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Hallmarks of primary headache: part 1 – migraine

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Abstract

Background and aim Migraine is a common disabling conditions which, globally, affects 15.2% of the population. It is the second cause of health loss in terms of years lived with disability, the first among women. Despite being so common, it is poorly recognised and too often undertreated. Specialty centres and neurologists with specific expertise on headache disorders have the knowledge to provide specific care: however, those who do not regularly treat patients with migraine will benefit from a synopsis on the most relevant and updated information about this condition. This paper presents a comprehensive view on the hallmarks of migraine, from genetics and diagnostic markers, up to treatments and societal impact, and reports the elements that identify migraine specific features.

Main results The most relevant hallmark of migraine is that it has common and individual features together. Besides the known clinical manifestations, migraine presentation is heterogeneous with regard to frequency of attacks, presence of aura, response to therapy, associated comorbidities or other symptoms, which likely reflect migraine heterogeneous genetic and molecular basis. The amount of therapies for acute and for prophylactic treatment is really wide, and one of the difficulties is with finding the best treatment for the single patient. In addition to this, patients carry out different daily life activities, and might show lifestyle habits which are not entirely adequate to manage migraine day by day. Education will be more and more important as a strategy of brain health promotion, because this will enable reducing the amount of subjects needing specialty care, thus leaving it to those who require it in reason of refractory condition or presence of comorbidities.

Conclusions Recognizing the hallmarks of migraine and the features of single patients enables prescribing specific pharmacological and non-pharmacological treatments. Medical research on headaches today particularly suffers from the syndrome of single-disease approach, but it is important to have a cross-sectional and joint vision with other close specialties, in order to treat our patients with a comprehensive approach that a heterogeneous condition like migraine requires.

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Introduction

Migraine is a common neurological disorder with higher prevalence rates in the productive age, between the second and fourth decade, particularly among women. According to the 2021 estimates of the Global Burden of Disease study (GBD) [1], migraine prevalence is 15.2% globally (18.9% among women and 11.4% among men), a figure which is similar to that of a recent review [2], and is among the leading causes of health loss as measured by GBD's years lived with disability (YLDs). Globally, it is ranked second after major depression for both sexes combined, as it accounts for 4.73% of all-cause YLDs (6.92% among people aged 15–49); among women, it is ranked first, as it accounts for 5.57% of all-cause YLDs (7.51% among women aged 15–49). The core symptom of migraine is a moderate or severe headache, which is often accompanied by a large amount of reversible symptoms, such as photophobia, phonophobia, cutaneous allodynia, nausea vertigo, and dizziness [3]. In around 30% of the cases, a set of reversible neurological symptoms lasting 5–60 min can occur before the onset, during, or in the absence of pain (migraine aura), the most common being visual ones [3]. In addition to this, migraine is associated to a wide variety of comorbidities, such as anxiety, depression and hypertension (pooled proportions comprised between 23 and 25%) [4], which makes migraine impact even higher.

Migraine impacts on a variety of daily life domains, to the point that almost all kind of activities are likely to be impacted [5], and the degree of such an impact is likely underestimated, due to the partial recognition of several mediators, in particular the effect of ageing process and of the use of medications, which can be considered as proxy indicators for migraine severity [6]. The objectification of migraine-related disability is of importance to monitor treatment effects and make management decisions, and to account for migraine impact on inter-ictal phases [6]. Such a situation, at the global level, is made event more complex by the fact that around 80% of the persons with migraine live in low and middle income countries, with limited access to care [7], and a poor recognition of the real burden of migraine that requires more data, and innovative approaches, in order to be recognized [6, 8].

Raising awareness on migraine is needed, as poor recognition of such condition has been reported both among patients and among healthcare professionals [9, 10]. This is critical as, given the large prevalence of migraine and the lack of specialized clinics in many low and medium income countries, most of migraine care has to be carried out at primary and secondary levels [7, 11–13], a situation that might also involve high-income countries in the near future, where better access to treatment for people with migraine is needed [14]. Specialty centres and neurologists with specific training on headache disorders have knowledge and skills to provide specific care, from diagnosis to treatment [15–17]. However, healthcare professionals and researchers who do not deal with migraine for clinical work-up and on a regular basis might benefit from a synopsis on the most relevant and updated information about migraine, from genetics and diagnostic markers, up to treatments and societal impact.

This paper is aimed to present the hallmarks of migraine in all these fields. It is organized into a set of sub-sections, and each of them is aimed to report the elements that identify migraine specific features, summarizing the most comprehensive and precise evidence possible for each topic.

Genetic basis

Migraine results from the interplay between genetic and environmental factors [18, 19]. Monogenic forms of migraine are caused by a pathogenic mutation in a single gene, and include Familial Hemiplegic Migraine (FHM) and migraine with aura associated with hereditary disorders such as CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) [20–24]. Other forms of migraine are considered polygenic, where combined genetic risk factors (and not causal mutations) may contribute to the disease aetiology. Genome-Wide Association Studies (GWAS) have identified more than 180 susceptibility variants for migraine [25]. Each variant slightly increases the risk of migraine, and the combination of variants creates a "pro-migraine" condition [26]. Finally, recent studies have highlighted the importance of shared genetic factors between migraine and its major comorbidities, including depression and hypertension [27, 28].

FHM is an autosomal dominant disease, with four genes identified to date. FHM-1 is attributable to mutations of *CACNA1A*, encoding a subunit of a voltage-dependent calcium channel expressed in cerebral and cerebellar presynaptic terminals [20]. Mutations in *ATP1A2*, encoding a subunit of a Na + /K + transmembrane pump, are involved in FHM-2 [21], while mutations

in *SCN1A*, encoding a subunit of a voltage-dependent neuronal sodium channel, lead to FHM-3 [22]. *PRRT2*, known as the major gene for paroxysmal kinesigenic dyskinesias, is considered responsible for type 4 FHM [23]. These genes all encode neuronal or astrocytic proteins expressed at synapses. Their mutations result in cortical hyperexcitability, which facilitates the onset of cortical spreading depression, the mechanism behind migraine aura [29]. However, these four genes account for only a minority (about 20%) of cases suspected of having FHM and referred for genetic assessment [30].

Hemiplegic Migraine (HM) can be familial or sporadic. In FHM, patients have at least one first- or second-degree relative with similar attacks. In sporadic forms, no relatives are affected. Both forms manifest with auras that include motor deficits associated with visual, sensory and/or speech/language symptoms [31]. HM is rare, with a prevalence estimated at 0.01% [32]. It typically manifests with an early onset at a mean age of 12–17 years. During typical attacks, muscle weakness varies from mild weakness of a limb to flaccid hemiplegia [33]. The frequency of attacks varies from more than one per week to a few throughout life, with an average of 3–4 per year. Their severity often decreases in adulthood. HM is characterized by great clinical variability in terms of aura symptoms (location, intensity, duration) and headache characteristics in a patient over their lifetime and among affected relatives within the same family. While patients with HM do not experience migraine attacks without aura more often than the general population, the prevalence of typical migraines with aura and migraines with brainstem aura is higher in patients with HM [34]. Depending on the involved genes, HM may be associated with inter-ictal manifestations such as epilepsy, cerebellar syndrome, or neurodevelopmental disorders. Permanent cerebellar ataxia is present in about 60% of cases of FHM-1 but is very rare in FHM-2 or FHM-3 [31]. Epilepsy is possible in all types of HM and affects 20–30% of FHM-2 cases [35].

Other forms of monogenic migraine with aura have been described in the context of genetic syndromes. Migraine with aura is frequently observed in patients with CADASIL, a hereditary small-vessel disease responsible for recurrent lacunar infarcts caused by mutations in the *NOTCH3* gene [24]. Other hereditary small vessel diseases caused by mutations in *COL4A1*, *COL4A2*, or *TREX1* also include migraine, often with aura [36, 37].

Mutations in the genes *KCNK18*, *CSNK1D* and *ALPK1* have been reported in some families with migraine with aura, but further studies are needed to confirm the link between these mutations and the development of migraine with aura. *KCNK18* encodes the TRESK channel, a potassium channel involved in membrane excitability. A frameshift mutation was found in a family presenting with visual auras in an autosomal dominant pattern [38]. *CSNK1D*, one of the "clock genes" involved in advanced sleep phase syndrome, has been reported in two large families presenting with this sleep disorder associated with migraine [39]. An autosomal dominant missense mutation in the *ALPK1* gene has been identified in five families affected by ROSAH syndrome (Retinal dystrophy, Optic nerve oedema, Splenomegaly, Anhidrosis, and migraine Headache) [40].

Apart from those monogenic forms, more common migraine also has a heritability estimated between 35 to 60% [18, 19], but is attributed to a polygenic mechanism involving the interaction of multiple genetic variants, each conferring a low risk of developing the disease (Fig. 1). GWAS analyse millions of polymorphisms called Single Nucleotide Polymorphisms (SNPs) in large cohorts of patients and controls. Over the past 10 years, more than 180 SNPs have been identified as significantly associated with migraine [25, 41, 42]. The identified variants are located in non-coding regions or in affected genes whose functions are not all known. However, there appears to be higher expression of the genes involved in pro-migraine network in vascular and neuronal tissues, confirming that migraine is a polygenic neurovascular disorder. The latest GWAS study by Hautakangas in 2022 showed that three variants were relatively specific to migraine with aura, two were specific to migraine without aura, and nine were associated with both types of migraine [25]. Each of these SNPs explains only a small fraction of the genetic risk, and their sum does not account for the entire heritability of migraine.

The Polygenic Risk Score (PRS) assesses the overall genetic risk of migraine as the sum of all pro-migraine SNPs in an individual [26]. Studies show that the PRS is higher in familial cases, in migraine with aura compared to migraine without aura, and in forms with an earlier onset [43].

Finally, genetics has highlighted the importance of shared genetic factors between migraine and its major comorbidities. Several analyses of GWAS data have revealed a shared genetic susceptibility between migraine and psychiatric disorders [27], ischemic stroke [44], coronary artery disease [45], hypertension [28], sleep disorders [46], and also endometriosis [47].

