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Chapter

Chronic Migraine

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Abstract

Chronic migraine as a disease was initially recognized in patients with a large burden of disability from frequent headaches and a history of prior migraines. Over time, this observation was operationalized into multiple diagnostic criteria with requirements for frequent headache days, typically 15 or more, which, on at least 8 days in a month, have the features of migraine headache. Chronic migraine affects 1–2% of the general population, and about 8% of patients with migraine. Understanding disease mechanisms still remains a challenge. Inflammation and central sensitization play significant role in the evolutive mechanisms of chronic migraine. Treatment of this condition should primarily focus on the prevention. The currently available evidence-based prophylactic treatment options are topiramate, valproic acid, onabotulinumtoxin A and recently developed promising anti-CGRP monoclonal antibodies. Chronic migraine research is a dynamic and rapidly advancing area. New developments in this field have the potential to improve the diagnosis, to provide more personalized treatments and to reduce burden of disability.

Keywords: chronic migraine, epidemiology, pathophysiology, risk factors, symptoms, diagnosis, treatment, prevention

1. Introduction

Chronic migraine (CM) is a distinct and relatively recently defined type of migraine initially recognized in patients with a large burden of disability from frequent headaches and a history of prior migraine.

The International Headache Society (IHS) defines CM as more than 15 headache days per month over a 3-month period of which more than eight are migrainous [1].

Disability rates and burden of disease among individuals with CM has more-severe impact on socioeconomic functioning and quality of life than does episodic migraine (EM) [2–4]. About 25% patients with CM report a very severe headache-related disability, as defined by the Migraine Disability Assessment Scale (MIDAS) to compare with 3% of patients with EM [2]. The proportion of patients with CM who report reduced household productivity, missed family activities and missed household work is two to three times higher than that of EM patients [4]. The annual per-person costs of CM—consisting of direct costs caused by health care utilization and treatment expenses (~30%) and indirect costs attributable to absenteeism from work and loss of productivity (~70%)—are about fourfold higher than those concerning with EM [5, 6].

Acknowledgment the severe effect of CM on socioeconomic functioning and quality of life, effective treatment of this disorder and preventing progression from episodic to CM—are one of most important problems in management of headache disorders.

2. History

The current definition of CM as outlined in the International Classification of Headache Disorders, 3rd edition (ICHD-3) [1] is relatively new. This definition has been tested multiple times and has gone through multiple revisions.

Although migraine as a distinct condition of headache with other accompanying symptoms has been known for thousands of years from the early writings of Aretaeus of Cappadocia in 30–90 A.D. [7]. The first formal modern definition of migraine was outlined in 1962 [8]. This first definition did not contain operational rules for migraine diagnosis and in 1988 the IHS published operational diagnostic criteria entitled the International Classification of Headache Disorders (ICHD-1) [9]. Criticism has been raised by experts that the ICHD-1 was not comprehensive enough to introduce diagnostic criteria for chronic headaches [10].

It was recognized in the 1980s that a chronic frequent headache patient population had a history of migraine [11, 12]. The daily and near daily headache patients were classified with multiple diagnoses but likely represented a single pathophysiological entity of migraine transformation with increased frequency. Recognizing this drawback, the Silberstein—Lipton criteria 1994, 1996 were proposed [13, 14]. They stipulated that chronic daily headaches defined as headaches on 15 or more days a month for at least 1 month, there was a subcategory of transformed migraine (TM) [6].

The term chronic migraine the first time in the literature was used by Manzoni et al. [15]. The results of a population study of chronic daily headache patients in Italy showed that 72% had fulfilled an IHS diagnosis of migraine [15]. For the first time CM appeared in the International Classification of Headache Disorders, 2nd edition (ICHD-2), 2004 [16]. There the CM category was defined as a complication of migraine, in patients having migraine without aura on at least 15 days per month, for at least 3 months, before the diagnosis was established. In the comments were stated that chronicity may be regarded as complication of EM and if medication overuse is present this is the most likely cause of chronic symptoms and it was suggested to code probable CM and probable medication- overuse headache (MOH). The requirement of having 15 migraine days per month was likely too stringent [17] and in a field trial of the ICHD-2 criteria [18] only 5.6% could be classified with CM, and only 10% could be classified to probable migraine with probable MOH.

Further, as it was recognized in prior studies, in the process of migraine transformation or chronification, the migraine features of some of the headaches may be lost [11–14].

Recognizing the drawbacks, in an appendix to ICHD-2R the CM definition was specified by requiring only 8 days per month to meet the definition of migraine or be responsive to migraine specific medications. This criterion is still present in the ICHD-3 [1].

ICHD-3 criteria of CM include a mixture of migraine and tension-type-like headaches and do not account for patients with high-frequency migraine attacks in the absence of other types of headaches [19].

Patients with migraine on eight or more days but not 15 days with headache a month are as disabled as patients with ICHD-3 defined CM [19]. Following this data a criticism regarding the existing CM criteria was raised and suggestion to revise the CM criteria was iniciated [19].

3. Epidemiology

The prevalence of CM worlwide ranges is reported to be between 0.9–5% [20], in a general population, and about 8% among patients with migraine [2, 21–24].

However, the true prevalence of CM is difficult to estimate because of heterogeneus data collection instruments.

CM accounts for about one-third of chronic headache (with more than 180 days per year) in general population [23]. This headache disorder is almost three times more common in women than in men with prevalence rate peaks at the ages of 18–29 years with repeating at 40–49 years [2, 22]. Most studies suggest that annually, from about 2.5% of people with EM evolves CM [25, 26], while only a limited portion with CM revert back to EM [25, 27].

The course of CM can change—spontaneous or medically induced remission is possible. About 26% of patients can experience remission within 2 years of the onset of CM [24]. Large-scale epidemiological studies have identified various factors associated with progression from episodic to CM, and also factors that promote migraine remission [27].

Most important nonmodifiable risk factors for migraine chronification are age, female sex and low educational status [2, 7, 14, 23]. Individuals with CM have increased incidence of certain somatic and psychiatric comorbidities—in comparison with people with EM [23, 25]. However, the understanding of complex factors and mechanisms leading to an increased migraine frequency and consequently to the development of CM are only in the beginning and needs further investigations.

4. Pathophysiology

Generally the pathophysiology of migraine is intricate and in spite of substantial progress in recognizing its mechanisms over the past several decades, it still remains not fully elucidated. Even more, so is the pathophysiology of CM. Current evidence defines migraine as a disorder of brain dysfunction with genetic background and environmental triggering [28]. To date there is limited number of scientific studies exploring the chronic form of migraine, therefore the reasons why the disease sometimes takes a turn and attacks become more frequent are not fully clarified yet. The key components proposed in the pathogenesis of migraine chronification include atypical pain processing, central sensitization, cortical hyperexcitability and neurogenic inflammation [29] (**Figure 1**).

