can be used as combination with aspirin,acetaminophen and caffeine. It treats symptoms but does not affect the migraine process. Drugs in combination with butalbital but without codeine are usually well tolerated and can additionally decrease anxiety. As Cady and Farmer write, the most common side effect associated with their use is drowsiness in addition to the side effects of each additional component of the combination treatment [163]. Lipton *et al.* report, that non-randomized, placebo-controlled studies show controversial data about the efficacy of butalbital-containing drugs for acute migraine treatment [164]. Wenzel *et al.* stress, that usage of butalbital-containing products should be limited and carefully monitored to avoid overuse or development of MOH [165].

2.3 Specific treatment

Specific medications proposed for acute treatment of migraine can be used to treat moderate to severe pain intensity. They include triptans and ergot derivatives; the last one should be avoided and can be prescribed to patients non-responding to other safer treatments, because of their side effects and ability to cause addiction.

2.3.1 Triptans

According to Belvis *et al.* triptans are called serotonin 5-hydroxytryptamine receptor agonists and are the mainstay of treatment for acute migraine attacks. As Cady and Farmer state, triptans are considered to be the first-line abortive medication for treatment of moderate and severe migraine attacks. They are often the medication of choice for patients who have shown poor response to NSAIDs and combined analgesics [166,167].

According to Diamond *et al.*, triptans are believed to relieve migraine pain by interfering with the vasoconstriction cascade. As Diamond *et al.* explain, all triptans are serotonin receptor agonists. They bind to 5HT1B receptors on the trigeminal vasculature and result in vasoconstriction of dilated blood vessels. Triptans also bind to 5HT1D receptors on trigeminal nerve endings that surround blood vessels, whereby they block the release of neuropeptides from the trigeminal afferents, reducing vasodilation and inflammation [168].

According to Capi *et al.,* today, seven triptans are avaliable for acute treatment of migtaine attack. These are: sumatriptan, zolmitriptan, eletriptan, naratriptan, rizatriptan, almotriptan and frovatriptan. As Capi *et al.* write, all triptans are biochemically similar but differ in their pharmacokinetic and pharmacodynamic profiles [169]. Interestingly, it has been observed that a particular triptan can be efficacious in migraine treatment where another triptan has failed as stated in the EFNS guideline 2009 [170,171].

According to Capi *et al*. and Bigal *et al*. statements, the relief with or without absence of pain after 2 hours and a decrease of rescue medication use has been shown when treatment with triptans was initiated at the very onset of the migraine attack. They also state, that triptans are effective in the reduction of nausea, vomiting, photophobia and phonophobia [172,173].

Antonaci *et al.* describes different routes of administration of triptans. Namely, they may be taken orally (tablets, capsules, wafers), subcutaneously (injections), intranasal (intranasal sprays), rectally (suppositories) and transdermal (patches) [174]. As Vikelis *et al.* state, efficacy of treatment (headache response, freedom from pain, sustained headache response, response of other migraine symptoms), tolerability and the severity and duration of adverse effects depends on the particular triptan and its formulation. The differences between triptans should be discussed when choosing specific one for migraine treatment. The advantages and disadvantages of different routes of administration of acute migraine attack medications are compared in Table 4 below.

Table [4]. Comparison of strengths and weaknesses of different routes of administration of acute migraine attack medications adjusted by Vikelis *et al.* [175]

Route of Administration of acute migraine attack medications	Advantages	Disadvantages
Oral	Patients prefer and are more comfortable with taking tablets. Convenient, easy to use. Cost effective.	Gastrointestinal dysfunction may result in delayed absorption and can also result in patients postponing or even avoiding the use of tablets.
Nasal	Drug bypasses gastrointestinal tract and first pass metabolism; acts despite presence of gastrointestinal dysfunction. Faster onset of action than tablet form. Easy to use.	A significant portion of drug is swallowed and absorbed in the small intestine. Some patients are uncomfortable with nasal administration.
Injectable	Drug bypasses gastrointestinal tract and first pass metabolism; acts despite	Often considered as the invasive, more complicated and uncomfortable choice. Higher recurrence rates and more adverse events than other formulations.

	presence of gastrointestinal dysfunction. Fastest onset of action. Most effective at 1 and 2 hours.	
Transdermal	Drug bypasses gastrointestinal tract and first pass metabolism; acts despite presence of gastrointestinal dysfunction. Easy to use, no injection discomfort, better for those who dislike nasal sprays.	Novel technology. Patients may be unfamiliar with apparatus. Possibility of application site adverse reactions.

By comparing different routes of drug administration it can be concluded, that each route has its advantages and disadvantages. As well as the choice of drug, its optimal formulation may differ for each patient. The onset of action, side effects and recurrence rate vary depending on the route of administration. The choice of drug and its formulation also depends on the severity of headaches, convenience of use and its pharmacokinetic profile. Thus, the drug and its formulation should be individually matched for each patient taking into account all of these factors and the patient's preferences.

2.3.1.1 Administration routes of triptans

As Helfand and Peterson write, currently available triptan formulations include tablets, subcutaneous injections, nasal sprays and suppositories [176].

Oral. Ferrari *et al*. state, that triptan tablets are the most commonly used form of triptans for acute migraine treatment. According to Ferrari *et al*. statement, sumatriptan is the first and most widely prescribed triptan and most European countries use sumatriptan oral at 100 mg [177].

Subcutaneous. As Moore and Miner explain, the advantage of sumatriptan injection is a rapid absorption. The effect is achieved in 10 minutes. The disadvantages are high recurrence rate and more serious adverse events compared to other formulations. Moore and Miner also state, that many patients consider an injection to be an uncomfortable route of administration [178].