Concluding remarks

In summary, there have been substantial advancements in the genetics of migraine in the past years. The investigation of monogenic migraines has underscored the strong links between migraine and neurovascular disorders. Genome-wide association studies have identified more than 180 variants mainly expressed in vascular and

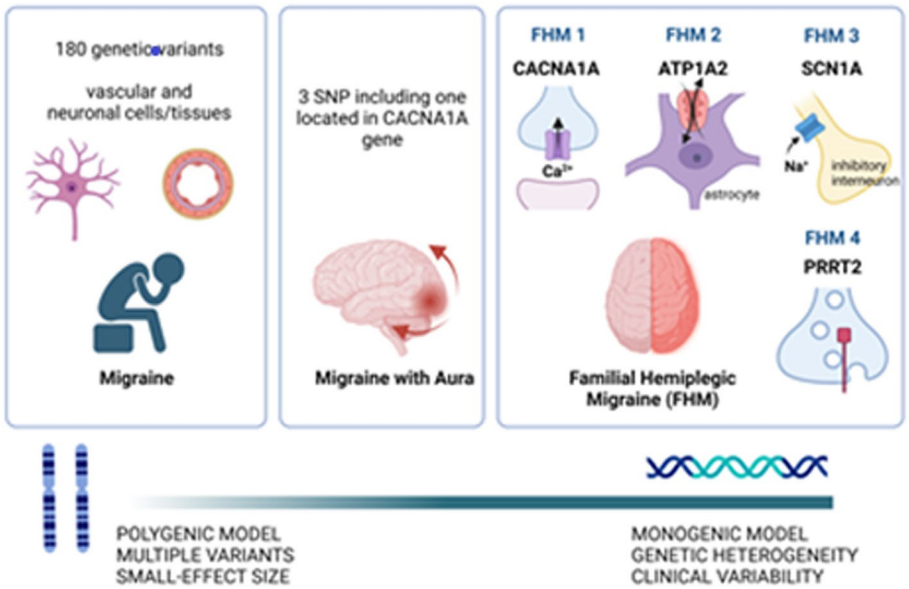

Fig. 1 Overview of migraine genetics. *Notes.* An overview of the complex genetic architecture of migraine, from polygenic model on the left, to monogenic model on the right

neuronal tissues, which are predisposing for migraine. In the future, advances in genetics might help to better quantify the genetic susceptibility to migraine and specific associated comorbidities for each patient, guide the choice of treatment, and inform prevention strategies.

Molecular pathways

The Trigeminovascular System (TVS) plays a pivotal role in migraine headache pathophysiology. Activation of this system results in the release of vasoactive neuromodulators, such as the Calcitonin Gene-Related Peptide (CGRP), amylin, the Pituitary Adenylate Cyclase Activating Polypeptide (PACAP), and Nitric Oxide (NO), amongst others. This section will discuss the pharmacology of these neuromodulators and the downstream signaling involved after the activation of the TVS.

CGRP

CGRP is recognized as a key mediator of migraine. Elevated levels of CGRP have been detected in the plasma, saliva, tears, and cerebrospinal fluid of migraine patients [48, 49]. Most importantly, intravenous administration of CGRP has been shown to induce migraine-like headaches in 57% of migraine patients [50].

In the TVS, CGRP has been shown to be expressed in C-fibers, whereas its receptor has been described to be present in Aδ-fibers and Schwann cells [51, 52]. The canonical CGRP receptor is a heterodimer comprised of the Calcitonin-Like Receptor (CLR), and the Receptor Activity-Modifying Protein 1 (RAMP1). The CLR is a G-Protein Coupled Receptor (GPCR), coupled to a Gs protein, therefore, binding of CGRP to its receptor activates the adenylate cyclase, leading to the accumulation of cyclic Adenosine Monophosphate (cAMP) [53].

Despite the clear role of CGRP in migraine, its specific site of action is still unclear. As shown in Fig. 2, the main site of action of CGRP is certainly the TVS [54]; however, the release of CGRP has several roles, including dilation of meningeal vessels, promotion of local neurogenic inflammation and dural mast cells degranulation, which, in turn, releases pro-inflammatory and pro-nociceptive molecules [55]. Additionally, mechanical allodynia and hyperalgesia could be mediated by shear stress and enhanced pulse waves in vessels, caused by mechanosensitive channels present in the trigeminal ganglion (TG) and surrounding satellite glial cells [56].

Amylin

The neuroendocrine hormone amylin has been shown to be involved in pain signalling (Fig. 2). In preclinical models of migraine, amylin administration has been shown to increase neuronal activation of the TVS and orofacial allodynia [57, 58]. Moreover, infusion of pramlintide, an amylin analogue, induced migraine-like attacks in 41% of migraine patients [57]. The actions of amylin in the TVS are thought to be mediated via activation of the Amylin 1 (AMY1) receptor, with studies describing the

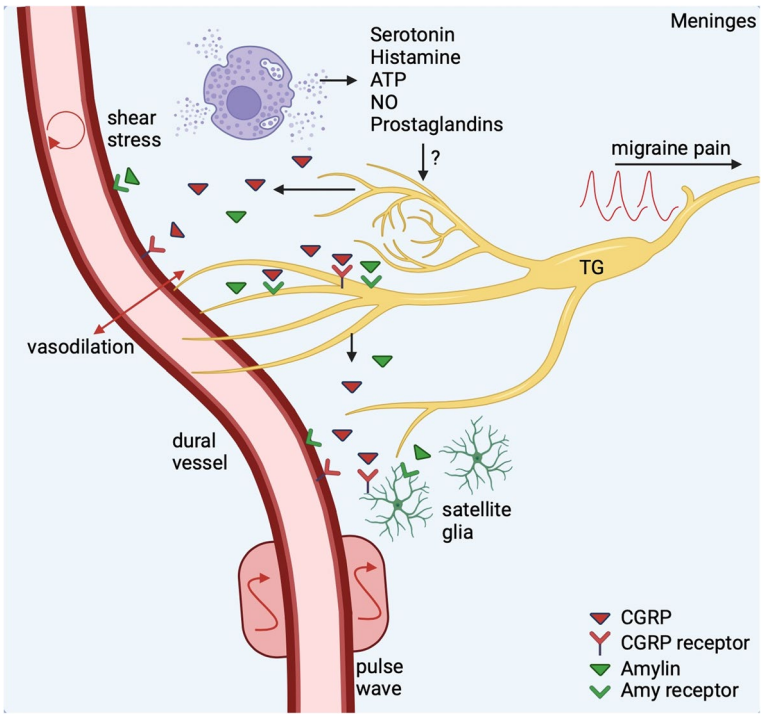

Fig. 2 Role of CGRP and Amylin in the trigeminovascular system. *Notes.* Representation of the key elements of the trigeminovascular system, comprising meningeal blood vessels, local mast cells and trigeminal nerve fibres during a migraine headache attack. Binding of CGRP and amylin to their receptors results in dilation, and shear stress in the meningeal vessels. CGRP additionally activates mast cells, triggering the release of a plethora of pro-nociceptive compounds such as serotonin, histamine, leukotrienes, prostaglandins, ATP, and NO, further exciting the nociceptive fibres and promoting more CGRP release. ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; NO, nitric oxide

expression of this receptor in C-fiber neurons in the TG [59]. CGRP can also bind to this receptor, with an affinity similar to amylin [53]; therefore, CGRP may exert its biological effects through various receptors and signalling pathways, while amylin exclusively acts on the AMY1 receptor.

As part of the calcitonin family of receptors, the AMY1 receptor is also a heterodimer comprised by the Calcitonin Receptor (CTR) and RAMP1. However, the pharmacology of this receptor is complex, since several CTR splice variants (i.e. isoforms) have been described. Of relevance for migraine, activation of the AMY1 receptor can result in either accumulation of cAMP, or in activation of Protein Kinase C (PKC) that leads to inhibition of large conductance Calcium-Activated Potassium (BKCa) channels [53, 60]. Determining the differential expression of these isoforms could shed light on which variants are the best candidates to target, and which may lead to unwanted side effects.

PACAP

PACAP belongs to a wider family of peptides that also includes the Vasoactive Intestinal Peptide (VIP) [61]. Two isoforms of PACAP have been reported, a 38 amino acid peptide (PACAP-38), and a cleaved 27 amino acid peptide (PACAP-27), with PACAP-38 being most prevalent form [62]. Infusion of these peptides has been shown to provoke migraine-like attacks in 58–72% of migraine patients [63, 64].

Studies have described the expression of PACAP and its receptors in the TVS [65]. PACAP acts via three GPCRs, the PAC1, VPAC1 and VPAC2 receptors [61]. While PACAP and VIP bind to VPAC1/2 receptors with similar affinity, PACAP exhibits a 100-fold higher activity than VIP at the PAC1 receptor. All three receptors lead to activation of the AC; nevertheless, alternative splicing of the PAC1 receptor gene results in different receptor variants [65]. For each variant, the PAC1 receptor can activate AC and PKC, with activation of AC being the predominant pathway [66]. Understanding the expression profile of these splice variants would enable developing novel drugs with higher efficacy, reducing off-target effects, leading to more personalized medicine.

Nitric oxide

The molecular basis of migraine is intricately linked to NO, a key blood flow regulator. As shown in Fig. 3,