Distinct phases of migraine are associated with different anatomical areas and driven by different processes. Prodromal symptoms that can develop prior the onset of migraine pain are believed to be a result of abnormal activity in cortical, diencephalic and/or brainstem areas. Migraine aura, experienced by approximately one third of patients, is most probably caused by cortical spreading depression (CSD)—a phenomenon defined as a slowly propagating depolarization wave followed by a prolonged period of inhibition of cortical activity [28, 30]. Going further, the pivotal process of the headache phase is activation of the trigeminovascular system. As the brain itself has been known to be rather insensate, the intracranial nociceptive impulses are generated in pain-sensitive structures like pial, arachnoid and dural blood vessels, venous sinuses as well as large cerebral arteries, all of which are innervated by nociceptive nerve fibers originating in the trigeminal ganglion. Activation of these structures by various stimuli is responsible for generation of migrainous pain and its associated features [31–33]. Extracranial afferent nociceptive innervation is largely received through the divisions of trigeminal nerve, mainly the ophthalmic, as well as the upper cervical dorsal root ganglia [34]. The intracranial and extracranial neural afferents enter caudal medulla via trigeminal tract and terminate in the spinal trigeminal nucleus caudalis and upper cervical spinal cord (C1-C3)—the trigeminocervical complex (TCC) [35, 36]. Next, the nociceptive information travels further via ascending pathways to the diencephalon

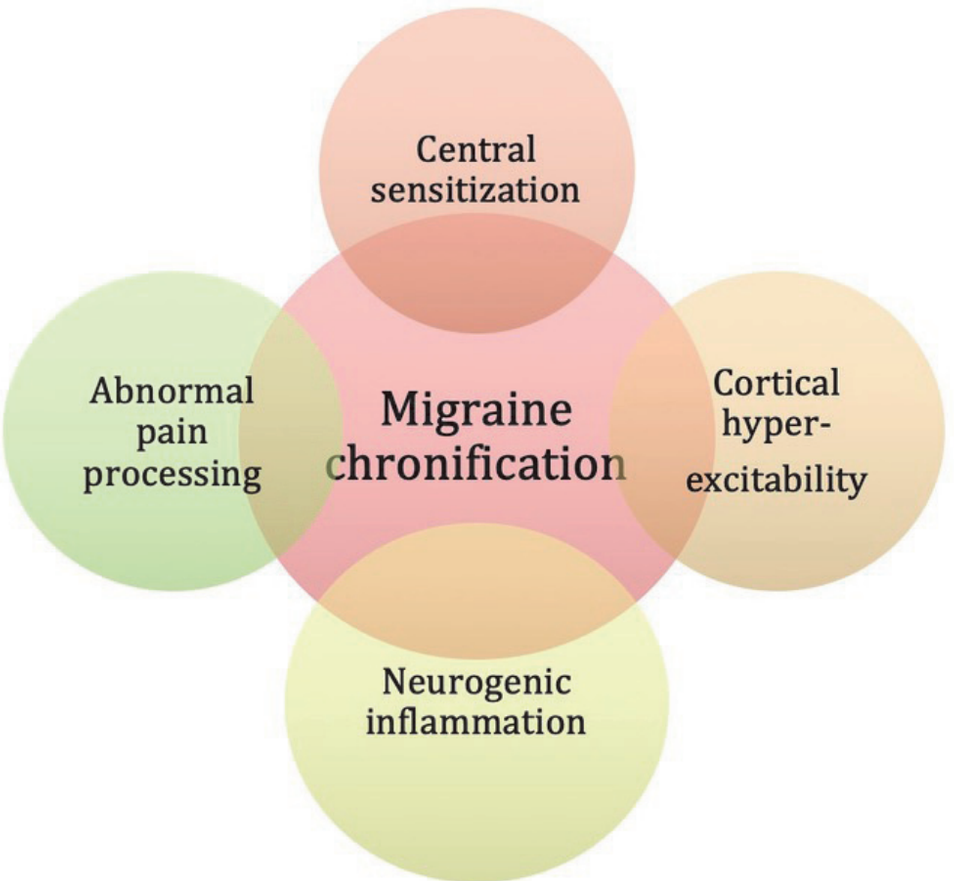

Figure 1.
Components of pathogenesis of migraine chronification. Data from Ref. [29].

and cortical areas, including insula and cingulate cortex. [28] The role of the limbic system is also significant: central pain processing and further relaying of sensory information depend largely on the thalamus [28, 37]; moreover, the amygdala and hippocampus participate in affective and cognitive perception of pain [38, 39]—features contributing to migraine notoriety as a disabling and burden-causing disease with strong emotional implications.

Under normal physiological circumstances activation of the nociceptive system is counterbalanced by pain modulation. It is known that in migraine, descending pain-modulating pathways are dysfunctional and pain inhibition is atypical, therefore susceptibility to migraine attacks is increased [40, 41]. Modulation system originates in the cerebral cortex and is carried out via cortico-trigeminal pathways with participation of brain structures, such as hypothalamus, locus coeruleus, nucleus raphe magnus and rostral ventromedial medulla. A core structure controlling pain and providing endogenous analgaesia is the periaqueductal gray matter (PAG) [42, 43]. Due to repetitive migraine attacks and prolonged exposure to pain, PAG and other structures, comprising the descending pain-modulating network, are excessively activated, which results in oxidative stress and subsequent dysfunction. Thereby adequate pain modulation is not ensured and susceptibility to generation of migraine attacks increases [42–44].

Some authors propose that migraine chronification can be seen as a threshold problem [45]. Pain threshold exists in order to protect from situations where daily non-noxious stimuli could induce pain, therefore it takes a stimulus of certain potency to actually be perceived as painful. Pain threshold is inconstant and shifts depending on cyclic changes that are thought to originate in the limbic system [46]. Those changes allow threshold fluctuations making individuals periodically more

susceptible to migraine attacks. During the interictal period threshold is normal, but when it decreases sufficiently, certain events, like stress or changes in hormonal or sleep rhythm, can provoke a migraine attack [47, 48]. Frequent attacks are among the major risk factors of migraine chronification, as they shorten the interictal period thus preventing restoration of the pain threshold to normal level [27, 49]. Consequently the sensory threshold stays below-baseline for most of the time and susceptibility to migraine attacks increases. Likewise, the most common risk factors, as obesity, physical inactivity, psychiatric illnesses and stress, might affect the threshold and make individuals more prone to migraine episodes [45].

Further alteration of pain threshold and increased sensitivity to attack-inducing triggers can be influenced by central sensitization [45]. Cutaneous allodynia, which represents central sensitization, is significantly more prevalent in chronic migraine patients than those with episodic one, suggesting that frequent attacks and higher pain intensity contribute to the development of central sensitization [50, 51]. This also explains why ineffective attack management is a risk factor for chronification: if migraine attacks are not treated completely, it results in a longer and more intense state of pain, leading to pronounced central sensitization, lowered pain threshold and increased susceptibility to migraine transformation [50, 52]. Overuse of acute pain medications is another risk factor for migraine progression, as it has been shown to promote central sensitization and susceptibility to CSD [27, 53].

There has been increasing evidence on altered cortical excitability in migraine [54]. Studies with transcranial magnetic stimulation have demonstrated reduced visual suppression in CM patients compared with EM patients and healthy controls, which proves the presence of cortical hyperexcitability [42]. In addition, assessment of visual evoked potentials shows that interictal excitability of the visual cortex is persistent and matches that of a migraine attack thus creates a "never-ending" migraine [55]. The underlying mechanisms of cortical hyperexcitability have not been uncovered yet, but evidence suggests that it may be induced by dysfunction of the pain modulatory pathways [55].