Intranasal. Vikelis *et al.* highlight, that the advantages of intranasal route of administration are rapid onset of action and easy administration. It significantly enhances the bioavailability and onset of action of the drug compared to the oral route of administration. Vikelis *et al.* note that a portion of the drug is swallowed and absorbed in the small intestine and therefore it is not a fast or effective route of delivery for migraine patients with gastric stasis [179]. However, as write Láinez *et al.*, nasal spray formulation can be a good option for patients with migraine associated nausea and vomiting [180].

Rectal. Triptans are available as rectal suppositories. As Derry *et al.* note, this route of administration is preferable for individuals experiencing nausea and vomiting during migraine attacks [181].

Transdermal. Vikelis *et al.* describe an iontophoretic transdermal system formulation of sumatriptan that has been developed for the acute treatment of migraine with and without aura in adults. The patches deliver sumatriptan transdermal into the subcutaneous tissue. Skin patches prove to be a good choice for patients with migraine-associated events such as nausea, vomiting and gastroparesis. Patients who do not respond to oral medications could also benefit from transdermal formulation. As Vikelis *et al.* write data from randomized, double-blind controlled clinical trials have shown minimal triptan-related side effects and superior efficacy compared to other formulations of sumatriptan [182]. According to American Food Drug Administration (FDA), in the post-marketing phase, side effects in the form of skin reactions have been reported. They included severe redness, cracked skin, welts and burns or scars on the skin area where the patch was worn. As FDA states many cases were resolved within hours to weeks. However, there were reports of cases with non-reversible skin reactions such as skin discoloration and others, thereby in 2016, the sale, marketing and distribution of the first transdermal triptan was suspended [183].

Fleischhacker and Brooks state, that triptans are usually well tolerated but sometimes patients do experience side effects. Some of the most common adverse events are sleepiness or fatigue, chest tightness, dizziness and a warming sensation. For some patients, triptans may be contraindicated with conditions such as vascular disease, coronary heart disease, stroke and multiple vascular risk factors [184].

Volpi-Abadie *et al*. describe that in some rare cases, triptans can cause a serotonin syndrome. The serotonin syndrome is thought to develop due to the high serotonin levels generated with triptan treatment. Volpi-Abadie *et al.* explain that the synthesis of serotonin may increase when central and peripheral serotonin receptors are over-activated. Common symptoms are hypertension and tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus,

and hyperreflexia. In moderate cases hyperthermia (40 ◦C) may also occur [185,186].

According to Capi *et al.* and Bigal *et al*., when selecting triptan medication for patient, the following factors should be taken into account: speed of onset, intensity of pain, duration of the migraine attack, onset of action of the drug, individual patient response and tolerance, relief of associated symptoms, headache recurrence, consistency of the response, different delivery systems and the patients individual characteristics such as medical history and lifestyle [187,188].

2.3.1.2 Comparing triptans

Results from a combination of approximately one hundred double blind, randomized trials have proved the efficacy of triptans in migraine treatment. Evaluation of efficacy of triptans treatment has been determined through factors including pain free after 2 hours, headache response, pain free response, recurrence of headache and rescue-medication use as described by Nett *et al*. [189].

As Cameron *et al.* write it is hard to say which triptan is the most effective for migraine treatment as a triptan that is highly effective for one patient may show lower efficacy for another. The line of treatment also depends on patient's preferences and expectations. Sometimes it is necessary to try more than one triptan to find the most suitable one for each individual.

Cameron *et al*. have provided a systematic review and meta-analysis of 133 randomized controlled trials that compared triptans with placebo-controlled or active migraine treatments and concluded that a standard dose of triptans relieved headaches within 2 hours in 43 to 76% of patients. Cameron *et al.* highlighted, that between 18 and 50% of patients experienced freedom from pain within 2 hours and 29 to 50% of patients experienced sustained headache relief at 24 hours. Sustained freedom from pain at 24 hours was observed in 18 to 33% of patients with use of rescue medications varying between 20 and 34%. As Cameron *et al.* write analysis also showed that most triptans, with the exceptions of frovatriptan and naratriptan, provided similar

pain relief in the acute treatment of migraine. Cameron *et al*. also accentuated, that standard dose triptans were associated with more favorable results than ergots for 2- and 24-hour outcomes. They also showed equal or more favorable results than NSAIDs, ASA, and acetaminophen for 2-hour outcomes. Cameron *et al.* concluded that sumatriptan subcutaneous injection, rizatriptan ODT, zolmitriptan ODT, and eletriptan tablets have presented the best efficiency compared to other triptans [190].

Thorlund *et al.* with the aim to determine the relative efficacy of all available triptans for acute migraine treatment and to establish which triptan has the highest efficacy provided another, multiple treatment comparison meta-analysis of 74 randomized clinical trials.

This study found statistically significant differences between available triptans. As expected, all triptans were superior to placebo. As Thorlund *et al*. write it was concluded that eletriptan consistently showed the largest treatment efficacy in terms of 2 hours pain-free response and 24 hours headache response in relation to other triptans, both for short-term and sustained outcomes. Thorlund *et al.* also outline that rizatriptan, zolmitriptan and sumatriptan doses of 100 mg also appeared effective at two hours, whereas only zolmitriptan and high-dose sumatriptan maintained their efficacy at 24 hours. Frovatriptan data were not available at the 24 hours endpoint [191].

When comparing the fastest onset of efficacy of different triptans, the triptan class can be divided into three categories: ultra-fast acting triptans, fast acting triptans and slow acting/long lasting triptans (Table 5).