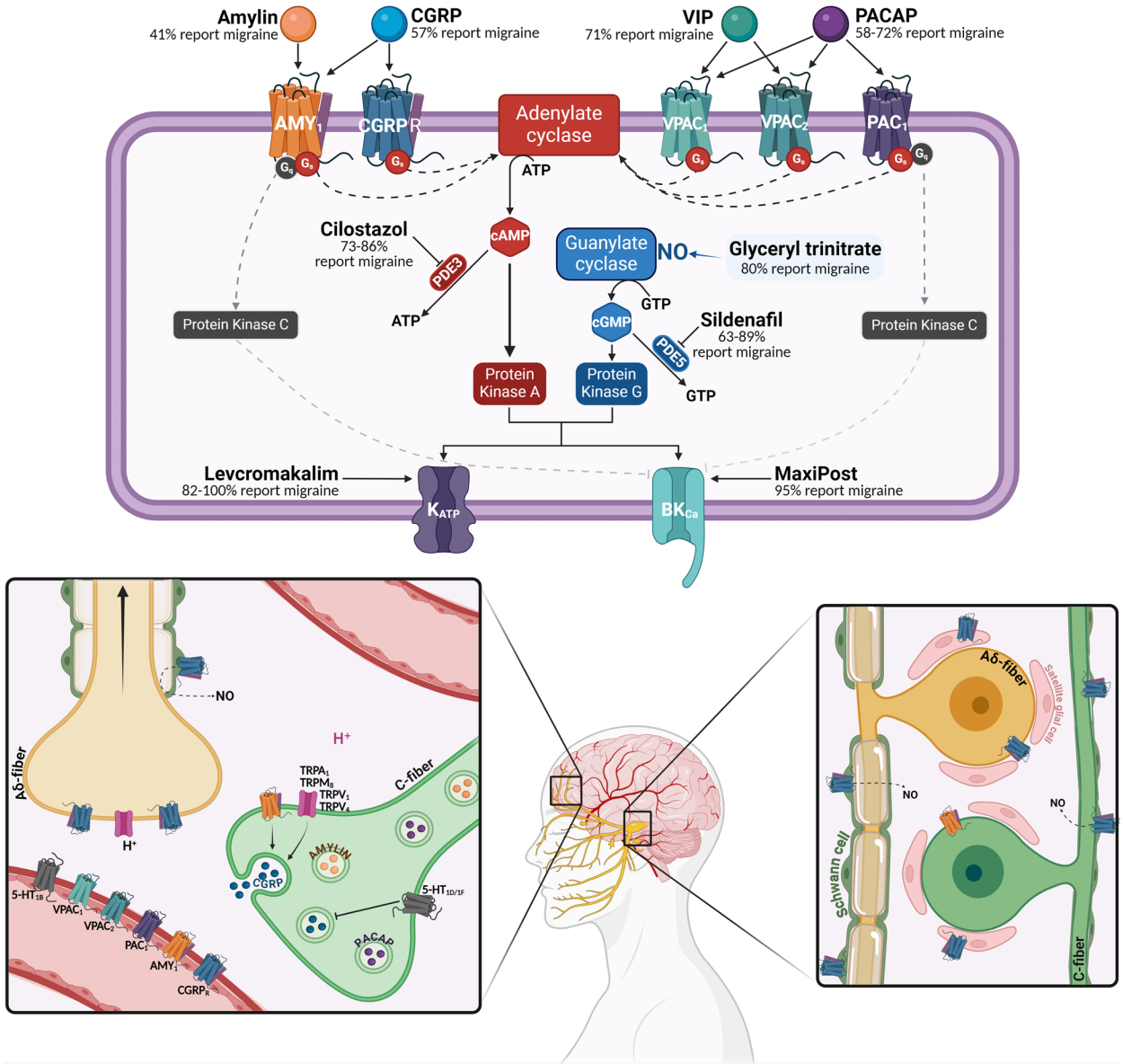

Fig. 3 Molecular pathways underlying the pathophysiology of migraine headache. *Notes.* Activation of the trigeminovascular system results in the release of CGRP, amylin and PACAP from c-fibers, and their release can be modulated via de activation of presynaptic receptors. Binding of these peptides to their receptors results in changes in vascular tone and nociceptive transmission. These responses can be regulated by modulating the different components of their signalling cascades, which has been studied using provocation models, in which potential trigger molecules are used to induce migraine attacks in humans. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; CGRPR, CGRP receptor; GTP, guanosine triphosphate; NO, nitric oxide; PACAP, Pituitary adenylate cyclase activating polypeptide; PDE3, phosphodiesterase 3; PDE5, phosphodiesterase 5; VIP, vasoactive intestinal peptide

NO diffuses into cells and activates the soluble guanylate cyclase, increasing the levels of cyclic Guanosine Monophosphate (cGMP), leading to vasodilation, and further causing the release of neuropeptides [67]. Accordingly, glyceryl trinitrate, a precursor for NO, triggers migraine-like headaches in migraine patients [68]. Moreover, inhibiting NO synthases has been shown to effectively treat migraine attacks [69]. In contrast, substances such as reserpine, m-chlorophenylpiperazine, fenfluramine, and prostacyclin can trigger migraine attacks via activation of NO synthases [67].

Second messengers

The main neuromodulators described to be involved in the pathophysiology of migraine headache, bind to GPCRs that lead to the accumulation of cAMP or cGMP

(Fig. 3). A strict regulation of the levels of these nucleotides is crucial for maintaining cellular homeostasis; accordingly, Phosphodiesterases (PDEs) hydrolyze cAMP and cGMP. Eleven families of phosphodiesterases have been described, each one with tissue- and nucleotide-specific profiles. Of relevance for migraine, PDE3 and PDE5 have been shown to be expressed in endothelial and vascular smooth muscle cells of cerebral arteries [70, 71], with preclinical studies also suggesting expression in the different components of the TVS [72]. Due to their role in vascular function, PDE inhibitors have been developed for cardiovascular disorders. Of interest, cilostazol and sildenafil were developed for PDE3 and PDE5, respectively [67]. Therefore, inhibition of these PDEs causes accumulation of their respective nucleotides. In accordance with this, cilostazol has been shown to induce migraine-like headaches in 73–86% of migraine patients [73, 74]. Similarly, infusion of sildenafil provokes migraine like headaches in 63–89% of migraine patients [75, 76].

Potassium channels

Accumulation of cAMP and cGMP leads to activation of protein kinase A and protein kinase G, respectively. These kinases modulate the activity of the ATP-sensitive potassium channels and the BKCa channels [77].

The ATP-sensitive potassium channels are composed of two subunits, an inward rectifier potassium (Kir) channel, and a Sulfonylurea Receptor (SUR) subunit [78]. Different isoforms exist of each subunit, all with specific properties and tissue distribution. In the TVS, Kir6.1, Kir6.2, SUR1 and SUR2B have been described. Interestingly, administration of NN414, a neuronal-specific Kir6.2/SUR1 channel opener did not provoke migraine-like headaches [79]. In contrast, levcromakalim, a selective Kir6.1/SUR2B channel opener expressed in cerebral vasculature [80], induced migraine-like headaches in 82–100% of migraine patients, with 59% of patients developing aura [81, 82], suggesting migraine-specific isoforms.

The BKCa channels are also formed by two subunits, α and β. Four different β subunits have been reported, with the β1 subunit described to be expressed throughout the TVS [60]. In accordance, infusion of the BKCa channel opener MaxiPost triggered migraine-like attacks in 95% of migraine patients [83]. Together with levcromakalim, MaxiPost is one of the most effective experimental migraine triggers, reinforcing the role of these channels in migraine pathophysiology.

Presynaptic modulation

Modulation of the TVS can also be achieved via the activation of presynaptic receptors present in the trigeminal sensory fibers. For example, the Serotonin (5-HT) 1D/1F receptors, are GPCRs coupled to an inhibitory G protein, therefore, upon activation, these receptors will inhibit the release of neuromodulators from the synaptic terminal, such as CGRP [84, 85]. In contrast, activation of the channels belonging to the Transient Receptor Potential (TRP) family, namely, the ankyrin 1 (TRPA1), vanilloid 1 and 4 (TRPV1 and TRPV4,), and melastatin 8 (TRPM8), results in vesicle release (e.g. CGRP) [86]. Similarly, studies have shown expression of the AMY1 receptor in C-fibers, suggesting than CGRP (and amylin) could activate this receptor in an autocrine manner, thus, facilitating trigeminovascular sensitization [53].

Concluding remarks

In summary, studies have shown that activation of the TVS results in the release of vasoactive neuromodulators like CGRP, amylin, PACAP and NO, which play a crucial role in migraine headache, as well as migraine chronification. Binding of these molecules to their receptors and their subsequent signalling cascades, results in changes in vascular tone and nociceptive transmission. Understanding these pathways will allow to not only develop novel targets, but to also optimise current therapeutic interventions for migraine.

Central Nervous System (CNS) and Peripheral Nervous System (PNS) implications

Migraine is a complex neurological disorder that causes ictal and interictal symptoms. Its manifestations include not only headache, but also hypersensitivity to certain stimuli, cranial autonomic symptoms, transient neurological symptoms, cognitive manifestations, homeostatic, and/or affective symptoms, which can present before, during, or after the headache [87]. The ictal and periictal phase has been frequently divided into four possible sub-phases: premonitory symptoms, aura, the attack itself and the postdromal phase [88]. Current knowledge suggests that this classification is more academic than clinical, since many symptoms and phases overlap during the attacks, and some may not always be clinically evident [87, 88]. Regarding interictal manifestations, some patients may exhibit symptoms such as allodynia, sensory hypersensitivity, mood disorders or cognitive symptoms, among others [89]. Research has associated many of these features with CNS and PNS abnormalities, which will be summarized.

Regarding migraine episodes, premonitory symptoms may precede the onset of pain up to 48 h [90]. The most commonly reported symptoms include fatigue, altered mood, and hunger [91]. These symptoms have been associated with the activation of certain brain areas, with the hypothalamus, the dorsal pons, the limbic system, and the ventral tegmentum being the most frequently

reported in imaging studies [92]. Other premonitory symptoms are typical, or even diagnostic, migraine symptoms such as nausea, vomiting, photophobia, phonophobia or osmophobia [90, 91, 93]. This overlap, along with the anatomic and functional interconnection of these regions with other areas more associated with the ictal phase, such as the brainstem and the thalamus, contribute to the network pathophysiology of migraine [94].

The second phase is aura; however, it is not consistently reported by all patients. Around 20–30% of patients report experiencing aura preceding or coinciding with migraine attacks [95]. These symptoms can vary but often include visual disturbances, such as seeing flashing lights, zigzag patterns, or temporary blind spots in the visual field. Some individuals may experience sensory symptoms like tingling or numbness in the hands, face, or mouth. In rare cases, people may have difficulty with speech or experience muscle weakness. Aura usually lasts from 5 to 60 min and can serve as a warning sign for the impending headache phase. The pathophysiology of aura has been linked with Cortical Spreading Depression (CSD) [96]. The combination of positive and negative visual, sensory, motor, and speech symptoms of aura seems to be explained by the wave of depolarization that occurs during CSD [95, 97]. It propagates across the cortex, usually in a postero-anterior direction, initiating a series of events at the cortical surface, leading neuronal and glial depolarization, the release of inflammatory mediators and neurotransmiters, and degranulation of the dural mast cells. This process results in the constriction and dilation of surface vessels housing trigeminal afferents, along with the direct depolarization of nociceptive afferents via the release of K + and other mediators into the extracellular space [98]. The net result is an increase in the spontaneous firing rate of both TG and TNC neurons.

During the ictal phase, both CNS and PNS structures are relevant. These include trigeminovascular system activation, and trigeminal nerve activation and autonomic nervous system involvement. Craniofacial nociceptive afferents originate from the TG and the dorsal root ganglia of cervical roots C1–C3. Their central projections terminate in the trigeminocervical complex, which includes the Trigeminal Subnucleus Caudalis (TNC) and the dorsal horn of the first cervical segments, representing the initial CNS relay in craniofacial nociceptive circuitry [99, 100]. TNC neurons extend projections to the Ventroposteromedial and posterior nuclei of the thalamus. Ventroposteromedial neurons primarily innervate the somatosensory cortex, while posterior neurons project more broadly to various sensory cortices, the insula, and association cortex regions. Additionally, TNC neurons establish connections with affective and motivational circuits via the nucleus tractus solitarius and parabrachial nucleus, which have diffuse projections to the hypothalamus, thalamic nuclei, amygdala, insular cortex, and frontal cortex [100]. Moreover, TNC neurons directly project to output structures involved in pain modulation and autonomic regulation, including the hypothalamus, periaqueductal gray, superior salivatory nucleus, and rostral ventromedial medulla [101]. These connections play essential roles in coordinating pain perception, emotional responses, and autonomic functions associated with craniofacial nociception. In summary, craniofacial afferents synapsing within the TNC project, either directly or indirectly, to regions associated with the sensory/discriminatory, salience/alerting, and affective/motivational dimensions of pain.