Another contributor to the pathophysiology of CM is neurogenic inflammation [29, 56]. Upon nociceptive stimulation by chemical, mechanical or electrical stimuli, a number of vasoactive substances are released from the axon terminals, causing vasodilation of the blood vessels and further plasma extravasation, edema and mastocyte degranulation. This so-called "sterile inflammation" results in sensitization and activation of the trigeminal meningeal receptors [28, 56], promoting the induction of migrainous pain [56]. Among the best-studdied vasoactive substances are calcitonine gene-related peptide (CGRP), substance P, neurokinin A, serotonin (5-HT) and pituitary adenylate cyclase-activating peptide (PACAP). CGRP is one of the most significant central pronociceptive agents expressed in the trigeminovascular system and associated with pain processing and migraine symptoms. It takes part in the development of peripheral and central sensitization and enhanced abnormal pain perception [28]. Vasoactive intestinal peptide (VIP) is another important parasympathetic neurotransmitter with a headache-eliciting effect [57, 58]. These pro-inflammatory vasoactive substances have been in the spotlight of research for years with regard to their potential role as biomarkers for chronic migraine. The levels of CGRP and VIP have been measured and compared during the interictal state of episodic and chronic migraine, showing an increase of either in the latter [59]. This provides additional evidence on altered interictal activity of the trigeminovascular system in chronic migraineurs. Moreover, the role of other substances, such as leptin, adipoleptin, TNF-α and glutamate, in the processes related with persistence and progression of migraine, has been demonstrated. This provides reasonable hopes on future implementation of biomarkers for migraine chronification [57, 58, 60].

In terms of anatomic changes in migraine, white matter lesions are considered to be more common in migraineurs than in general population. Moreover, increase in lesions correlates with attack frequency [61]. Recent neuroimaging studies revealed some other neuroanatomical differences correlating with headache frequency that could even be considered indirect markers of migraine chronification: it showed that migraineurs with more frequent attacks had thicker somatosensory cortex, anterior cingulate cortex and inferior temporal gyrus, compared with those with low-frequency attacks [62]. Also correlation with thickness of left middle frontal gyrus and left central sulcus was noted. Moreover, patients with CM had volumetric changes in amygdala, hippocampus, putamen and brainstem areas [63]. These data once again prove the role of these cerebral structures in the pathogenesis of chronic migraine [64].

Genetic influence on the progression from episodic to CM is yet to be established as more large-sample studies are needed [64, 65]. However it looks that chronic migrain has a polygenetic background. Data suggest the role of certain gene groups linked to migraine and pain progression, addiction and medication overuse, hyperexcitability and oxidative stress in migraine chronification [66]. Furthermore, it is becoming clear that epigenetics is also related to migraine as to many other multifactorial diseases. Although to date there are no specific genetic studies in chronic migraine patients, there is some evidence that neuronal activity occuring during CSD may cause epigenetic changes involved in neuronal plasticity, neuroprotection and regulation of basal synaptic activity [67, 68].

5. Risk factors

Not all patients with EM progress into chronic form [69]. The American Migraine Prevalence and Prevention (AMPP) Study [70], the International Burden of Migraine Study (IBMS) [3] and the others have explored at the prevalence of different features in episodic and CM. Some of them have been found to be more prevalent in the chronic form of migraine, suggesting that these features should be seen as risk factors associated with migraine conversion that may serve as prognostic markers enabling prediction of possible migraine progression from episodic to chronic form. Knowing these factors can assist in identifying patients at risk of transformation and take appropriate measures to prevent it (**Table 1**).

The risk factors can be divided into non-modifiable and modifiable. Some of them carry more weight in predisposing CM than the others do. The most significant risk factors are overuse of acute medication [27], ineffective acute treatment [51], obesity [71], depression [72] and stressful life events [27]. The risk factors are listed in **Table 1**.

Studies show that higher prevalence of CM is related to some non-modifiable demographic characteristics, such as female sex [73, 74] and Caucasian race [75]. Regarding age, CM tends to be increasingly more prevalent from 18 to 50 years in both sexes [2]. In terms of the modifiable risk factors, there is evidence for correlation between lower level of education and CM, but data are inconsistent [3, 24, 25, 75]. In addition, some studies propose lower economic status [76], being unmarried [25] and unemployed [3, 25] as risk factors for chronic migraine.

Some modifiable lifestyle features have also been listed as risk factors of CM. First, high caffeine intake is connected with migraine transformation, especially when excessive consumption has started before the onset of chronic daily headache [77]. Second, obesity, especially in women, is more prevalent in chronic than in EM

thus it can be considered a risk factor for migraine chronification [71]. In fact, similar relation also exists between increased body weight and other headache disorders like MOH and benign intracranial hypertension [78–79]. The mechanisms linking obesity and frequent headaches are not known yet, but it may be related to hyperleptinemia [80–82]. Next, sleep disorders, including sleep apnea, snoring, disturbed sleep and oversleeping, have been found to elevate the risk for developing CM [83, 84]. Therefore it is obvious that patient education and counseling on lifestyle is extremely important, as reducing caffeine intake, normalizing body weight and sleeping patterns early enough may help to prevent migraine progression.

Another tendency is that patients with CM report various comorbidities more commonly than those with CM. According to the CaMEO study, patients with the most comorbidities were 5 times more likely to progress to CM than those with the fewest [84, 85]. Psychiatric comorbidities, especially anxiety and severe or moderate depression, are particularly prevalent in CM patients [72, 84, 86] as are some personality traits and disorders, in particular obsessive-compulsive, dependent, avoidant and passive-aggressive [87]. Chronic pain conditions, including fibromyalgia, chronic back and neck pain, are also a strong prognostic factor for migraine progression from episodic to chronic state as they are much more commonly reported by chronic migraineurs [88]. Other comorbidities such as cardiovascular disorders, asthma and allergies [25] are also considered risk factors for migraine progression. Moreover, various major life changes, like divorce, change of employment status or being recently widowed also play a role in migraine conversion, partially by accompaniment of anxiety and depression [27]. Therefore it is critically

Demographic characteristics
Female sex
Caucasian race
Increasing age
Lower level of education
Lower economic status
Being unmarried
Unemployment
Lifestyle factors
High caffeine consumption
Obesity
Sleep disorders
Sleep apnea
Snoring
Sleep deprivation
Excessive sleeping
Headache features
Frequent attacks
Cutaneous allodynia
Treatment-related factors
Acute medication overuse
Insufficient treatment
Comorbidities
Psychiatric disorders
Depression
Anxiety
Bipolar disorder
Personality disorders and traits
Obsessive-compulsive
Avoidant
Dependent
Passive-aggressive
Concomitant chronic pain disorders
Fibromyalgia
Back and neck pain
Painful neuropathy
Cardiovascular disorders
Arterial hypertension
Hypercholesterolemia
Asthma
Stress related with major life changes
Divorce
Change of employment status
Grief

Table 1.
Risk factors for chronic migraine [27, 51, 71, 72].

important to adequately treat these comorbidities in order to prevent migraine chronification, impaired quality of life and development of disability.