Table [5]. Triptans classified by onset action, elimination half-life, bioavailability and clinical use (EFNS 2009, S. Miller 2012) [192,193].

Category of Triptan, formulation	**Dose (mg)**	**Usage for migraine type**	**Time to peak levels (h)**	**Elimination half-life**	**Bioavailability (%)**	**Clinical use**
Ultra-fast acting						
Sumatriptan SC	6	Quick onset, severe pain	10 min.	2	97	For rapid onset attack
Fast acting						
Rizatriptan NS PO ODT	5, 10	Moderate onset, moderate pain	1 2-3	2	40-50	ODT/NS for nausea and vomiting
Eletriptan PO	20, 40		1.5-2	4	50	-
Sumatriptan PO	50, 100		2-3	2	14	For nausea or vomiting occur
Almotriptan PO	12.5		1.5-2	3.5	70	Previous adverse effects

Zolmitriptan PO ODT NS	2.5, 5 5		2.5-3	2.5-3	40-50	PDT/NS for nausea and vomiting
Slow onset/long acting						
Frovatriptan PO	2.5	Slow onset, long duration, menstrual, prodrome	2-4 h	26	20-40	Long lasting attacks
Naratriptan PO	2.5		2-3 h	6	60-70	Previous adverse effects and long lasting attacks

According to EFNS guideline 2009 subcutaneous sumatriptan has a very fast onset of action. Therapeutic effect can be achieved in 10 minutes. This is followed by oral rizatriptan and eletriptan, which require about 30 minutes as stated in the EFNS guideline 2009. According to EFNS guideline 2009, oral sumatriptan, almotriptan, and zolmitriptan take effect in 45 to 60 minutes and naratriptan and frovatriptan have the longest onset of action at up to 4 hours. Intranasal zolmitriptan acts faster compared to its oral formulation. As stated in the EFNS guideline 2009, subcutaneous sumatripan has the best pain relief after 2 hours with up to 80% response rates [194].

Ferrari *et al.* state that the efficacy of intranasal and oral sumatriptan (50-100 mg) formulations is equal. Unsurprisingly, 25 mg oral sumatriptan is less effective than doses of 50 mg and 100 mg but it clearly manifests less side effects [195]. According to Becker *et al.,* sumatriptan rectally should be prescribed to patients who present vomiting as their efficacy is similar to the oral sumatriptan dose of 50 or 100 mg [196,197].

As Capi *et al*. write naratriptan and frovatriptan at dose 2.5 and 5 mg have longer half-lives compared with all other triptans and thus the duration of onset of their efficacy is longer [198]. As stated in the EFNS guideline 2009, naratriptan 2.5 mg and frovatriptan 5 mg compared with sumatriptan at a dose of 50 or 100 mg are less effective in migraine treatment but they present less side effects. According to EFNS guideline 2009, rizatriptan 10 mg shows to be more effective than sumatriptan 100 mg; oral zolmitriptan 2,5 or 5 mg, almotriptan 12,5 mg and eletriptan 40 mg show similar efficacies and also similar side effects; eletriptan 80 mg is the most effective oral triptan but unfortunately, side effects are also more pronounced [199,200,201].

As Geraud *et al.* state, the disadvantage of subcutaneous sumatriptan administration is its high recurrence rate. Naratriptan and frovatriptan present the lowest recurrence rates but they also demonstrate poor initial response rates. According to Geraud *et al.* statement, it is assumed that triptans with a longer half-life possess a lower recurrence rate [202].

Consequently, it can be stated, that sbcutaneous sumatriptan, oral formulations of eletriptan, rizatriptan and zolmitriptan show the best treatment responses compared to other triptans.

As Werner J. Becker writes, each migraine patient possesses individual disease characteristics and traits and thus responds in different ways to a chosen triptans. Medication tolerability may also differ significantly. Werner J. Becker states that the differences between patients may play a more significant role for treatment than the differences between profiles of oral triptans [203].

Headache frequency and severity, response to therapy, side effect profiles and tolerability, headache recurrence rates and of course patient's preferences are all factors that should be taken into consideration when choosing a triptan for acute migraine therapy.

2.3.2 Ergot derivatives

According to Huma *et al*. statement, the ergot alkaloids were the first specific agents indicated for the abortive management of migraine. Ergotamine tartrate and dihydroergotamine mesylate are used today for such abortive treatment of migraine attack [204].

As George De Maagd explains, the ergot derivative impact at serotonergic 5-HT1 A/D/F/B and 5-HT2 receptors. Additionally they may bind to the alpha-adrenergic and dopaminergic receptors. Often ergots may also result in more side effects compared to other treatment types. George De Maagd states that since the introduction of triptans, ergots were partly replaced as acute anti-migraine drugs [205]. Kalra and Elliott state, that in patients not responding to triptan therapy, ergots still may play a significant role in the acute treatment of migraine [206].

Ergotamine and dihydroergotamine

Schiff describes ergotamine as an alkaloid derivative of ergot. It exerts a powerful vasoconstrictive action. Ergotamine acts as an agonist at 5-HT1B and

5HT1D receptors. It may be used for treatment of moderate to severe migraine attacks [207]. According to WHO, the use of ergotamine tartrate is considered only when other treatments failed. The suggested dose in adults according to WHO is 1–2 mg at the first sign of an attack, which could be increased to a maximum of 4 mg a day. If there is a need to repeat the dose, an interval should be complied of at least 4 days between doses. As the WHO states, the weekly maximum dose is 8 mg. The treatment should not to be used more than twice a month [208].