Migraine postdromes may include sensory, gastrointestinal, neuropsychiatric and general symptoms [98]. Interestingly, the most frequently reported postdromal symptoms are fatigue, concentration difficulties and mood changes [102, 103]. In addition, in the few studies that have specifically examined postdromes, no unique features have been observed [97]. This could suggest that the clinical presentation of postdromes may reflect the persistent activation of some of the brain structures that are implicated in the premonitory and/or ictal phases.

Migraine patients also exhibit structural and functional abnormalities between attacks, referred to as the interictal phase of migraine. The two main functional features are lack of habituation and sensitization [104]. The first refers to the inability of the migraine brain to decrease the amount of attention directed towards non-relevant stimuli, such as disturbing ambient noise [104]. The second is related to the decreased threshold that patients exhibit regarding the exaggerated perception of some sensory inputs, such as lights, sounds, smells, touch, or cranial movements [105]. Allodynia is an example of sensitization, where the response of nociceptive neurons is heightened [106]. Sensitization has been subdivided into peripheral and central sensitization, depending on the body regions where the patient perceives it and the neurological structures involved. Peripheral sensitization is limited to the cranial area and has been linked to the heightened response of the trigeminal ganglion afferents [107]. In contrast, central sensitization may be observed when patients exhibit symptoms beyond the head and has been associated with second, third or fourth-order neurons in the trigeminal nuclei, thalamus, or somatosensory cortex, respectively. Sensitization is not exclusive of migraine and can be observed in other headache disorders or pain syndromes [108]. In the case of migraine, its occurrence is more frequent in patients with higher frequency of attacks, being one of the changes linked to migraine chronification, by amplifying pain

signalling and contributing to the persistence and intensity of migraine attacks [109].

Another aspect related with the interictal phase of migraine is the triggering of episodes. Some patients associate their episodes with weather changes, sleep deprivation or excess, stress, hormonal changes, alcohol intake or certain foods [110]. However, there is a notable variability both within attacks and among patients. The threshold for triggering attacks varies over time, and has also been associated to the frequency of episodes [111].

Concluding remarks

In summary, migraine is a disorder that involves both the central and peripheral nervous system, with the activation and inter-connection of multiple regions during the episodes and along with the chronification of the disorder.

Neuroimaging in migraine

Despite inconsistent findings in migraine neuroimaging studies and the fact that there are no reliable and robust neuroimaging biomarkers due to both not completely understood pathogenesis and clinical and neuroimaging heterogeneity [112], emerging advanced neuroimaging techniques are helping to elucidate common neuroanatomical substrates and functional abnormalities in migraine patients. In particular, we presented the neuroimaging hallmarks associated with Episodic Migraine (EM) with a special focus on migraine with aura, and Chronic Migraine (CM), highlighting key findings from recent research.

Burke et al. employed novel brain network mapping techniques to link neuroimaging findings to a common neuroanatomical substrate [113]. Their study demonstrated that regions of grey matter volume loss in migraine patients localize to a brain network involving the visual cortex, insula, and hypothalamus. These regions are strongly connected to the visual cortex V3/V3A, previously implicated in cortical spreading depression mechanisms [114, 115]. The specificity of these findings compared to chronic pain and neurological control groups suggests that these connectivity relationships may be present across all migraine subgroups, not just those with visual aura. Furthermore, Puledda et al. concluded that altered visual cortex excitability may be a neuroimaging hallmark of migraine [116]. In addition, the hypothalamus has been closely implicated in migraine as a hallmark of migraine attack initiation, along with the brainstem [117, 118]. These regions are thought to contribute to the autonomic and pain-processing abnormalities observed in migraine patients.

Functional Magnetic Resonance Imaging (fMRI) studies have consistently shown atypical brain responses to sensory stimuli, the absence of the normal habituating response between attacks, and atypical functional connectivity of sensory processing regions in migraine patients [119]. In particular, specific fMRI studies investigating thermal pain-induced brain activations revealed differential activation in migraine patients compared to healthy controls in several brain regions, including the temporal pole, parahippocampal gyrus, anterior cingulate cortex, lentiform nuclei, fusiform gyrus, subthalamic nucleus, hippocampus, middle cingulate cortex, somatosensory cortex, dorsolateral prefrontal cortex, secondary somatosensory cortex, precentral gyrus, superior temporal gyrus, and brainstem [120, 121]. Furthermore, fMRI studies suggest an imbalance of pain facilitation and inhibition as a neuroimaging hallmark of migraine [119, 122]. In other words, migraineurs exhibit stronger activation in pain-facilitating regions and hypoactivity in pain-inhibiting regions, indicating a disrupted pain modulation network.

Resting-state functional connectivity MRI studies have shown that migraine is associated with atypical connectivity in several brain regions and networks. Tessitore et al., Schwedt et al., and Chong et al. demonstrated that migraine patients exhibit altered connectivity in the somatosensory cortex, anterior and posterior insula, middle and anterior cingulate cortex, hippocampus, amygdala, parahippocampal gyrus, periaqueductal grey, nucleus cuneiformis, and hypothalamus [119, 123, 124]. Additionally, there are abnormalities in resting-state networks, including the default mode network, salience network, frontoparietal network, executive network, and sensorimotor network [119, 123, 124]. Moreover, the salience network, somatosensory network and default mode network showed altered connectivity during the attack versus outside of the attack [125]. In addition, Szabo et al. reported lower fractional anisotropy in the frontal lobe, indicating altered white matter integrity [126]. Moreover, MR Spectroscopy (MRS), a non-invasive method of investigating the biochemical composition of the brain, has been used to highlight various biological changes within the brain in patients with migraine. Phosphorous (31P)-MRS studies have implied abnormal energy metabolism and potential mitochondrial dysfunction may occur in patients with migraine. Imaging changes in migraine patients who do not experience aura are subtler, with studies varying widely in the literature [127].

Migraine with aura is likely mediated by widespread brain dysfunction in areas involving, but not limited to, visual cortex, somatosensory and insular cortex, and thalamus [128]. Gaist et al. observed a thicker visual cortex in patients with migraine with visual aura [129]. These structural changes may contribute to the visual disturbances and heightened cortical excitability seen in

migraine with aura. Moreover, MRS studies have highlighted abnormal biochemical changes in the brains of migraine patients. Bridge et al. noted reduced GABA (γ-Aminobutyric Acid) levels in patients with migraine aura, suggesting reduced inhibition in the occipital cortex consistent with occipital hyperexcitability [130]. Additionally, there is a positive correlation between glutamate levels and BOLD (blood oxygenation level dependent) activation in the visual cortex during visual stimulation, indicating enhanced glutamate activation and abnormal excitation-inhibition coupling. Furthermore, Tedeschi et al. revealed that patients with migraine with aura have altered resting-state visual network connectivity compared to those with migraine without aura and healthy controls [131]. Datta et al. found a greater response to visual stimulation within the primary visual cortex in patients with migraine with aura, further differentiating between migraine subtypes [132]. In addition, Faragò et al. examined functional and structural brain differences between migraine patients with and without aura and concluded that these two subtypes of migraine should be handled separately in future studies [133]. Other fMRI imaging studies have also provided evidence of ictal and interictal alterations in functional connectivity within the visual and extrastriate cortex, somatosensory cortex, and executive cortical areas [112, 134, 135]. Perfusion abnormalities have been also observed in migraine patients, particularly those with aura. Lauritzen et al. first demonstrated objective alterations in regional Cerebral Blood Flow (CBF) during migraine aura using intra-arterial Xenon techniques [136]. Furthermore, Fu et al. reported higher CBF in regions such as the superior frontal gyrus and cerebellum, and lower CBF in the middle frontal gyrus and thalamus in patients with migraine with aura [137]. Increased vascular permeability, as a hallmark of inflammation, was mostly found in hemiplegic migraine, and was atypical in migraine with and without aura [138]. In general, it seems that cerebral hypoperfusion in one or more vascular territories occurs mainly unilaterally early during aura in the ictal phase and persists throughout the aura phase [128].

Silvestro et al. suggested that higher extrastriate brain changes may lead to the propagation of aura from simple visual symptoms to more complex phenotypes [139]. Pure visual aura compared to visual aura with other sensory or speech symptoms as well, may involve different functional reorganization of brain networks and additional mitochondrial dysfunction mediating more aura symptoms [128]. Several studies have underscored the notable distinctions between individuals experiencing pure visual aura and those who in addition experience somatosensory and dysphasic aura [139–144]. These findings hold significant potential for enhancing the accuracy of diagnosis, classification, and identification of biomarkers specific to distinct migraine with aura subtypes.

Patients with CM show increased resting-state functional connectivity of pain-processing areas, including the anterior cingulate cortex and the dorsal raphe nucleus, while resting-state functional connectivity between pain-processing areas and the hypothalamus is decreased [145]. In addition, Coppola et al. found decreased grey matter volume in patients with CM in regions such as the right cerebellum, left pallidum, amygdala, and orbitofrontal, temporal, and occipital cortex [146]. Patients with medication overuse headache show further reductions in grey matter volume, particularly in the bilateral orbitofrontal cortex and left middle occipital gyrus [147]. In addition, Li et al. demonstrated decreased neurovascular coupling in the orbitofrontal cortex [148].

Concluding remarks

In summary, atypical brain responses to sensory stimuli and altered functional connectivity in sensory processing regions and default mode network are consistent findings in migraine patients. Further neuroimaging research should focus on distinguishing between migraine subtypes to discover specific biomarkers and accurate predictive models, allowing therapeutic strategies tailored to each subtype.

Neurophysiological aspects of migraine

The complex neurophysiological mechanisms underlying migraine pathology have yet to be fully elucidated. The hallmark neurophysiological features of migraine (Fig. 4), identified through behavioural, electrophysiological, or neuroimaging investigations, are outlined in the following section; nonetheless, these features warrant further validation in the future.