In addition to what has been set out before, some headache features have been established as risk factors too. One of the majors is headache frequency [27, 69]. Scher et al. has shown that the risk for chronification increases with the increase of headache frequency in a non-linear fashion. A minimum of three attacks per month is enough to elevate the risk for new-onset chronic headache [27]. This is based on the fact that prolonged exposure to pain induces central sensitization and decreases the attack threshold. Hence this once again emphasizes the importance of rapid and adequate treatment of migraine attacks to prevent pathophysiological alterations leading to migraine chronification.

Another specific clinical feature of migraine attack is cutaneous allodynia, which affects approximately 63% of migraineurs [89]. According to Burstein et al. and Louter et al. it is not only a clinical marker of central sensitization but can also be considered an independent predictor of migraine chronification [50, 52]. From therapeutic point of view, triptans should be administered to terminate a migraine attack within 30 minutes for subjects with cutaneous allodynia in order to minimize exposure to pathological processes leading to migraine chronification [90].

Aditionally some treatment-related factors are proven to play a role in the pathogenesis of CM. The Akershus study [91] among other data has confirmed that acute medication overuse has substantial impact to the processes leading to migraine progression. Acute medication overuse is defined as medication intake on 10–15 days per month [92]. Among the different analgesic groups opioids, barbiturates and combination drugs are associated with the highest dose-dependent risk, while triptans show moderate association with migraine progression and it is more likely in patients with higher baseline attack frequency. Interestingly, some data reports protective effect of NSAIDs against migraine progression, but only in patients with less than 10 attacks per month [79, 92]. The impact of medication overuse in migraine progression is supported by the fact, that attack frequency and disability decreases after discontinuation of acute medication, which also allows more effective preventive treatment [91].

On the other hand, the AMPP study states that ineffective or insufficient treatment can also promote chronification processes [90]. Patients using triptans are more likely to successfully abort the attacks than those using NSAIDs and simple analgesics therefore they are at less risk for chronification [51].

In conclusion it is crucial that effort is made to treat migraine attacks rapidly and adequately as well as to modify other risk factors relevant to the patient so that the pathophysiological mechanisms responsible for migraine progression from episodic into chronic form could be precluded [45, 64].

6. Symptoms and diagnosis

Although the most obvious difference between episodic and CM seems to be the frequency of attacks, clinical migraine features may change too as the disease progresses from less frequent to chronic form. Usually over time the pain becomes more “featureless”, thus resembling tension-type headache for most of the time with some more prominent migraine-like attacks interjected [69].

Typical migraine attacks generally manifest as severe, usually unilateral headache of throbbing quality, increasing intensity with physical activity and a combination of associated features: nausea, vomiting, hypersensitivity to visual, auditory, olfactory and cutaneous stimuli. The headache can change sides during or between the attacks [64]. The pain in patients with CM is more commonly bilateral and the

associated symptoms are less pronounced than in those with EM [93]. Some patients report prodromal symptoms up to 48 hours before the onset of pain, including fatigue, asthenia, impaired concentration, irritability and other that can warn against an upcoming attack. However, it can be difficult to distinguish prodromal periods in CM as the attacks are very frequent or continuous [24].

Migraine with aura affects 20–40% of all migraineurs [93] and features a selection of transient focal neurological symptoms that usually but not invariably present before the onset of pain. The most common aura type accounting for approximately 90% is visual [84], but patients can also experience sensory, brainstem or hemiplegia-related aura [69, 84, 94]. Both types of migraine, with and without aura, can progress into chronic form.

According to the newest ICHD-3 criteria (**Table 2**), CM should be diagnosed when headache is experienced on 15 or more days per month over more than 3 months. The headache on 8 or more days per month should meet the criteria for migraine with or without aura and/or should be relieved by specific migraine treatment [1].

Not always it is easy for the patients to remember the exact number of days of pain per month, hence keeping a headache diary can come to help. Patients should be encouraged to not only mark the days of pain, but also elaborate what the pain was like, what features it was accompanied by, was any medication required and with what outcome. This is a good and easy tool for a physician to not only accurately know the count up of the headache days, but also make a full picture of its characteristics [95, 96].

Physician making a diagnosis should obtain a detailed history, as history is where the diagnosis of migraine lies. A thorough neurological examination, including fundoscopy, should be the following step during consultation [97].

In case of presentation of typical features of CM and normal examination, no further testing is required. However vigilance is needed to suspect any possible secondary headache causes, such as infections, tumors or hydrocephalus (**Table 3**), when additional investigation is warranted [29]. The set of tests required depends on clinician's judgment in each situation and may include certain blood tests, imaging of brain, cervical spine and sinuses, scanning of cranial and extracranial arteries and performing a lumbar puncture with measuring of the CSF opening pressure. The method of choice for brain imaging is usually MRI [97]. The most consistent indicators for such conditions ("red flags") include thunderclap headache, associated focal neurological deficit or systemic features, headache of onset in patients over the age of 50 years and more [29, 97–99].

After stating that the patient has a primary headache disorder, the pattern of the headache should be established. Episodic headache occurs on less than 15 days per month while chronic headache—on 15 or more days in a month. Headaches lasting up to 4 hours are considered "short" in contrast to "long" headaches that last more

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C;
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*;
C. On ≥8 days/month for >3 months, fulfilling any of the following: 1. Criteria C and D for 1.1 *Migraine without aura*; 2. Criteria B and C for 1.2 *Migraine with aura*; 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative;
D. Not better accounted for by another ICHD-3 diagnosis.

Table 2.
Chronic migraine diagnostic criteria, ICHD-3, 2018.

Etiology		Examples
Anatomic disorders		Cervical pain, temporomandibular joint disorders, myofascial pain
Changes in intracranial pressure	**Intracranial hypertension**	Tumor, hemorrhage, brain infection, primary benign intracranial hypertension, hydrocephalus, pituitary apoplexy
	Intracranial hypotension	Post-lumbar puncture, post-epidural/spinal analgesia, spontaneous CSF leak
Infection		Meningitis, encephalitis, sinusitis, abscess
Medication and substance disuse		Medication overuse headache, medication side-effects, substance abuse or withdrawal
Metabolic disorders		Uremia, hepatic encephalopathy, hypoxia
Neuralgias		Trigeminal neuralgia, occipital neuralgia
Psychiatric		Somatoform disorder, psychosis, aggravation
Trauma		Traumatic brain injury
Vascular disorders		Stroke, dissection of carotid or vertebral arteries, giant-cell arteritis, arterial hypertension, CADASIL, venous sinuses thrombosis

Table 3.
Possible Causes of Secondary Headaches (alphabetically ordered) [29, 45, 97].

than 4 hours [100]. CM should be differentiated from other chronic long-duration primary headaches (**Table 3**). *Hemicrania continua* is strictly unilateral continuous headache condition with superimposed exacerbations of pain that display ipsilateral autonomic symptoms. CM can also present with autonomic features, but they are much less pronounced. In addition to this, *hemicrania continua* features a distinguishing absolute responsiveness to indomethacin which is a key factor in differential diagnosis [29]. Chronic tension-type headache usually manifests as bilateral ache of non-throbbing quality and mild to moderate severity, while CM can be unilateral or bilateral and of moderate to severe intensity. Importantly, chronic tension-type headache is considered "featureless"—it is not usually accompanied by migrainous symptoms like nausea, vomiting, photophobia, phonophobia, and is not exacerbated by exertion. As migraine progresses into chronic form, the headache may resemble tension-type on some days [29]; nonetheless, typical migraine features must be present on at least 8 days per month for the diagnosis of chronic migraine to be validated [1].