Goadsby and Sprenger describe another ergot derivative for migraine treatment - dihydroergotamine (DHE) and state, that DHE is usually better tolerated than ergotamine and tends to cause less nausea and vomiting. Due to its poor oral bioavailability it is less effective than other treatments but intranasal As Goadsby and Sprenger write, DHE does present a better bioavailability at about 40 %. The onset of action is relatively slow. DHE has clearly shown to be inferior to intranasal and subcutaneous sumatriptan. Parenteral DHE is more effective in severe migraine attacks, but the side effects are also more expressed [209].

Schiff describes common side effects are dizziness, nausea and vomiting, cold, clammy hands and feet, muscle pain, numbness, feeling discomfort or anxiety. Overdose or chronic overuse of ergotamine increases the risk of ergotism, a rare case of arterial insufficiency [210]. Brancaccio focuses on ergots ability to cause widespread systemic arterial vasoconstriction, leading to development of organ ischemia. He states that in such cases the therapy with ergots should be interrupted [211].

Consequently, the selection of drugs for migraine treatment is very wide for today. There are some specific intended drugs for acute migraine treatment and some certain drugs that can be used as an alternative if the previous are contraindicated or not effective. Different formulations allow the patient to have ease use and to avoid specific side effects.

The summary of specific and non-specific drugs used for acute migraine treatment, level of efficacy, appropriate dosages and common side effects are presented in Table 6 below.

Table [6]. Specific and non-specific anti-migraine drugs for acute treatment of migraine with evidence of efficacy, side effects and contraindications as recommended by EFNS and EHF [212,213,214, 215,216,217].

Medication	Dose (mg), Dosage interval	Level of efficacy	Side effects	Contraindications	Comment
ASA	1000 mg (oral),max 5,6 g/day Every 4 h	A	Gastrointestinal side effects, risk of bleeding, kidney failure.	Elderly, pregnancy, patients with gastrointestinal (ulcer disease, gastritis) or cardiovascular diseases. Interaction with other drugs may occur.	Reduces migraine-associated symptoms.
Ibuprofen	200 – 800mg, Max 2400 mg/day Every 4 h	A			-
Naproxen	500-1000 mg, max 1375 mg/day Twice a day	A			-
Tolfenamic acid	200 mg, max 400 mg	B			-
Diclofenac	50-100 mg, Max 150 mg/day	A			-
Paracetamol	1000 mg (oral), max 4000 mg/day Every 4 h	A	Caution in liver and kidney failure	-	For migraine treatment during pregnancy.

Butorphanol	1 mg, nasal spray	A	Side effects include sedation, respiratory and cardiac depression, and increased risk of dependency.	-	Opioids can sensitize the central nervous system to pain. Increase of risk of medication nover-use headache.
Butalbital	50 mg	C	Weakness, addictive potential.	-	Rescue therapy. Limit use.
Sumatriptan	25,50,100 (oral), 25 mg suppositories, 10 and 20 mg nasal spray, 6 mg subcutaneous injection Max 200-300 mg/day 2 h	A	General side effects for all triptans: chest symptoms, nausea, distal paraesthesia, fatigue, pins and needles sensation, elevated blood pressure.	General contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular	100 mg sumatriptan is reference to all triptans
Zolmitriptan	2,5,5 MG (oral), 5 mg nasal, max 10 mg/day, 2 h	A			-

Naratriptan	2.5 mg (oral), 5 mg max/day, 4 h	A		disease, Raynaud's disease, pregnancy and lactation, age under 18 (except sumatriptan nasal spray) and age above 65, severe liver or kidney failure, basilar or hemiplegic migraine. Use of CYP3A is a contraindication to use of triptans because of potential serious adverse effects.	Less but longer efficacy than sumatriptan
Risatriptan	5 mg, 10 mg (including mouth dispersable wafes), max 20 mg/day, 2 h	A			5 mg when taking propranolol wafer form.
Almotriptan	12.5 mg (oral), max 25 mg/day, 2 h	A			Dizziness, weakness, hot flushes, nausea and vomiting. 80 mg allowed if 40 mg not effective. 80 mg allowed if 40 mg not effective.
Eletriptan	20, 40 mg (oral), max 80 mg/day, 2 h	A			Less but longer efficacy than sumatriptan. Linear dose-efficacy relationship.

Frovatriptan	2.5 mg (oral), max 5 mg/day, 4 h	A			-
Ergotamine tartrate	1 mg (oral), 2 mg suppositories Max 6 mg/day	A	Nausea and vomiting, rebound headache.	Cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, and pregnancy and lactation. 4CYP3A inhibition is known to elevate serum levels of ergotamine and dihydroergotamine mesylate an increase the risk of ergotism	Rescue therapy. Limit use.
Dihydroergotamine	2 mg, nasal spray	A	Less nausea and vomiting compared to ergotamine. Nasal sprays may cause bitter or foul taste in the mouth or throat and irritation in the nose.		0,5 mg/nostril repeat in 15 min. 1× For 2 mg total dose. Rescue therapy. Limit use.

Acetaminophen/aspirin/ caffeine	500/500/130 mg	A	For each component individual.	Elderly, pregnancy, patients with gastrointestinal or cardiovascular diseases.	-
Sumatriptan/naproxen	85/500 mg	A	For each component individual.	-	Combined drug of naproxen/sumatriptan shows to be superior compared to the single compounds.
Butalbital/acetaminophen/ caffeine	50/325/40 mg	C	For each component individual.	-	Occasional use for moderate-to-severe migraine. Limit use due to risk of overuse.

The drugs variations proposed for acute treatment may vary depending on the country, as well as dosage and accepted level of efficacy. Drugs presented in a Table 6 are recommended by European guidelines for acute treatment of migraine headache in Europe. The EFNS and EHF propose some approaches for migraine treatment and recommendations if the treatment fails.