Regarding the neural circuitry responsible for and encoding the subjective experience of pain, the migraine brain is characterized by alterations in perception and processing of noxious inputs; this dysfunction manifests in patients through several phenomena. *(a) Temporal summation.* Individuals with migraine often exhibit enhanced temporal summation, where quickly occurring repetitive noxious stimuli evoke progressively increasing levels of pain [149]. This indicates sensitization in pain processing at both the spinal cord and the supraspinal levels leading to exacerbation of headache intensity during attacks. *(b) Conditioned pain modulation (CPM) dysfunction*. Also known in animals as diffuse noxious inhibitory control, CPM is a surrogate measure of descending inhibitory system whereby a noxious stimulus applied to one part of the body inhibits pain perception in another part. Dysfunction of the CPM system

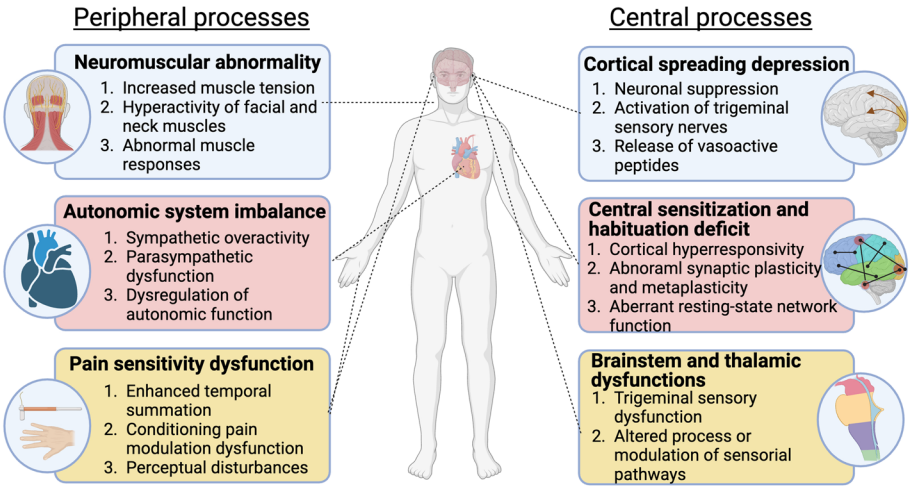

Fig. 4 Neurophysiological hallmarks of migraine: peripheral to central processes

has been observed in individuals with migraine [150]; it might reduce pain inhibition and enhances pain sensitivity. Impairment in pain modulation may contribute to the persistence and severity of migraine attacks. *(c) Sensory sensitivity disturbances.* Individuals with migraine often report a combination of altered multimodal sensorial perceptions during attacks—including changes in visual, auditory, olfactory, and tactile sensations, all part of the multidimensional neural activity related to pain [151]. Notably, multimodal sensitivity dysfunctions are not limited to the migraine attack itself; it can also manifest during the interictal period, indicating persistent alterations in multisensory pain-related information processing.

Imbalance in the autonomic nervous system is a neural process that can be indirectly evaluated through Heart Rate Variability (HRV) analysis. In individuals with migraine, HRV can be used to detect dysregulation of autonomic function. Migraine attacks are often associated with activation of the sympathetic nervous system leading to increased heart rate and blood pressure or parasympathetic dysfunction characterized by reduced vagal tone and impaired baroreflex sensitivity [152, 153]. One study showed that HRV parameters are associated with the effects of preventive medication [154]. However, further research is required to fully understand the complex interplay between HRV, autonomic regulation, and migraine.

Altered peripheral processes in migraine involve neuromuscular abnormalities in the neck and facial muscles. Altered electromyographic readings have been reported to be associated with migraine, reflecting the complex neuromuscular interactions involved in this condition. The abnormalities observed in migraine include various manifestations. *(a) Increased muscle tension* individuals with migraine often exhibit increased muscle stiffness in the neck and facial muscles [155]. *(b) Muscle hyperactivity*: elevated activity in muscles such as the trapezius, sternocleidomastoid, and temporalis indicates hyperactivity or spasms, contributing to or resulting from migraine pain [156]. *(c) Abnormal muscle response:* individuals with migraine may exhibit abnormal muscle responses to stress or stimuli that reflect altered neuromuscular control [157, 158]. Altered electromyographic activity in the neck and facial muscles is a major finding in migraine research. Further investigations are needed to verify whether muscle activity involvement it is the consequence of migraine recurrence or part of its pathophysiology.

Regarding the central processes, CSD is a fundamental event in the pathophysiology of migraine with aura. CSD involves a wave of neuronal depolarization followed by prolonged neuronal suppression that propagates across the cerebral cortex at a rate of 2–5 mm/min [29]. This phenomenon transiently disrupts normal neuronal function and is accompanied by changes in cerebral blood flow and metabolic activity. It is believed to underlie the aura phase of migraine and may, at least in the animal model, be induced or sustained by the activation of trigeminal and parasympathetic afferents through brainstem connections [159]. CSD likely contributes to the pathophysiology of migraine by promoting neuronal dysexcitability, disrupting ion homeostasis, and inducing neurovascular changes that predispose individuals to migraine attacks [160]. To what extent CSD is an electro-cortical phenomenon specific to migraine or rather is a general trigger for various diseases such as epilepsy, stroke, transient ischemic attack, remains to be determined.

Habituation deficit and central sensitization, are pivotal features of migraine cerebral responsivity. They are two processes that blend variably according to the different phases of the migraine cycle and its frequency. The increased central sensitization to sensory and nociceptive inputs leads to aberrant brain network function, even during resting-state conditions. Accumulating neurophysiological evidence supports this mechanism. *(a) Habituation deficit.* Habituation is a fundamental neurophysiological process where the response to a repeated stimulus decreases over time. In the context of migraine, a habituation deficit refers to a reduced ability to develop decreased responsiveness to repeated stimuli in the visual, somatosensory, or auditory cortex [161, 162]. Assessing habituation patterns can aid in diagnosing migraine. The presence of a habituation deficit may serve as a neurophysiological marker for distinguishing individuals with migraine between attacks from those with other headache disorders [163]. *(b) Altered synaptic plasticity and metaplasticity.* They refer to the activity-dependent modification of the strength or efficacy of communication between synapses, and their abnormalities are key characteristics of the migraine brain. Patients with migraine exhibit paradoxical and short-lived synaptic learning processes and altered cortico-subcortical metaplasticity in response to visual and sensorimotor learning techniques. [164, 165]. This state of altered basic neuronal mechanisms of learning and memory, probably genetically determined, can be observed across neural circuits and brain regions and plays a pivotal role in the pathophysiology of migraine. *(c) Aberrant network function.* Dysfunctional operation of hemodynamic and electro-cortical resting-state networks has been implicated in various neurological conditions, including migraine. Pain-related and salience networks may contribute to the sensory abnormalities in migraine [166–168]. The inability to cognitively and emotionally switch between the internalizing default-mode network and the externalizing executive and visual attentional networks by an aberrant salience network characterizes individuals with migraine [169–171].

Dysfunction of the sensorial thalamus and brainstem, which are involved in sensory/pain processing and modulation, may contribute to the initiation and propagation of migraine attacks. Key findings regarding such dysfunctions include the following. *(a) Trigeminal spinal and caudal nuclei dysfunction.* The trigeminovascular system, which is the major pain-signalling pathway of the visceral organ brain, originates in the brainstem, innervates the meninges and blood vessels of the brain and plays a crucial role in the migraine attack ignition. Dysfunction of the trigeminal sensory pathways—for example, abnormal processing of the brainstem nociceptive signals, as verified using blink and noxious-flexion reflexes, and pain-related cortical evoked potentials—may contribute to the pathophysiology of migraine [117, 118]. *(b) Altered processing or modulation of somatosensory pathways.* The brainstem and the thalamus contain nuclei involved in the modulation of spinal and cortical sensory processes, neuro-vascular coupling, and filtering of irrelevant peripheral inputs. Dysfunction of these sensory-modulatory circuits can lead to alterations in information processing and contribute to the development of migraine accompanied symptomology, such as photo-phono phobia and allodynia, and of the attack's recurrence [172]. A recent study confirmed the dynamics of brainstem activation throughout the migraine cycle [173].

Concluding remarks

In summary, understanding the neurophysiology of migraine is crucial for developing effective diagnostic tools and treatment approaches targeting the mechanisms underlying this condition. Despite considerable advances having been made, much remains to be discovered regarding migraine; ongoing research continues to shed light on this complex condition.

Cardiovascular, cerebrovascular and psychiatric comorbidities of migraine

Cardiovascular diseases, psychiatric disorders, and migraine are among the ten neurological conditions with the highest age-standardized disability-adjusted life years over the past decades [1, 174]. In migraineurs, prevalence of cardiovascular diseases and psychiatric disorders revealed to be way greater than general population [4, 175]. A bidirectional association between migraine and these comorbidities has been hypothesized and documented, suggesting that they likely share a common biology despite some unclear details [176]. To obtain a complete clinical assessment of migraine subjects, comorbidities should be considered, and their assessment could orient treatment strategies and contribute to evaluate impact on subjects' life [177].

Cerebrovascular and cardiovascular disorders comorbidity with migraine

In general, the risk factors for cerebrovascular events are age- and sex-dependent with traditional risk factors dominating in the age group of 44 years and older [178]. Hypertension is the most important risk factor in the age group above 44 years and migraine the most non-traditional risk factor in the age group below 35 years. The exact frequency of migrainous infarcts is unclear, especially since the differentiation between a migraine with aura associated infarct and a secondary aura triggered

by a cerebral ischemia might be impossible in individual cases [179].

Population-based cross-sectional studies showed an increased risk of deep white matter lesions in patients with migraine depending on the frequency of migraine attacks, and also more often lesions in the cerebellar region and posterior circulation. Especially migraine with aura with more than 1 attack per month showed an increased risk [180–182]. There are some reports which showed a link between white matter lesions and the occurrence of right-left shunts [183]. Especially, permanent large right-left shunts are connected to migraine with aura [184]. Otherwise, it seems that the frequency of migraine does not have an effect on the frequency of white matter lesions [185].

Risk of haemorrhagic stroke may be increased in migraine [186], but not all studies showed such a correlation and no association with special forms of haemorrhagic strokes is known. Which factor increases the risk of white matter lesions is not completely elucidated; in a small number, there may be genetic reasons. In CADASIL, a hereditary small vessel disease, up to 54.5% of the patients have a history of migraine and 84% of them have a history of migraine with aura [187]. Otherwise right-left shunts could be one risk factor for ischemic strokes. The main risk factor for cerebral strokes is arterial hypertension and indeed there is evidence that women with migraine have a 21% increased risk of developing arterial hypertension during a follow-up period of more than 12 years (defined as values above 140 to 90 mmHg [188]).

As mentioned above, increased blood pressure is one main risk factor for stroke and the Genetic Epidemiology of Migraine study presented some evidence that migraine patients have a 27% increased risk of arterial hypertension [189]. Results from a summary of the literature conducted in 2020 regarding Relative Risk (95% CI) of ischemic stroke in migraine versus not migraine subjects are reported in Table 1 [190]: this study was the first study which showed an increased risk of death from myocardial infarction in migraine patients, especially for migraine with aura. A recent Danish population-based matched cohort study compared more than 50 000 patients with migraine with 510 000 matched patients without migraine and found that migraine patients had an increased risk for myocardial infarcts, venous thromboembolism, and arterial fibrillation but not for peripheral artery disease or heart failure [186]. Otherwise, there is no sign of increased coronary artery calcification as a surrogate marker of coronary arteriosclerosis [191].