The main feature of new daily persistent headache is a distinct and clearly remembered onset and rapid development to an unremitting state of pain over 24 hours. This distinguishes it from chronic migraine that develops slowly over the course of months or years while attacks become more and more frequent and merged together. Besides, the localization and accompanying symptoms of new daily persistent headache are usually undefined and nonspecific, thus alleviating the differential diagnosis [29, 45, 97].

Another point to remember is the importance of assessing the patient for possible acute medication overuse, as it is one of the major risk factors for migraine progression. Sometimes it may be challenging to tell if medication overuse is a cause or a consequence of CM. The ICHD-3 criteria encourage coding both CM and MOH diagnoses in case when medication overuse is confirmed [1]. The diagnoses should be reviewed and specified later after assessing the effect of medication withdrawal: the headache may revert to episodic migraine or remain chronic. The former case would suggest that medication overuse indeed was a causative factor that had led to chronification. In the latter scenario the diagnosis of medication-overuse headache

Headache type/ causative problem	Localization	Duration	Associated and distinguishing features	Diagnostic tests
Chronic migraine	Unilateral or bilateral	• Hours to days or continuous • Headache present on at least 15 days per month	• Throbbing nature • Accompanying nausea, vomiting, photophobia, phonophobia • Exertional exacerbation	ICH-3 criteria
Hemicrania continua	Side-locked	• Daily, continuous pain with superimposed exacerbations	• Ipsilateral autonomic features • Indomethacin-responsiveness	ICH-3 criteria Indomethacin trial [12]
Chronic tension-type headache	Usually bilateral, but can be unilateral	• Hours to days or continuous	• "Featureless"—no or rare accompanying symptoms	ICH-3 criteria
Medication overuse headache	Undefined	• Hours to days or continuous	• History of acute medication overuse • Improved after withdrawal	ICH-3 criteria
New daily persistent headache	Daily persistent headache with a distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours	Undefined	Undefined	Individual approach: • Brain imaging (CT, MRI) • Lumbar puncture • Blood tests

[*] *Data from Refs. [29, 45, 97].*

Table 4.
Differential diagnosis for long-duration primary headaches[*].

should be revoked, as it would seem that the overuse had taken place simply as a result of increased attack frequency [101]. Points of the differential diagnosis are summarized in **Table 4**.

Once the diagnosis of CM has been confirmed, standard questionnaires, such as Migraine Disability Assessment (MIDAS) or Headache Impact Test-6 (HIT-6) should be used for patient assessment in order to evaluate the burden of disease and monitor the effects of prescribed treatment [95]. Episodic and treatment-responsive migraine can be diagnosed and managed in the primary care, while chronic or refractory patients should be referred to a specialist neurologist, preferably with an expertise in the field of headache disorders [95].

7. Treatment

There are three broad approaches to treating CM [97]:

- Lifestyle and trigger management.

- Acute headache treatments.
- Preventive treatment.

7.1 Lifestyle and trigger management

Lifestyle modification, as well as trigger reduction can, be helpful in reducing the fequency of migraine attacks and stopping or slowing down the process of migraine chronification. That includes regularity of regimen with regard to meals, hydration, sleep and stress. It could be also helpful to detect and understand the obvious triggers. It is important to know other problems that exacerbate the tendency to headaches: such as: depression, anxiety, other pain syndromes such as fibromyalgia, localized pain in head and neck structures, and conditions that create 'metabolic' strain such as obesity, sleep apnoea or postural orthostatic tachycardia syndrome [102, 103]. It is particularly important to recognize and manage medication overuse (including caffeine overuse), as failure to do so will render most attempts at preventive treatment ineffective [92].

In order to identify the factors mentioned above it is very important to take a detailed history of the particular patient and to evaluate the headache questionnaires and diaries, which are suggestable in many headache centers worldwide.

7.2 Acute headache treatments

The natural course of CM presents a variation in headache frequency meaning that patients can fluctuate between EM and CM [97] and exacerbations of chronic pain. Acute CM treatments are necessary to treat these conditions; e.g., **migraine attacks or exacerbations of chronic pain**.

For the patients with CM often is difficult to know when to take acute treatments. The physician should discuss this question with the patient and also explain about the possibility of co-existence of MOH, which now is considered a sequela rather than a cause of migraine and can co-exist with CM [1, 92].

In order to prevent the development of MOH, it is very important to avoid using painkillers and triptans too often in the early stages of management [104]. The detailed anamnesis and analysis of patient headache questionnaire and diary will help to understand and count the" good days and bad days "or the days with clearly exacerbated headaches. For the acute headache treatment are recommended the same groups of medications as for migraine attack treatment. This includes simple analgesics, combinated analgetics, triptans if the analgetics are not effective, and neuromodulating procedures [97, 99, 105] (Reference to section on treatment of migraine attacks to be included).

Opioids are not recommended for the treatment of acute headache because of the significant risk of medication overuse and the most protracted withdrawal [106].

Triptans are migraine-specific medications that inhibit the release of CGRP by activation of presynaptic 5HT1 receptors [107, 108]. However, patients should not take triptans more than 10 days in a month to avoid developing MOH [1].

Non-invasive stimulation procedures could be used in patients who refuse to use pharmacological migraine therapy or it is contraindicated or not tolerated. That includes external trigeminal nerve stimulation [109], single transcranial magnetic stimulation [110] and transcutaneus vagal nerve stimulation [111].

Effective acute treatment of migraine attacks may help to prevent progression from EM to CM, but rather than relying on taking drugs to stop migraine attacks after they have started, the aim of treatment for CM should be the prevention of migraine attacks [20].

7.3 Preventive treatment

The goals of CM prophylactic treatment are to prevent attacks, thereby reducing headache frequency, severity and associated disability and decreasing reliance on acute treatment, which may be contributing to concurrent MOH [92, 104]. An additional goal may be to prevent progression of EM to CM in patients with high-frequency attacks [45]. The first-line treatment of CM is pharmacological [45].

Numerous orally administered drugs are used for the prophylaxis of CM, including beta-blockers, calcium-channel blockers, tricyclic antidepressants, serotonin antagonists, antihypertensives, and antidepressants [112]. The drugs that are effective for EM are not necessarily effective for CM [54], but evidence for the efficacy of oral agents in CM is generally extrapolated from studies in patients with high-frequency EM [97, 113]. Insufficient efficacy, not suitable route and dose of drug administration and/or adverse events leading to treatment discontinuation often occur with these drugs in patients with CM [114, 115].

The only currently available evidence-based prophylactic treatment options for CM are topiramate and onabotulinumtoxinA (OBT-A) which is a formulation of botulinum toxin A administered by intramuscular injection, from more than one randomized controlled trial [97, 113].