2.3.3 Approaches for migraine treatment

A key aspect of acute migraine treatment is the type of approach taken. Depending on the country, guidelines, patient's preferences and physician's opinion, migraine therapy is conducted differently.

According to Antonaci *et al*., there are two types of approaches for migraine treatment: stepped care and stratified care. The approach to treatment is different in both cases and each case presents different advantages and disadvantages. Which type of approach is the most effective still remains under debate [218].

The European Headache Federation recommends stepped care for migraine therapy. It is stated that this strategy safely provides the most effective and cost-effective individualized care [219].

Guidelines for stepped care are well defined and simplifies the treatment decision [220]. In the EHF guideline the major principles of stepped care are explained. This type of approach is divided into two steps of sequential treatment. Usually three attacks are treated at each step and if there is no progress or success at this initial step, the treatment proceeds to the next one. Step one begins with symptomatic therapy i.e. a simple analgesic. If needed, an anti - emetic can additionally be taken. The patient is proposed to start treatment with the safest and the cheapest medication. If this initial treatment fails, the patient is advised to proceed to the next step. Step two proposes migraine specific treatment [221]. Antonaci *et al*. stress that the disadvantage of such an approach is that patient is not involved in the treatment decision and so the

time when the appropriate treatment will be found can be protracted, and result in a worsening of the disease [222].

Xu *et al*. describe the second approach proposed for migraine treatment, stratified care, which is currently suggested to be a primary strategy. It is often used in selecting medications for migraine therapy. According to Pringsheim *et al*., this type of approach depends on the severity of the disease and the presence of associated symptoms and degree of disability are assumed to be taken into account [223,224]. Using this type of approach, patients are involved in the treatment decision and migraine-specific medication is preferred for treatment. As Rothrock states, the stratified care approach allows the patient to select their own therapy based upon the headache's characteristic as well as presence or absence of migraine-associated symptoms [225]. An important feature is that patients must be clear and straightforward when consulted about their medication. Treatment choice must be based on consideration of clinical evidence of efficacy and importantly, the patient's expectations should be discussed in detail.

Lipton and colleagues conducted a prospective study in which they showed that the stratified care approach provides the optimal clinical outcome. This type of approach was associated with lower costs compared to others [226]. Silberstein recommends stratified care with the use of triptans for patients suffering from moderate or severe migraine. Stratified care is also recommended for patients poorly responding to NSAIDs [227].

2.3.4 Management of medication overuse

The ICHD –III identifies MOH as a headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication, namely when used on 10 or more days per month, depending on the medication for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped [228].

Goadsby and Sprenger state, that almost all medications for acute treatment of migraine attack, when they are inadequately used, can be associated

with the development of MOH. It is typical for patients with frequent headaches, because they often overuse analgesics, opioids, ergotamine derivatives and triptans.

Consequently, as Goadsby and Sprenger state, analgesic overuse should be reduced and eliminated to avoid some complications, like migraine chronification or development of MOH. There is no universally accepted, evidence-based approach to the management of MOH [229]. As Kristoffersen and Lundqvist state, the best can be done to abolish abused drug, to inform and to provide the patient with pharmacological support and to prevent relapse [230].

In some cases when the patient experience severe and frequent migraine attacks or when a patient knows the definite trigger provoking an attack, like menses, migraine prophylaxis might be a good treatment decision and will help to avoid often attacks or overuse of acute migraine treatments.

3. Preventive treatment

D'Amico *et al*. state, that the goal of prophylaxis is to generate a decline in frequency of migraine attacks. Thus, an appropriate prophylaxis could reduce the global prevalence and severity of migraine [231]. According to Khalid *et al.* statement, only 13% out of 38% of migraine sufferers receive preventive therapy. Effective preventive therapy of migraine also leads to reduction of headache duration [232, 233], enhances patient's response to acute therapy and results in a better quality of life according to Shapiro [234]. Through new advances in migraine prevention, development of medication, overuse headache and chronic daily headache can also be avoided [235].

As Fumal and Schoenen state, prophylactic anti-migraine treatment has to be individually selected for each patient taking into account efficacy, tolerability, comorbid disorders, type of migraine and disability. Additionally and very importantly, patient's demands and expectations must be taken into account [236]. According to Canadian Headache Society Guideline for Migraine Prophylaxis 2012, prophylaxis should be started with a preventive

medication on a low dose, increasing by degrees to optimal dosage. The preventive treatment should last at least two months for appropriate evaluation of its effectiveness and feasibility. As stated in the Canadian Headache Society Guideline for Migraine Prophylaxis 2012, the preventive therapy is considered effective, if the headache frequency decreases by 50% or more. As stated in the Canadian Headache Society Guideline for Migraine Prophylaxis 2012, if prophylaxis is successful, the administration of preventive medication can be reduced gradually and discontinued after six to twelve months. If there is a relapse or an appearance of headache with dose reduction, the dosage should be increased [237].

Goadsby and Sprenger outline recommendations for migraine prophylaxis of American and European guidelines. According to American guidelines, it is recommended to start prophylaxis when attacks regularly exceed two times per week. European guidelines recommend migraine prophylaxis if two attacks or more occur per month [238]. Regardless of whether migraine attack occurs or not, medication for preventive treatment should be taken daily.