A review including 2 meta-analyses, 11 controlled trials, and further studies saw evidence that regular intake of non-steroidal anti-inflammatory drugs over a longer period even with a frequency of only 5–14 days a month is correlated with an increased statistical risk of hypertension (RR = 1.21, 95% CI = 1.12–1.31) [192]. This was also true for paracetamol users. Triptans are migraine-specific drugs with a slight vasoconstriction due to the binding to the 5-HT 1B receptor and therefore contraindicated in patients with ischemic heart disease or ischemic stroke. A study from Denmark, again using the nationwide Danish patient register, found 429 612 patients; of the patients, who initiated the triptan therapy for the first time, 11 had a myocardial infarction, and 18 an ischemic stroke. All the patients had a high-risk cardiovascular profile, and the mean age was 60 years old [193].

Concerning prophylactic migraine medication, only a low number of studies are published. There is an animal study, which showed in a stroke model for mice a significant increased infarct volume in mice who were pretreated with olcegepant or rimegepant. Both substances are small CGRP antagonists and thereby block the compensatory vessel relaxation mediated due to CGRP [194]. In a analyses of data from the veterans' health administration there was no evidence that CGRP-pathway blocker induces arterial hypertension in patients with normal blood pressure. Otherwise, there was some evidence that these CGRP-pathway blockers can increase the blood pressure in patients with a history of arterial hypertension [195].

Psychiatric disorders comorbidity with migraine

Psychiatric disorders include a wide spectrum of clinical and behavioural manifestations [196] and knowledge on their epidemiology and aetiology importantly evolved in the last decades, leading to clarify that genetics and epigenetics play a key role in their onset and evolution across lifespan [197]. These disorders are also associated with other several factors, such as events occurred

Table 1 Migraine and risk of ischemic stroke (results are reported as RR and 95% CI), adapted from Øie et al., 2020 [190]

Study	Etminan et al. 2005	Schürks et al. 2009	Spector et al. 2010	Hu et al. 2017	Mahmoud et al. 2018
Migraine without aura	1.83 (1.06–3.15)	1.23 (0.90–1.69)	1.24(0.86–1.79)	1.02(0.68–1.51)	1.11(0.94–1.31)
Migraine with aura	2.27(1.61–3.19)	2.16(1.53–3.03)	2.25(1.53–3.33)	2.14(1.33–3.43)	1.56(1.30–1.87)

in early childhood (e.g., traumas and abuse), personality traits (e.g., neuroticism and introversion), environmental stressors and lifestyle, social conditions, as well as other disorders or conditions, including sleep disorders, substances addiction, and cognitive patterns [196, 198]. Most of these factors also have a key role in influencing migraine pattern [199, 200], which, in turn, also recognize a genetic predisposition [176]. The biological predisposition of migraine subjects to show psychiatric disorders is further evident from the analysis of personality traits and distinctive cognitive styles of such individuals [176]. Distinctive personality traits of migraine sufferers include apprehensiveness, avoidance, persistence, introversion, and neuroticism [201]. Migraineurs also differ from general population regarding emotional distress, locus of control, coping strategies, illness perceptions, and pain catastrophizing [197].

Anxiety disorders, bipolar spectrum disorders, depression, abuse (physical or emotional), and post-traumatic stress disorder showed high association with migraine, while also other psychiatric conditions seem to be associated with migraine, such as suicidal behaviour, psychosis, and panic disorder, other than sleep disorders [4, 199, 200, 202]. A stronger relationship was documented in subjects with CM, medication overuse, and migraine aura [199, 201, 203]. Several theories have been proposed to explain the relationship between psychiatric disorder and migraine. Theories are also referred to the predictive power of psychiatric disorders towards negative migraine evolution and complications, such as CM and medication overuse, although it was not demonstrated that improving the psychiatric disorder also improves migraine [199, 200]. In general, the association between psychiatric disorders and migraine is probably related to shared genetic basis, and to the influence of other biological and environmental factors able to impact both conditions. These factors encompass serotoninergic and dopaminergic pathways, involvement of the autonomic nervous system and the hypothalamus-pituitary axis, inflammation, hormones, central sensitivity/sensitisation of the sensory and emotional neural networks, and chronic stress, which, in turn, determines allostatic dysfunction and central sensitivity [176, 199, 200]. Theories have been also assessed through neuroimaging and considering subjects' response to treatments indicated for both disorders. Neuroimaging showed that areas with a mood- and pain-modulating actions have a similar functional, structural, and connectivity alterations in subjects with migraine and psychiatric disorders often co-existent with migraine. These regions include anterior cingulate cortex, anterior insula, prefrontal cortex, hippocampus, amygdala, and periaqueductal gray [199, 200, 204].

Regarding psychiatric disorders more often associated with migraine and investigated in the literature, a summary of these theories, involved circuits and mechanisms, neuroimaging evidence, and shared treatment response is reported in Table 2 [199, 200, 204–207]. In terms of preventive therapy, the presence of psychiatric comorbidity needs careful consideration. Generally, a unified treatment approach for both conditions is advisable, if possible, and if the psychiatric disorder is mild [199, 200]. These considerations need to be performed by considering also disorder-specific treatment guidelines.

Concluding remarks

In summary, cardiovascular, cerebrovascular and psychiatric conditions constitute the most relevant comorbidities of migraine with relevance to the frequency of their co-occurrence. Shared mechanisms of action are hypothesized and common therapeutic pathways exist, which enable providing a valid treatment which might impact on the both migraine and of these comorbidities, thus helping to reduce the impact of these burdensome conditions.

The migraine cycle: prodromes, ictal phase, and postdromes

Migraine prodromal phase is the symptomatic non-painful period that precede up to 48 h the headache in migraine attack, according to ICHD-3 (International Classification of Headache Disorders, 3rd version) [33], and they are reported in a range from 30 to 80% of patients [208]. Most frequent prodromal symptoms reported in literature are mood changes, photophobia, fatigue, neck pain/stiffness, yawning, dizziness, difficulties in concentration, craving and nausea [111]. Some patients can even predict migraine attacks when experiencing prodromal symptoms, with a pretty accurate rate [209, 210]. Migraine triggers are elements capable of initiating a migraine attack, i.e. stress, odors, foods and alcohol, sleep deprivation, or fatigue are among the reported triggers in studies [111, 211]. Among them we can recognize *endogenous triggers* as stress, periods, sleep deprivation and *exogenous triggers* as foods or alcohol and visual stimulation [212].

Some doubts about the strict distinction between prodromes and trigger. Indeed, commonly reported trigger factors are not independent precipitators of migraine pain, but they could be misinterpreted as enhanced attention to some stimulation facilitated by premonitory symptoms [213]; moreover, triggers that overlap with corresponding special premonitory symptoms may be just a form of premonitory symptoms [214].

Ictal phase of migraine is composed by pain, associated symptoms and aura phenomenon. The typical pain of the ictal phase is widely accepted as result of TVS activation, that leads nociceptive information from the meninges

Table 2 Summary of hypothesized relationship between migraine and its mostly associated psychiatric disorders, involved circuits, neuroimaging evidence, and shared drug response derived by the literature

Psychiatric disorder	Hypothesized relationship	Shared involved circuits and mechanisms	Neuroimaging evidence	Shared treatment response
Anxiety disorders	- Bidirectional and/or shared genetic predisposition - Facilitates migraine chronification	- Serotonergic dysfunction - Dysregulation of the HPA axis - Hormonal influences - Altered autonomic regulation - Central sensitization - Action on trigeminovascular thalamic neurons - Somatization - Interoceptive conditioning - Fear of pain - Anxiety sensitivity - Avoidance behaviours	- Changes in hippocampal volume	- Tricyclic antidepressants - SSRIs
Bipolar spectrum disorders	- Common pathophysiology and/or shared genetic predisposition - Comorbidity with migraine seems to be a subtype of bipolar disorder	- Serotonergic dysfunction - Dopaminergic dysfunction - Glutamatergic dysfunction - Calcium and sodium channels alterations - Imbalance between pro-inflammatory and anti-inflammatory cytokines	–	- Anti-seizure (valproate)
Depression	- Bidirectional and/or shared genetic predisposition - Facilitates migraine chronification	- Serotonergic dysfunction - Dopaminergic dysfunction - Dysregulation of the HPA axis - Hormonal influences - Sensitization of the sensory and emotional neural networks - Probably GABA	- Amygdala, anterior cingulate cortex, and periaqueductal gray present similar connectivity	- Tricyclic antidepressants, SNRIs, onabotulinumtoxinA (chronic migraine) monoclonal CGRP-antibodies
Abuse (physical or emotional)	- Risk factor for migraine chronification, more disabling migraines, allodynia and earlier onset of migraine	- Cortisol dysfunction - Grater stress reactivity mediated by HPA axis modifications	–	–
Post-traumatic stress disorder	- Mutual causality and reinforcement - PTSD mediates the association between trauma and migraine	- Stress-induced abnormal activation of the trigeminal nucleus caudalis - Stress-mediated alterations in neurotransmitter balance, neural circuits, autonomic and endocrine responses - Stress-mediated activation of the trigeminovascular system through HPA axis - Impairment of normal limbic response - Prolonged inflammation	- Reduction in hippocampal volume	- Cognitive-behavioral therapy (CBT)

HPA axis Hypothalamic–Pituitary–Adrenal axis, *SSRIs* Selective Serotonin Reuptake Inhibitors, *GABA* γ-Aminobutyric Acid, *SNRIs* Serotonin–Norepinephrine Reuptake Inhibitors, *CGRP* Calcitonin Gene-Related Peptide, *PTSD* Post-Traumatic Stress Disorder, *CBT* Cognitive-Behavioral Therapy

to deep nucleus and to the cortex; the activation of the TVS take place peripherally where nociceptive terminals from the dura mater release vasoactive neuropeptides (i.e. calcitonin gene-related peptide CGRP, PACAP-38) [88]. The features of migraine pain are a clinical hallmark, typically described as moderate or severe, unilateral, and throbbing or pulsatile, aggravated by physical activity [33]. Aside from pain, patients usually report some other symptoms, such as nausea, vomiting, photophobia or phonophobia, reported as the most bothersome symptoms [33, 88, 215–218]. Up to 30% of patients with migraine presents aura phenomenon, defined as a fully reversible recurrent episodes of visual, sensory or other CNS symptoms that arise gradually, last less than 60 min,

and are usually followed by typical migraine attack. Aura is thought to be generated by CSD a neurophysiological depression phenomenon discovered by Leao in 1944 followed by a prolonged phase of oligemia [33, 88, 95, 216, 219].