7.3.1 OnabotulinumtoxinA

To date, OBT-A is the only treatment specifically approved for the prevention of CM in the EU and North America (class of evidence I, level of recommendation A) [116–119]. In the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials [117, 118] OBT-A has been shown to be an effective and generally well tolerated treatment for the prevention of CM, and tends to be better tolerated than various oral prophylactic treatments, including topiramate [120–123]. Based on the PREEMPT clinical trial protocol, OBT-A is administered to at least 31 injection sites across 7 head and neck muscles, and is currently recommended as a second-line option for patients who have not responded adequately or are intolerant of commonly prescribed oral migraine prophylaxis [124]. Treatment should be repeated every 12 weeks. This data was confirmed in recently finished Chronic migraine OnabotulinuMtoxinA Prolonged Efficacy open Label (COMPEL) study, aim to investigate the long-term safety, efficacy and tolerability of nine cycles of repetitive BoNT-A injections. The Compel Study concluded that OBT-A treatment was well tolerated over 108 weeks, and no new safety signals were identified [125].

The molecular biological mechanism of action of OBT-A is well established, whereby it inhibits fusion of intracellular vesicles with the nerve membrane [125] by cleaving synaptosomal-associated protein (SNAP-25) [126, 127]. By impairing intraneuronal vesicular fusion, OBT-A modulates neuropeptide release and downregulates receptors and ion channels important in nociception [128, 129].

So, it is thought that OBT-A blocks release of CGRP from peripheral nociceptive neurons and interferes with transient receptor potential cation (TRP) channels in the trigeminally-innervated cranio-facial-cervical region, thereby reducing neuronal hyperexcitability and peripheral and central sensitisation [54, 130]. It is hypothesized that trigeminal-targeted preventative treatments counteract the impingement of nociceptive input from highly sensitized trigeminal neurons on brainstem second-order neurons, thus preventing central sensitisation, a key pathophysiological mechanism of CM [131].

Additionally recent clinical data demonstrates that OBT-A has been shown to reduce serum CGRP concentration in patients with CM (pretreatment median, 74.1 pg/mL; 1 month post-treatment median, 51.9 pg/mL, $P < 0.001$) [132]. One

month after treatment, CGRP levels significantly decreased in patients defined as OBT-A responders.

There is no consensus in the literature regarding the number of OBT-A cycles required for the preventive treatment of CM. Some trials suggest an increasing efficacy with regular cycle repetition for more than 1 year, including in patients with MOH (three class II trials, level B recommendation) [133–135]. To date, no clinical features predicting responses to OBT-A (recommendation level B) have been identified [136, 137].

The adverse effects of this treatment are rare, transient and mild. The most frequently reported were neck and shoulder muscle weakness, post-application headache, palpebral pseudoptosis and other facial mimics asymmetries, in addition to pain at injection sites (class of evidence I) [117–119, 137–139].

7.3.2 Topiramate

Although not specifically licensed for CM, orally administered anticonvulsant topiramate is an effective prophylactic treatment for patients with migraine, and may be effective in patients with CM [140]. Topiramate reduced headache days versus placebo and was relatively well tolerated in patients with CM in two large randomized controlled trials [141, 142]. The initial dosage should be started slowly with 2 × 12.5 mg or 2 × 25 mg and a dose of 2 × 50 mg (if necessary up to 2 × 100 mg) per day as final target dose. Adverse events commonly associated with topiramate include paresthesia, memory and concentration disturbances, fatigue, nausea, and weight loss [143, 144].

It is thought that topiramate has dual effects on neurotransmission—enhancing inhibitory effects while minimizing excitatory effects, both of which are implicated in migraine physiology [145]. The pharmacologic mechanisms underlying this antimigraine activity may include blockade of cell membrane ion channels and neurotransmitter release (e.g., inhibition of glutamate), resulting in inhibition of neuronal hyperexcitability. Studies have demonstrated topiramate's inhibitory effect on excitability in motor and visual cortices [54, 144, 145]. Based on this broad mechanism of action, topiramate may prevent the development of cortical spreading depression by reducing nociceptive transmission and generally inhibiting neuronal hyperexcitability [146]. Similarly, topiramate has demonstrated cognitive adverse events, which are likely a reflection of the central inhibitory effects [54]. Pooled analyses of clinical trial results suggest that preventive topiramate treatment in patients with episodic migraine may reduce the risk of headache-day increase, which in some cases may prevent migraine chronification [147].

7.3.3 Monoclonal antibodies

Deeper understanding the importance of CGRP and its receptor role in CM pathophysiology and need for more effective, better tolerated prophylactic therapies for CM or high-frequency EM gave background for the development of the new class drugs—anti-CGRP/R monoclonal antibodies (mAbs).

Four anti-CGRP/R antibodies are approved in the US and Europe for the prophylactic treatment of CM: erenumab (Aimovig) [148, 149], which targets the CGRP receptor, fremanezumab (Ajovy) [150, 151] and galcanezumab (Emgality) [152, 153] which target the CGRP ligand; and fourth anti-CGRP/R antibody against the CGRP ligand, eptinezumab (VYEPTI™), which was approved by FDA and EMA on year 2020 [154, 155]. These macromolecule anti-CGRP/R antibodies have been specifically designed for prophylactic use in CM and frequent EM, and to overcome safety issues associated with CGRP receptor antagonists [156, 157]. Eptinezumab

(VYEPTI™) is the first intravenous (IV) treatment for migraine prevention and the latest in a new class of mAbs. A brief review of all four mAbs, dose and rout of adminstration are provided in **Table 5**.

The anti-CGRP/R antibodies are highly specific for their CGRP/R target, have no ability to cross the blood brain barrier, and bypass liver metabolism so CNS-related effects and hepatotoxicity are unlikely [158]. Their long half-lives allow for dosing once a month for erenumab and galcanezumab, or and once every 3 months, for fremanezumab [159–161] and eptinezumab [162].

This very promising treatment with mABs for CM is proved in clinical trials [163].

Erenumab: A phase II RCT evaluated the safety and the efficacy of erenumab in subjects aged 18–65 years with CM with duration of treatment 3 months and preventive treatment not allowed [164]. Patients (n = 667) were randomized to monthly subcutaneous injection of erenumab 70 mg, erenumab 140 mg or placebo for 3 months. Exclusion by preventive failure of >3 drugs. At weeks 9–12, there was a reduction in monthly migraine days in the erenumab 70 mg (LSMD −2.5; SE −3.5 to −1.4; $P < 0.0001$) and in the erenumab 140 mg (LSMD −2.5; SE −3.5 to −1.4; P < 0.0001) groups compared to placebo group. There was a reduction in monthly number of days using migraines-specific medication in the erenumab 70 mg (LSMD −1.9; SE −2.6 to −1.1; P < 0.0001) and in the erenumab 140 mg (LSMD −2.6; SE −3.3 to −1.8; P < 0.0001) groups compared to the placebo group.