The circumstances requiring the implementation of migraine prophylaxis according to the US Headache Consortium guidelines outlined by D'Amico and Tepper are as follows:

- Recurrent attacks that significantly impact the patient's daily life, despite acute treatment (two or more attacks per month, producing at least 3 days of disability or infrequent headache attacks, leading to profound disability)
- Failure of acute treatment, contraindication to it or appearance of serious side-effects from it
- Overuse of acute medications
- Appearance of hemiplegic migraine or attacks that may lead to permanent neurological impairment
- Very frequent headaches (more than two a week)
- Patient preferences [239].

Silberstein *et al.* recommend measures for optimal pharmacological prevention of migraine:

- Preventive treatment should be started at a low dose
- Preventive treatment should last at least 2 months to evaluate its efficacy properly
- Avoid interfering, contraindicated or overused medications
- Reevaluate therapy; follow-up is important
- Use of contraception and the potential risk of medication use during pregnancy must be discussed with women
- Patients should be involved in their care to improve adherence
- If comorbidities are present, they should be taken into account. It may be possible to choose medication that treats the comorbid disorder and prevent migraine
- Level of drug efficacy is an important factor [240].

According to a statement from Estemalik *et al*., the main mechanism of action of preventive medication is inhibition of CSD. It implements through blockade of calcium and sodium channels, inhibition of matrix metalloproteinases, blocking gap junctions and correcting mitochondrial myopathy [241]. Ayata *et al.* referring to data from one study using CSD animal models where CSD was induced for evaluation of various migraine preventive medications, states, that migraine preventive medications increase the CSD threshold and cause suppression of CSD [242]. According to Estemalik and Tepper statement, some preventive medications exert antiadrenergic effects and serotonin modulatory effects. These can lead to inhibition of central neuronal hyperexcitability and so further enhances the effect of neurotransmitter gamma-aminobutyric acid (GABA), thus increasing the inhibitory tone and leading to a decrease in neuronal firing [243]. In support of these findings, D'Amico *et al*. find that chronic daily administration of migraine prophylactic drugs in a dose-dependent manner, suppresses CSD frequency by 40 to 80% [244].

3.1 Medications for migraine prevention

As S. Miller writes, the pharmacological classes of prophylactic antimigraine drugs proposed for migraine treatment are: ß-blockers, calcium

channel antagonists, antiepileptic drugs, NSAIDs, tricyclic antidepressants and other miscellaneous drugs [245].

According to the European Federation of Neurological Societies (EFNS) guideline, migraine preventive medications are defined into three categories according to the level of their efficacy: first-line, second-line and third-line drugs. They are presented in Table 7.

Table [7]. Migraine preventive medications recommended by EFNS task force members 2009, according to the level of efficacy [246].

First-line	Second-line	Third-line
Propranolol, Metaprolol, Flunarizine, Valproic acid, Topiramate	Amitriptyline, Venlafaxine, Naproxen, Petasites, Bisoprolol	Acetylsalicylic acid, Gabapentin, Magnesium, Tanacetum, Parthenium, Riboflavin, Coenzyme Q 10, Candesartan, Lisinopril, Methysergide

3.1.1 ß-blockers

S. Miller states, that ß-blockers are the most widely used class of migraine preventative medications and are 60-80% effective in reducing attack frequency by more than 50% of patients [247]. As it is stated in EFNS guideline 2009, metoprolol and propranolol in comparison to ß-blockers are considered drugs with high efficacy in migraine preventive treatment [248]. Estemalik *et al*. explain the potential mechanism of action of ß-blockers in migraine prevention to be through reduction of adrenergic tone overall. ß-blockers are thought to block presynaptic noradrenergic receptors, leading to a reduction of norepinephrine release and synthesis. As Estemalik *et al.* explain this in turn leads to inhibition of central ß-adrenergic receptors, and reductıon of activity at the level of the adrenergic locus ceruleus [249]. According to statement of Parsekyan, it has been observed that the effect of ß-blockers occurs gradually and it may take at least a month before efficiency is noticeable. An

additional thing to note is that ß-blockers do not affect the aura associated with migraine [250].

3.1.2 Calcium channel antagonists

According to D'Amico and Tepper statement, calcium channelopathies are involved in the pathogenesis of migraine and it has been found that some of the hemiplegic migraine subtypes and some patients with typical aura demonstrate to have some abnormalities in the channels within cells that transport calcium [251]. Estemalik and Tepper write, that the calcium-channel blockers are considered to be effective in migraine prophylaxis. Calcium-channel blockers exert selective inhibition of intracellular calcium ion influx [252]. According to EFNS guideline 2009, they also are often considered as medication of choice in prevention for aura patients.

EFNS guideline defines flunarizine at a dose of 5 - 10 mg as the most effective non-specific calcium channel blocker. And notes that women may benefit from lower doses than men [253]. D'Amico *et al*. state that flunarizine is the most widely used calcium channel blocker worldwide. It is one of the most frequently prescribed preventive drug in many European countries, however it is not available in the US due to its side effects [254].

Khalid *et al*. describe verapamil as an old agent for migraine prophylaxis, which is surrounded by conflicting data of evidence [255]. However, as write Silberstein *et al.,* verapamil at dose of 240 mg/day is proposed as an alternative to flunarizine [256].

3.1.3 Anti-epileptics

Valproate is an anti-epileptic drug used for migraine prevention [257]. As Shahien and Beiruti write valproate is available as valproic acid and divalproex sodium, with the same efficacy seen between the various forms [258]. EFNS considers valproic acid at a dose of at least 600 mg and topiramte

in at a dose of 25-100 mg to be effective in migraine prevention. Their efficacy rates are considered to be equal to those of metoprolol, propranolol, and flunarizine according to EFHS guideline 2009 [259].