Postdrome phase is characterized from many symptoms as fatigue, neck stiffness, difficult in concentrating, increased appetite, and dull head pain, and they are reported by almost the 80% of the patients; this phase is poorly understood, still can also contributes in a significant way to the global disability of the migraine attack, indeed recently they are focused as new therapeutic outcome for acute treatment [93, 220–224].

Concluding remarks

In summary, the whole course of migraine is composed of distinct phases, all of which are associated to specific neurobiological changes, which are well defined and move beyond the features of migraine headache attack. Understanding these phases is of importance for clinicians and patients in order to timely treat migraine.

Pharmacological targets for acute treatment and their side effects: serotonin and CGRP

Serotonin

Considering the involvement of serotonergic neurotransmission in the pathophysiology of migraine, serotonin receptors emerged as pivotal targets for acute migraine treatment [225]. In total, there are seven distinct classes of 5-HT receptors [225]. Current acute migraine therapies primarily focus on modulating the 5-HT1 receptor family, which encompasses receptors distributed across both the vascular and neuronal components of the TVS [226]. Activation of 5-HT1 receptors induces a reduction in cAMP levels, with 5-HT1B receptors eliciting vasoconstriction and 5-HT1D/1F inhibiting neurotransmitter and neuropeptide release [84, 226]. Two main classes of acute migraine treatments that act upon 5-HT receptors are available: triptans, with highest affinity to the 5-HT1B/1D receptor, and ditans, with highest affinity to the 5-HT1F receptor (Table 3) [226].

The first triptan that was developed was sumatriptan [227], which entered the market during the early 1990s, followed by six subsequent triptans with different formulations and pharmacokinetic profiles. The agonistic triptan activity to the 5-HT1B receptor on blood vessels induces vasoconstriction, particularly accentuated in the cranial vasculature [228]. Initially, this was perceived as the primary mechanism for alleviating pain, aligning with the vascular theory of migraine pathophysiology [229, 230]. However, the simultaneous activation of the 5 HT1D receptor on trigeminal nerve fibers also inhibits the release of CGRP and protein extravasation [226]. Furthermore, agonism at the 5-HT1B, 5 HT1D, and 5-HT1F receptors within central nervous system structures can modulate nociception [226]. While sumatriptan, due to its low lipophilicity, predominantly acts on vascular structures and the peripheral nervous system without crossing the Blood–Brain Barrier (BBB), some second-generation triptans, being more lipophilic, may exert effects on the central nervous system as well [226]. Meta-analyses evaluating the efficacy of triptans in acute migraine treatment revealed rates of pain freedom at 2 h ranging from 18–50% [231–233]. Adverse events are typically mild, leading to discontinuation of therapy in less than 10% of patients [234]. These adverse events often encompass the so-called "triptan symptoms" or "triptan sensations", such as tingling or sensation of warmth. While the incidence of cardiovascular events following triptan administration is exceedingly low [235], the use of triptans is indeed associated with a higher risk of ischemic stroke and myocardial infarction with odds ratios of 3.2 and 3.3, respectively [193].

Therefore, due to their vasoconstrictive effects, triptans pose contraindications in individuals with cardiovascular risk factors [236]. Consequently, research has pivoted towards exploring alternative medications targeting different receptors, notably directing attention towards the 5-HT1F receptor [237]. The presence of 5-HT1F receptors within the brain and on trigeminal neurons, while absent in vascular smooth muscle cells, indicates that ditans exert their effects only through neuronal

Table 3 Migraine acute medication targeting the 5-HT receptors or the CGRP receptor

Name	Class	Main targets	EMA approved dosages and formulations
Sumatriptan	Triptan	5-HT-1B/D/F	50 mg / 100 mg p.o 10 mg / 20 mg intranasal 3 mg / 6 mg s.c
Zolmitriptan	Triptan	5-HT-1B/D/F	2.5 mg / 5 mg p.o 2.5 mg / 5 mg ODT 5 mg intranasal
Naratriptan	Triptan	5-HT-1B/D/F	2.5 mg p.o
Rizatriptan	Triptan	5-HT-1B/D	5 mg /10 mg p.o 5 mg / 10 mg ODT
Almotriptan	Triptan	5-HT-1B/D/F	12.5 mg p.o
Eletriptan	Triptan	5-HT-1B/D/F	20 mg / 40 mg p.o
Frovatriptan	Triptan	5-HT-1B/D/F	2.5 mg p.o
Lasmiditan	Ditan	5-HAT-1F	50 mg / 100 mg p.o
Rimegepant	CGRP-R antagonist	CGRP-R	75 mg ODT
Ubrogepant	CGRP-R antagonist	CGRP-R	50 mg /100 mg p.o
Zavegepant	CGRP-R antagonist	CGRP-R	10 mg intranasal

5-HT 5-hydroxytryptamine (Serotonin), *CGRP* Calcitonin Gene-Related Peptide, *p.o.* per os, *s.c.* subcutaneous, *ODT* orally disintegrating tablet

mechanisms such as inhibition of trigeminal nociception and neuropeptide release rather than through vascular mechanisms [84, 228]. Among clinically developed ditans, lasmiditan has gained approval in 50 mg and 100 mg tablet formulations for the acute management of migraine attacks [238, 239]. In Phase-III randomized Clinical Trials (RCTs), administration of lasmiditan 100 mg resulted in pain freedom within 2 h in approximately one-third of participants, significantly surpassing placebo rates [237]. The most reported adverse events linked to lasmiditan affect the central nervous system, with dizziness, somnolence, and fatigue among the most prevalent. Cardiovascular events occurred at similar rates with lasmiditan and placebo across studies, even in participants with cardiovascular risk factors, confirming the absence of clinically significant vasoconstrictive properties of this drug.

CGRP

Due to the key role of CGRP in trigeminal nociceptive transmission and migraine pathophysiology [240–242], drugs antagonizing the CGRPergic system were developed initially for the acute treatment of migraine [243]. Gepants, selective small-molecule CGRP receptor antagonists, were synthetized and proved to be effective in RCTs [244]. However, the first generation of gepants (e.g., telcagepant and olcegepant) did not reach the market due to hepatotoxic and pharmacokinetic limitations [243]. In the last years, a new generation of gepants has been developed with no demonstrable changes in serum transaminases [245]; and all demonstrated efficacy in RCTs [246], leading to their approval for clinical use. As shown in Table 3, three gepants are currently available for the acute treatment of migraine, two administered orally (rimegepant and ubrogepant) and one intranasally (zavegepant) [247].

The new gepants bind with high affinity to the canonical CGRP receptor [248], however, cross-reactivity has been reported with AMY1 receptors [248], one of the three amylin receptors expressed in trigeminal sensory neurons [249]. Nevertheless, the clinical implications of antagonizing both CGRP and AMY1 receptors remains unexplored. Based on the small molecular weight of the gepants, these drugs could cross the BBB [243], antagonizing both peripheral and central CGRP receptors. However, different studies indicate that gepants have a very limited ability to cross the BBB [245], and do not require to block central CGRP receptors to exert their antimigraine action (reviewed in [247]). Therefore, it remains to be determined whether these drugs can enter central brain areas lacking a BBB (circumventricular organs) to interact with CGRP receptors, and the clinical relevance, if any [247].

Meta-analyses of gepants in acute migraine treatment revealed rates of pain freedom at 2 h ranging from 23–58% [250, 251]. Gepants have shown a more favourable safety and tolerability profile than triptans, and the lack of vascular adverse events make them a promising alternative to patients with cardio- and/or cerebro-vascular disease or risk factors [252]. Adverse events are typically mild and rarely lead to discontinuation, with nausea, dizziness, somnolence and dry mouth most commonly reported [251]. Dysgeusia and nasal discomfort were also reported after zavegepant [252]. Importantly, there was no evidence that these drugs led to medication over-use headache [252].

Concluding remarks

In summary, advancements in understanding migraine pathophysiology and the discovery of new targets have significantly enhanced acute treatment options. Serotonergic drugs, such as triptans and ditans, target specific 5-HT receptors involved in migraine pathophysiology to provide effective pain relief. Triptans act primarily on 5-HT1B and 5-HT1D receptors, while ditans specifically target the 5-HT1F receptor and do not engage in vascular mechanisms. Additionally, the advent of gepants targeting the CGRP receptor marks a new era in acute migraine management. These innovations underscore the potential for medications that precisely address the underlying mechanisms of migraine, promising improved outcomes for patients.

Pharmacological targets for prophylaxis and their side effects: CGRP and PACAP

CGRP

CGRP is a 37 amino acid vasodilatory peptide that is widely expressed in the central and peripheral nervous system, especially in the trigeminal and dorsal root ganglia [253]. There are two CGRP receptors, calcitonin receptor-like receptor / receptor activity-modifying protein 1 complex (CLR/RAMP1 or CGRP receptor) and CGRP-responsive calcitonin receptor/RAMP1 complex (CTR/RAMP1 or AMY1 receptor). CGRP is a key player in the trigeminal system and plays a pivotal role in migraine pathophysiology. Human trigeminal ganglion contains the highest concentration of CGRP expressing neurons [254]. Following the release of CGRP from the trigeminovascular system, CGRP binds to the CGRP receptor and is involved in vasodilation, inflammation and nociceptive transmission [255]. Increased CGRP levels were reported in serum and saliva during induced or spontaneous migraine attacks [241, 255, 256]. Intravenous injection of CGRP led to experimentally induced migraine attacks in migraine with and without aura patients [50, 257].

Monoclonal Antibodies (mAbs) targeting CGRP or CGRP receptor are effective for migraine prophylaxis in both EM and CM patients [258]. Erenumab is the first anti-CGRP mAb that targets the CGRP receptor while galcanezumab, fremanezumab and eptinezumab target the CGRP ligand. The antibodies have a half-life of weeks and because of their peptide nature they cannot be used orally. Erenumab, galcanezumab and fremanezumab are administered subcutaneously once per month while eptinezumab is administered via intravenous route once every trimester. Gepants are small molecule CGRP receptor antagonists that have been developed for acute and preventive treatment of migraine. Rimegepant, atogepant and ubrogepant are second generation gepants whereas zavegepant is the only third generation gepants. Rimegepant was documented to have efficacy in both acute [259] and preventive treatment in EM patients [260] while atogepant is used for migraine prophylaxis. Atogepant is effective in the preventive treatment of both EM [261] and CM patients [262]. Zavegepant intranasal spray was effective in acute migraine in a phase III, randomized, double blind, placebo controlled trial [263].