Fremanezumab: In this multicentre, randomized, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b study, were enrolled men and

Drug	Manufacturer	Target	Dose of administration	Route of administration	Dosing
Erenumab (Aimovig)	Amgen and Novartis Pharmaceuticals	CGRP receptor	70 mg	Once monthly	Autoinjector 70 mg/mL
			140 mg	Some patients may need 140 mg SC once monthly	Autoinjector 140 mg/mL
Fremanezumab (Ajovy)	Teva	CGRP ligand	225 mg	Once monthly	Syringe or autoinjector 225 mg/1.5 mL
			675 mg	Every 3 months (q)	
Galcanezumab (Emgality	Eli Lilly and Company	CGRP ligand	240 mg(2 consecutive 120 mg SC injections) loading dose once, maintainance dose 120 mg monthly	Once monthly	Single-dose prefilled pen 120 mg/mL and single-dose prefilled syringe 100 mg/mL and 120 mg/mL
Eptinezumab (VYEPTI™)	Alder Biopharmaceuticals and Lundbeck Seattle BioPharmaceuticals Inc.	CGRP ligand	100 mg IV every 3 months (q)	Every 3 months (q)	Injectable solution 100 mg/ml
			300 mg IV every 3 months (q)	Some patients may benefit from a 300 mg IV dose q3 months	

Table 5.
Brief review of administration of CRRP/R monoclonal antibodies.

women (aged 18–65 years) who had CM with duration of treatment 3 months [165]. Patients (n = 264) were randomized to three 28-day treatment cycles of subcutaneous injections of fremanezumab 225 mg, fremanezumab 900 mg or placebo. Exclusion by preventive failure of >3 drugs. At weeks 9–12, there was a reduction in moderate to severe headache days in the fremanezumab 675/225 mg (LSMD −1.84; 95% CI −3.54 to −0.14; P = 0.0345) and in the fremanezumab 900 mg (LSMD −1.96; 95% CI −3.66 to −0.26; P = 0.0237) groups compared to placebo group. There was a reduction in number of days using acute medication in the fremanezumab 900 mg (LSMD −2.04; 95% CI −3.9 to −0.2; P = 0.027) group compared to placebo group.

A phase III RCT, the HALO CM, evaluated the efficacy of fremanezumab in subjects aged 18–70 years with CM with duration of treatment 3 months [160]. Patients (n = 1130) were randomized to monthly subcutaneous injections of fremanezumab 225 mg (loading dose of 675 mg), to quarterly fremanezumab 675 mg, or placebo for 3 months. Exclusion by preventive failure of ≥2 drugs. During 12-week period, there was a reduction in the average number of headache days per month in the fremanezumab 675 mg (LSMD −1.8; SE 0.3; $P < 0.001$) and in the fremanezumab 675/225 mg (LSMD -2.1; SE 0.3; $P < 0.001$) groups compared to placebo group. There was a reduction in the monthly number of days using acute medication in the fremanezumab 675 mg (LSMD −1.8; SE 0.3; $P < 0.001$) and in the fremanezumab 675/225 mg (LSMD −2.3; SE 0.3; $P < 0.001$) groups compared to placebo group. There was an improvement in the HIT-6 [166] score in the fremanezumab 675 mg (LSMD −1.9; SE 0.5; $P < 0.001$) and in the fremanezumab 675/225 mg (LSMD −2.4; SE 0.5; $P < 0.001$) groups compared to placebo group.

Galcanezumab: A phase III RCT, the randomized, double-blind, placebo-controlled REGAIN study evaluated the efficacy of galcanezumab in subjects aged 18–65 years with CM with duration of treatment 3 months [161]. Patients (n = 1117) were randomized to monthly subcutaneous injections of galcanezumab 120 mg (loading dose of 240 mg at baseline), galcanezumab 240 mg, or placebo for 3 months. Exclusion by preventive failure of >2 drugs During the 3-month period, there was a reduction in monthly migraine days in the galcanezumab 120 mg group (LSMD −2.1; 95% CI −2.9 to −1.3) and with galcanezumab 240 mg (LSMD −1.9; 95% CI −2.7 to −1.1) compared to placebo groups. There was a reduction in monthly number of days using acute medication use in the galcanezumab 240 mg (LSMD −2.0; 95% CI −2.8 to −1.3) but not in galcanezumab 120 mg as compared to the placebo group. There was an improvement in the MIDAS score in the galcanezumab 120 mg (LSMD −8.7; 95% CI −16.4 to −3.1) but not in galcanezumab 240 mg as compared to the placebo group.

Eptinezumab: This was a phase 2b, parallel-group, double-blind, randomized, placebo-controlled, dose-ranging clinical trial with duration of treatment 12 weeks and preventive treatment, except botulin toxin, not allowed [162]. Men and women aged 18–55 years (n = 616) were included if they had a diagnosis of CM with onset at age 35 years and history of CM 1 year. During the 28-day screening period, patients must have had 15 headache days, including 8 migraine days, with five migraine attacks as recorded in the electronic diary. Exclusion is by preventive failure of ≥2 drugs. Patients were assigned in a 1:1:1:1:1 ratio to eptinezumab 300, 100, 30, 10 mg or placebo, administered as a single IV infusion. The primary endpoint was the percentage of patients with a 75% decrease in monthly migraine days over weeks 1–12 compared with the 28-day screening period. Secondary efficacy endpoints had results favoring the three higher eptinezumab doses versus placebo. The greatest effect of eptinezumab, as measured by the HIT-6 was observed at week 12, with changes in baseline scores of 10.0, 6.9, 6.5, and 6.5 for the 300, 100, 30, and 10 mg groups, respectively, compared with 5.8 for the placebo group. A prespecified

analysis of the percentage of patients for whom migraine had a severe impact on life demonstrated a reduction from 90.3% at baseline to 29.9% at week 12 with eptinezumab 300 mg, 86.4–43.0% with eptinezumab 100 mg, compared with 79.3–50.9% with placebo.

The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy–2 (PROMISE-2) study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with duration of treatment 12 weeks [167]. Adults with CM (n = 1072) were randomly assigned to receive IV eptinezumab 100 mg, eptinezumab 300 mg, or placebo administered on day 0 and week 12. Exclusion is by preventive failure of ≥2 drugs. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 1–12. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1–12 compared with placebo (placebo −5.6, 100 mg −7.7, $p < 0.0001$ vs. placebo; 300 mg −8.2, $p < 0.0001$ vs. placebo). The mean HIT-6 scores at baseline were 65.0 (eptinezumab 100 mg), 65.1 (eptinezumab 300 mg), and 64.8 (placebo). By week 12, the percentage of patients with HIT-6 scores in the severe range had been reduced to 51.4% in the eptinezumab 100 mg treatment group, 42.9% in the eptinezumab 300 mg treatment group, and 60.1% in the placebo group. Patients in the eptinezumab 300 mg group demonstrated a statistically significant improvement on the HIT-6 at week 12, with an estimated mean difference from placebo (95% confidence interval) of −2.9 (−3.9 to −1.8, $p < 0.0001$).

Adverse events of the mAbs: The results of four mABs clinical studies showed that no serious advers events (SAEs), no deaths deemed to be related to mAbs occurred in clinical trials with all fours mAbs. According the data of clinical trials, the most common adverse events (5 to >10% of the study population) for all three CGRP antagonists (erenumab, fremanezumab, galcanezumab) were injection-site reactions and pain. Specific adverse reactions for erenumab was constipation (1–3% of patients) and cramps, muscle spasms (<3%), hyperintensity for galcanezumab, and nasopharyngitis (6–8%) and hyperintensity (1–2%) for eptinezumab.

Recommendations on the use of the mAbs: Following the clinical studies results and expert opinion EHF on 2019 prepared recommendations about the use three mAbs (erenumab, fremanezumab, galcanezumab) in subjects with CM [163]. In these recommendations due to the then-unpublished original data eptinezumab was not included (**Table 6**). Keeping in mind the fact that this mAb belongs to the same class of drugs (e.g., anti-calcitonin gene-related peptide monoclonal antibodies) with similar profile it seems that the recommendations fits for it too.