Valproate acts centrally and peripherally. Martin *et al*. describe its potential anti-migraine mechanism to be via an increase of GABA in the brain. An increase in GABA levels inhibits central trigeminal nerve activation through a reduction of experimental neurogenic inflammation in the peripheral trigeminal vascular system [260].

As D'Amico *et al.* write patients treated with valproate, flunarizine, and propranolol for migraine prevention deal with a common problem and concern - weight gain. [261,262].

As Silberstein *et al.* write, it was found that during valproate treatment weight gain can occur where the average weight gain during therapy was 6 kg and where women tended to gain weight more compared to men [263]. Garza and Swanson state, that patients should therefore be carefully treated with these agents and it is important to test them systematically due to increased pancreatitis, liver failure, and teratogenic risks [264].

D'Amico and Tepper propose topiramate as another antiepileptic medication used for migraine prophylaxis [265]. An optimal dose is 100 mg per day [266] and is a drug that presents strong scientific and clinical evidence for effectiveness.

Silberstein *et al*. explain that topiramate exerts its action through blockade of voltage-sensitive sodium channels and voltage-activated calcium channels, thus changing nerve excitability. Silberstein *et al.* write, that topiramate also decreases activity of carbonic anhydrase, inhibits the excitatory glutamate pathway and enhances the inhibitory effect of GABA [267].

Garza *et al.* state, that topiramate at a dose of 100 mg a day shows similar results to propranolol 240 mg treatment for reduction in migraine frequency [268]. Mathew *et al.* write that the recommended dose starts at 25 mg a day and should be gradually increased by 25 mg a week until the goal dose of 100 mg a day is achieved.

Gabapentin is a structural analog of GABA [269]. Shahien and Beiruti write, that gabapentin exerts an anti-nociceptive and an anti-convulsant mechanism of action and can be a good treatment option of migraine in patients with comorbid epilepsy [270]. As Estemalik *et al*. explain, gabapentin exert its anti-migraine action through blockade of voltage-gated calcium channels. Increased levels of GABA modulate 5-hydroxytryptamine action and exerts further inhibitory effects [271].

3.1.4 Non-steroidal anti-inflammatory drugs for migraine prevention

According to Parsekyan, naproxen sodium at a daily dose of 1000 mg is the most commonly used NSAID for migraine prophylaxis [272]. Another NSAID, according to EFNS, that may be substituted for naproxen is acetylsalicylic acid at a daily dose of 300 mg [273].

3.1.5 Tricyclic antidepressants

Garza and Swanson describe amitriptyline as a tricyclic antidepressant that acts as a serotonin reuptake inhibitor to increase serotonergic activity [274]. As Cady and Farmer write, amitriptyline acts as an agonist at numerous serotonin, α-adrenergic and histamine receptors. The multitude of sites of actions helps to explain its anti-migraine and anti-depressive action [275]. Taking this into consideration, D'Amico and Tepper state that amitriptyline forms a good treatment option for patients with migraine and comorbid depression or sleep disturbance [276].

3.1.6 Other drugs for migraine prevention

There are some other drugs considered to have only probable efficacy in migraine prevention. There is lack of evidence for their efficacy or the data that does exist is contraindicating. By choosing one of these drugs, it is important to estimate the necessity, benefit/risk ratio and other advantages and disadvantages.

Antihypertensive drug such as lisinopril is suggested to be effective for migraine treatment. According to Weatherall statement, there is also evidence-

based data in favour of angiotensin blockers such as candesartan considering them to be useful and well tolerated in migraine prevention [277]. However, these results have to be confirmed before the drugs can be definitely recommended for migraine prevention.

According to S. Miller, Co-enzyme Q10 and Vitamin B2 both are potentially useful in migraine treatment. S. Miller also writes that Vitamin B2 significantly reduces headache frequency when given in high daily doses of 400 mg [278].

A low magnesium level in the body is thought to cause migraine and thus magnesium supplementation is considered to be effective in migraine treatment. However, EFNS state that for oral magnesium conflicting data have been published so its efficacy must be proven [279].

S. Miller describes methysergide as a semi-synthetic ergot alkaloid, which has shown to be effective in migraine prevention. S. Miller outlines, that methysergide was the first drug developed for migraine prophylaxis and accentuates that its effectiveness in reduction of migraine frequency is equal to propranolol and flunarizine [280]. According to EFNS task force 2009, methysergide is considered to be highly effective for prophylaxis but can only be recommended for a maximum period of 6 months because of potential adverse events [281]

Pareek *et al.* describe feverfew (Tanacetum parthenium) as an effective treatment for migraine prophylaxis. Herbal remedy feverfew is known to exert anti-inflammatory action trough inhibition of prostaglandin production and secretion of serotonin. [282].

Stovner *et al*. describe the second herbal drug used for prophylaxis is butterbur root extract (Petasites hybridus) [283]. As Grossmann and Schmidramsl describe, the two main active substances are petasine and isopetasine, which have shown to exert a strong vasodilative and anti-inflammatory actions [284] through blockade of leukotriene synthesis [285]. There is however, still some contradicatory data regarding its efficacy as stated in the EFNS guideline 2009 [286].

Onabotulinumtoxin A is more recent drug suggested to be effective in migraine prpophylaxis. Antonaci *et al.* stress that for optimal efficacy, the injection of onabotulinumtoxin A should be conducted whilst adhering fully to the the recommendations of use. The drug must be accurately delivered for optimal success. As Antonaci *et al.* write, the recommended dose is 155 units administered intramuscularly, 5 units per site, the drug is typically injected across 31 sites on the head and neck and the treatment should be repeated every 12 weeks [287]. It is difficult to make draw consequences on the effectiveness of onabotulinumtoxin A in migraine prevention due to insufficient evidence. The European Federation of Headache does not recommend it for migraine prevention [288].