7.3.4 Combinations

The strategy of combining different prophylactic drugs is not supported by high-level evidence [168]. However, the so-called rational polytherapy—the association of effective drugs with different mechanisms—can be used in monotherapy-refractory patients [169]. Regarding comparative efficacy, one single-center double-blind RCT showed equivalence between OBT-A (100 units at fixed points plus 100 units at "follow the pain" points) and topiramate (maximum dose of 200 mg), with better tolerability and adherence in the OBT-A [121] while one single-center open-label study showed comparable efficacy between amitriptyline (25–50 mg/day) and OBT-A (250 U/15 sites), also with better tolerability and compliance in the group treated with OBT-A [122].

Preclinical data suggest that anti-calcitonin gene-related peptide monoclonal antibodies and OBT-A have synergistic effects within the trigeminovascular system. Of note, findings indicate that fremanezumab—an antibody targeting the calcitonin

Clinical question	Recommendation	Strength of the recommendation
1. When should treatment with anti-CGRP monoclonal antibodies be offered to patients with migraine?		
	In patients with CM who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab	Experts' opinion
2. How should other preventive treatments be managed when using anti-CGRP monoclonal antibodies in patients with migraine?		
	In patients with CM who are on treatment with any oral drug with inadequate treatment response we suggest to add erenumab, fremanezumab, or galcanezumab and to consider later withdrawal of the oral drug In patients with chronic migraine who are on treatment with OBT-A with inadequate treatment response we suggest to stop OBT-A before initiation of erenumab, fremanezumab, or galcanezumab In patients with CM who are on treatment with erenumab, fremanezumab, or galcanezumab and who may benefit from additional prevention we suggest to add oral preventive drugs	Experts' opinion
3. When should treatment with anti-CGRP monoclonal antibodies be stopped in patients with migraine?		
	In patients with CM, we suggest to consider to stop treatment with erenumab, fremanezumab, and galcanezumab after 6–12 months of treatments	Experts' opinion
4. Should medication overuse be treated before offering treatment anti-CGRP monoclonal antibodies to patients with chronic migraine?		
	In patients with CM and medication overuse, we suggest to use erenumab, fremanezumab, and galcanezumab before or after withdrawal of acute medications	Experts' opinion
5. In which patients anti-CGRP monoclonal antibodies are not to be used?		
	In patients with migraine, we suggest to avoid anti-CGRP monoclonal antibodies in pregnant or nursing women, in individuals with alcohol or drug abuse, cardio and cerebrovascular diseases, and with severe mental disorders	Experts' opinion
6. Should binding and/or neutralizing antibodies be monitored?		
	In patients with migraine on treatment with anti-CGRP monoclonal antibodies, we suggest not to test binding and/or neutralizing antibodies in daily clinical practice; we suggest to further study the possible implications of binding and/or neutralizing antibodies	Experts' opinion

[*] *Adapted with permission: Sacco et al. [163].*

Table 6.
Recommendations on use of anti-calcitonin gene-related peptide monoclonal antibodies in subjects with chronic migraine[*].

gene-related peptide—mainly prevents the activation of Aδ-fibers, whereas botulinum toxin type A prevents the activation of C-fibers [168]. There is currently only indirect preclinical evidence to support a rationale for dual therapy with anti-calcitonin gene-related peptide monoclonal antibodies and OBT-A for CM prevention [170]. Rigorous studies evaluating clinical efficacy, safety, and cost-effectiveness of dual therapy with mAbs are needed.

8. Management of chronic migraine

CM is underdiagnosed and, thus, untreated disease. Only 20% of patients who meet the criteria for CM are properly diagnosed [65].Treatment options are available for these patients, but only if the patients are properly identified [171]. Successful management of CM will help properly diagnose this disease, optimize treatment and thus reduce the global burden of it. Important components of CM management involve correct diagnosis, optimal treatment plan, patient education, treatment of MOH and comorbid conditions and monitoring of patients response to treatment plan.

It is important for all physicians who are treating the patient to understand the treatment plan, in order to monitor the patient's response to treatment, using as well as continual assessment of the patient's Health-Related Quality of Life (HRQOL) [95]. Preventive therapy for migraines may take up to 6–8 weeks to begin to demonstrate efficacy, and up to 6 months before full efficacy is established [172]. Support and close follow-up are essential for patients, particularly in the first 3 months of treatment [172].

Additionally, physicians should try to identify and reduce aggravating risk factors, such as triggers of migraine or other behavioral habits that may have contributed to the patient's headaches (Section 7.1).

Thus, multimodal treatment concepts are superior to simple drug treatment in severely affected patients [95].

Box 1 contains the key components of chronic migraine management for physicians [95].

Complete and correct diagnosis
Referral to headache specialist/neurologist to confirm CM diagnosis and provide a treatment plan
Management of overuse of acute headache pain medications: providing limits to acute and rescue therapy
Patient education about CM and importance of treatment compliance
Explaining realistic expectations to patients
Consideration of important exacerbating factors
Treatment of comorbid conditions
Nonpharmacotherapy, including trigger management and behavioral therapy

CM, chronic migraine; HIT-6, headache impact test-6; HRQoL, health-related quality of life; MIDAS, migraine disability assessment.

*With permission: Diener et al. [95].

Box 1.
Important components of chronic migraine management.

9. Conclusions

CM is associated with higher burden of disease, more severe psychiatric comorbidity, greater use of healthcare resources, and higher total costs than EM. The current definition of CM has gone through multiple revisions, but the discussion about it is still continuing,

The pathophysiology of CM is not fully understood. However, recent advances in electrophysiology and neuroimaging have indicated that atypical pain processing, central sensitization, cortical hyperexcitability and neurogenic inflammation are important in the development of this disorder. The most significant risk factors such as overuse of acute medication, ineffective acute treatment, obesity, depression and stressful life events have been associated with migraine progression.

Unfortunately, CM is still undertreated because of its poor treatment response and limited therapy options. The currently available evidence-based prophylactic treatment options for CM are topiramate and OBT-A. According to the results of the clinical studies the new class of drugs—anti-CGRP/R monoclonal antibodies seems to be a very promising treatment for CM. Complete and correct diagnosis, optimal treatment plan, management of acute medication overuse and exacerbating factors, patient education and monitoring of the patient's response to treatment plan are the most important components for the successful CM management.

The next years seem to be inspiring for the field, as current research areas are being extended and novel areas are being covered, ultimately broadening our understanding of the complex syndrome of CM.

Conflict of interest

The authors declare that they have no conflict of interest related to the publication of this chapter.

Abbreviations

CM	chronic migraine
HIS	the International Headache Society
EM	episodic migraine
MIDAS	Migraine Disability Assessment
ICHD-3	International Classification of Headache Disorders, 3rd edition
ICHD-1	International Classification of Headache Disorders, 1st edition
ICHD-2	Classification of Headache Disorders, 2nd edition
MOH	medication-overuse headache
CSD	cortical spreading depression
VIP	vasoactive intestinal peptide
CGRP	calcitonin gene-related peptide
HIT-6	Headache Impact Test-6
5HT1	serotonin 1a
OBT-A	onabotulinumtoxinA
FDA	U.S. Food & Drug Administration
EMA	European Medicines Agency
HRQoL	health-related quality of life

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