When choosing a migraine preventive drug, the decision must be made in favour of a well-studied drug with a high level of efficacy in order to have sufficient effectiveness for the patient. As Fumal and Schoenen state, the efficacy of drugs, their potential side effects and their interactions with other drugs have to be personally considered for each patient and the dose should be chosen for each patient individually [289].

Table 8 presents medications for preventive treatment with the evidenced level of efficacy A and B that are recommended for migraine prophylaxis by European guidelines.

Table [8]. Medications of first and second choice for preventive treatment of migraine indicating dosage, side effects and contra-indications as recommended by EFHS and EHF guidelines. (EFNS task force members 2009, EHF, S. Miller, S. Diamond) [290, 291, 292, 293].

Drug	Dose, mg	Level of evidence	Side effects	Contraindications	Relative indication
Propranolol	40–240 mg	A	Reduced energy, tiredness, postural symptoms.	Asthma, chronic heart failure, diabetes mellitus, peripheral vascular disease, conduction defects or heart block, depression, Raynaud's disease, hypotension.	Hypertension, angina, performance anxiety
Metaprolol	50–200 mg	A			
Bisoprolol	5–10 mg	B			
Flunarizine	5–10 mg	A	Drowsiness, weight gain, depression, parkinsonism.	Depression, Parkinson's disease, heart failure, cardiac arrhythmia.	Aura, hypertension, angina, asthma, dizziness, vertigo
Valproic acid	500–1800 mg	A	Drowsiness, weight gain, tremor, hair loss, fetal abnormalities,	Obesity, pregnancy, liver disease.	Mania, epilepsy, anxiety

			haematological or liver abnormalities, bone marrow dysfunction, pancreatitis.		
Topiramate	25–100 mg	A	Paraesthesiae,fatigue, anorexia, nausea, and weight loss. Serious sideeffects are acute angle-closure glaucoma, hypohydrosis–hyperthermia, metabolic acidosis and nephrolithiasis.	Special care required for patients with a family history of glaucoma, nephrolithiasis.	Mania, epilepsy, anxiety, obesity
Amitriptyline	50–150 mg	B	Drowsiness, urinary retention, arrhythmias, note that some patients are very sensitive and might only need a total dose of 10 mg, although generally 1-1,5 mg/kg bodyweight is required.	Cardiovascular diseases (especially after a myocardial infarction), severe liver disease, and mania. Concomitant use of monoamine oxidase inhibitors is	Depression, anxiety, insomnia, pain

			Dry mouth, constipation, sedation, and weight gain, the latter from antihistaminic effects. Dry mouth, constipation, tachycardia, blurry vision, and urinary retention are all anticholinergic side effects, maximal in the elderly. TCAs can lower the seizure threshold and can cause cardiac arrhythmias and orthostatic hypotension. Overdose is frequently lethal. TCAs can cause the syndrome of inappropriate ADH secretion	contraindicated. It is category C in pregnancy, and excreted in small amounts in breast milk.	

			(SIADH), and precipitate mania in bipolar patients.		
Venlafaxine	75–150 mg	B	Drowsiness, urinary retention, arrhythmias.	Drowsiness, urinary, retention, arrhythmias	Anxiety, depression
Naproxen	250–500 mg	B	Gastrointestinal side effects, risk of bleeding.	Ulcer disease, gastritis	Arthritis, other pain disorders, high risk of MOH with triptans
Petasites	75 mg	B	Belching, headache, itchy eyes, diarrhea, upset stomach. Also asthma, fatigue, and drowsiness. Elevation of transaminases.	Pregnancy, breastfeeding.	-

Conclusion

Migraine is a neurological headache disorder, resulting from the interaction between multiple gene abnormalities and both environmental and biological precipitating factors.

Migraine management is an important health care issue. To provide a maximal effective therapy of migraine, many factors should be taken into consideration.

Firstly, the correct and exact diagnosis of migraine plays a fundamental role in targeting treatment types. Then, family history, type of headaches, frequency and severity of headaches, triggers, presence of symptoms associated with migraine, comorbidity of diseases, type of medication and level of its efficacy, side-effects and tolerability and patient priorities are all factors that should be taken into account.

Last but not least is adequate patient education. The condition must be carefully explained to the patient and they must be informed about all treatment aspects including correct dosage, frequency of use, maximal doses, contraindications and probable side effects.

Already available treatments ensure appropriate therapy of migraine. Today, triptans remain the best anti-migraine specific therapy option for acute treatment. Unfortunately, their efficacy in some cases for some patients is minor, thus leaving no choice than to use less qualitative medication or drugs that exhibit various and serious side effects.

Migraine prophylaxis plays an important role in treatment of the disease. On the one side it helps to prevent migraine attacks and improves the patient's life quality, sometimes even positively influencing the concomitant disease. On the other side, given the fact that these medications should be used long term, migraine prophylaxis may also carry some contraindications or result in adverse effects.

In cases when migraine prophylaxis occurs, it is very important to discuss the simultaneous use of preventive and acute medications to prevent unwanted interactions or side effects. Patients should have adequate expectations from the treatment and understand that it often takes time to establish the effect from treatment or to find an appropriate therapy. Patient-compiled headache diaries can be very valuable tools for planning and evaluating treatment.

The search for new and better medicines for migraines should continue. The new advances in research and discovery of genes involved in this disorder will enable a better understanding of migraine pathophysiology, thus enhancing the chances to develop new and more qualitative anti-migraine medications, some of which could even be individualized to for specific patient populations.

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