In a systematic review and network meta-analysis of phase 3 RCTs that evaluated the efficacy of CGRP mAbs and gepants, fremanezumab, galcanezumab, erenumab and eptinezumab showed significant reductions in Monthly Migraine Days (MMD) compared to placebo [264]. Only the reduction for eptinezumab 300 mg was not statistically significant [14]. All CGRP mAbs showed significantly ≥ 50% responder rate compared to placebo [264]. In the same network meta-analysis, atogepant and rimegepant reduced MMD compared to placebo with atogepant 60 and 120 mg having the highest effect and rimegepant 75 mg every other day showing the lowest effect [264]. Atogepant at all doses showed ≥ 50% responder rate compared to placebo, however, due to the small number of patients, the results were not statistically significant [264]. Recently, a double-blind, double-dummy RCT in EM patients assessed whether galcanezumab 120 mg/day was superior to rimegepant 75 mg (q.o.d) in migraine prevention and galcanezumab was not superior to rimegepant regarding ≥ 50% reduction in MMD [265]. A meta-analysis found that good response to triptans, unilateral pain with autonomic symptoms and presence of vomiting during migraine were associated with good response to CGRP mAbs [266]. Conversely, absence of accompanying symptoms, obesity, interictal allodynia, psychiatric comorbidities, daily headaches and high number of unsuccessful previous migraine preventive treatments were predictors of a poor response to CGRP mAbs [266]. In clinical practice, up to one third of patients are defined as non-responders to CGRP mAbs [267]. Half of the patients not responding to CGRP mAbs within the first 3 months of treatment benefited from a longer treatment and were defined as late-responders [268]. Therefore, evaluation of treatment outcomes may be extended to 6 months [269].

PACAP

PACAP, a peptide discovered in the hypothalamus of sheep, belongs to the glucagon/secretin superfamily alongside peptides like vasoactive intestinal peptide (VIP), secretin, and others [270, 271]. It exists in two main forms: PACAP-38 and its truncated version, PACAP-27, with PACAP-38 being predominant [272]. Several neurological structures related to migraine express PACAP-38, including trigeminal ganglion, sphenopalatine ganglion, and trigeminal nucleus caudalis [273–276]. PACAP-38 activates three receptors – PAC_1, $VPAC_1$, and $VPAC_2$ – leading to increased intracellular cAMP concentration [277]. PACAP receptors are found in various locations, including intracranial arteries, dura mater, trigeminal ganglion, and immune cells [278–280]. Both PACAP-27 and PACAP-38 induce migraine when administered intravenously, with responses to sumatriptan, a specific migraine treatment [63, 64, 281]. Plasma levels of PACAP-38 are elevated during migraine attacks and reduced between attacks [282, 283]. Mechanisms of PACAP-induced migraine include modulation of nociceptive transmission and mast cell degranulation, although infusion of PACAP38 does not increase blood markers for mast cell degranulation [284, 285]. Initially, it was thought that PAC_1 receptor activation triggers migraine, leading to the development of AMG 301, a monoclonal antibody targeting the PAC_1 receptor. However, a phase II trial showed no therapeutic benefit [286]. Two anti-PACAP monoclonal antibodies, Lu AG09222 and LY3451838, are in development. Lu AG09222 showed promise in preventing PACAP38-induced physiological responses and headache in a proof-of-mechanism study conducted in healthy volunteers [287]. A phase 2a trial of Lu AG09222 in migraine prevention demonstrated significant reduction in monthly migraine days compared to placebo (NCT05133323). In a phase II trial, LY3451838 was not more effective than placebo in preventing migraine, but the study only enrolled 19 individuals per treatment arm (NCT04498910).

Concluding remarks

In summary, the development of targeted treatments for migraine prophylaxis is advancing by focusing on specific mechanisms underlying the disorder. The identification of key pharmacological targets, such as CGRP and PACAP, has led to the creation of new medications that directly address these mechanisms. Monoclonal antibodies and gepants have demonstrated efficacy in reducing

migraine frequency and severity by specifically targeting CGRP or its receptor and provide better treatment options for migraine compared to previous prophylactic treatments such as antidepressants and antiepileptics. Similarly, ongoing research into PACAP-related therapies aims to provide more targeted options for patients. These advancements highlight the potential for more effective and personalized migraine management, offering hope for better outcomes for individuals suffering from this debilitating condition.

Non-pharmacological targets: neuromodulation

The term "neuromodulation" is referred to any intervention able to safely interfere with the physiological nerve transmission within central or peripheral nervous system by inhibiting or potentiating it. Since the discovery of neurostimulation as a useful tool for pain relief, devices and approaches gradually evolved from invasive to non-invasive in order to guarantee effectiveness with lower risk of complications [288]. Non-invasive brain stimulation techniques can induce plastic changes that outlast the period of the stimulation not only in the cortex but also in brainstem and diencephalic structures. Although approved guidelines are often lacking due to heterogeneous stimulation targets and settings, different protocols have been used with encouraging results [289].

Non-invasive neuromodulation treatments for migraine are all carried out with electrical or magnetic stimulation, and applied to stop acute attacks or to prevent migraine recurrence [290]. The most known techniques include Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), Supraorbital Nerve Stimulation (SNS), Occipital Nerve Stimulation (ONS) and transcranial Direct Current Stimulation (tDCS) or transcranial Alternate Current Stimulation (tACS).

In 2008 FDA approved the use of TMS for the treatment of depression and obsessive–compulsive disorders. This technique involves the generation of magnetic field delivered to the superficial layers of cerebral cortex through a coil placed against the scalp, with single pulse TMS or repetitive TMS stimulation protocols [291]. In migraineurs brain hyper-excitability or deficient intracortical inhibitory tone have often been reported and TMS therapeutic effects have been related to the increase of brain threshold and the inhibition of thalamic nociceptive neurons [292, 293]. Repetitive TMS can better influence brain plasticity beyond the stimulation period and is therefore used in prophylaxis whereas single pulse TMS has been tested in the acute phase of migraine [294]. Although limited due to methodological flaws and heterogeneity of studies, a recent overview confirmed that TMS may improve migraine severity and frequency [295]. Clinical trials also confirmed the feasibility and the efficacy of single pulse TMS for migraine associated with aura, supporting the FDA approval for its use either in acute and preventive setting [296].

Electric current based devices may be placed over the neck or several parts of the head, resulting in non-invasive stimulation of different available targets. In VNS, the Gammacore device is placed against both sides of the neck in order to electrically stimulate the vagus nerve, with the rationale of the treatment lying in the reduction of trigeminal nucleus caudalis glutamate concentration, decreased inflammation, oxidative stress and sympathetic activity and potentiation of opioids activity. Common protocols are based on stimulation between 30 to 60 min after a migraine attack [297–299].

The PRESTO study proposed VNS as a treatment for acute migraine, showing significant effectiveness if compared to the sham condition. The efficacy of the Gammacore was also demonstrated by an open-label study in patients with menstrual migraine whereas a meta-analysis published in 2023 reported the effectiveness of VNS in EM and encouraging results in the management of CM (in terms of monthly reduced headache days, pain-free rates, ≥ 50% responder rate, headache intensity and monthly acute medication reduction days) [300–302]. The VNS approach with Gammacore has been approved in US and all European countries for acute and preventive treatment of migraine in adults and adolescents.

SNS has been approved by FDA in 2014 for the treatment of EM and is based upon the transcutaneous stimulation of supraorbital and supratrochlear branches of the ophthalmic nerve (V1) through a bipolar self-adhesive electrode targets. Different studies showed promising results of supraorbital stimulation in the treatment of EM and CM, likely through the inhibition of trigeminal sensory pain routes. Protocols commonly are based on a 20-min daily session for prevention or impromptu for acute migraine attack [303–305].

Contrasting cortical hyperexcitability has been postulated as a mechanism underlying the effectiveness of ONS, in which two electrodes are placed over bilateral occipital nerves and may deliver currents in a common frequency range from 2 to 100 Hz [306]. ONS may reduce the monthly headache days and improve pain relief in patients with EM and CM but not significantly different when compared with pharmacological treatments [307].

tDCS may affect several cortical areas due to double stimulation: one electrode may deliver anodal facilitating and the other one a cathodal inhibiting current (typically 1–2 mA of amplitude). Therefore, the device may simultaneously or selectively affect the activity of different cortex areas depending on whether one of the electrodes is placed on an active or inactive site, respectively

[308, 309]. Two recent systematic reviews and meta-analysis of randomized controlled trials reported that tDCS with primary motor and visual cortex activation (anodal) or visual cortex inhibition (cathodal) could reduce the number of migraine days per month [310, 311]. Other stimulation sites include the primary sensory cortex and dorsolateral prefrontal cortex. People undergoing stimulation occasionally reported burning sensations, dizziness, drowsiness, fatigue, headache, itching, nausea, pain, skin redness, and tingling with no statistical difference between active or sham.

In tACS there is no fixed anode/cathode position because current owns a sinusoidal waveform and the polarity alternates between the electrodes during stimulation. Therefore, this modulation seems to mimic in a more physiological way the endogenous brain oscillations if compared to tDCS [312]. In a double-blind, sham-controlled, randomized study, tACS over the visual cortex confirmed the potential to terminate migraine attacks although the high drop-out rate due to poor compliance seems to limit the treatment reliability [313].

Concluding remarks

In summary, contrasting evidence on the effectiveness of neuromodulation in migraine. Further randomized placebo-controlled studies with homogeneous protocols are needed in order to develop guidelines and clarify the long-term effectiveness of neuromodulation and its role in migraine management.

Non-pharmacological targets: cognitive behavioral therapy, relaxation and mindfulness

Pharmacological treatments for migraine are essential, however they often provide incomplete relief or cause side effects. Therefore, a multidisciplinary approach is crucial. Research indicates that behavioural treatments can reduce headache frequency and severity, enhance medication effectiveness, empower patient self-management, and decrease reliance on medication with potential side effects [314–316].

Cognitive Behavioural Therapy (CBT) has gained increasing attention as a complementary approach to headache management, offering potential benefits beyond traditional pharmacotherapy. Numerous clinical trials have demonstrated the efficacy of CBT in reducing the frequency, severity, and duration of primary headaches, with effects that are sustained over time, also compared with pharmacotherapy alone [317, 318]. This result was also confirmed in a sample of children and adolescents diagnosed with migraine, where the addition of CBT to medication led to a greater reduction in headache frequency and a reduction in migraine-related disability [319]. CBT typically involves several components, including education about headache triggers and mechanisms, relaxation techniques, cognitive restructuring, and behavioural interventions. Moreover, CBT has been associated with improvements in mood, quality of life, and medication adherence among headache sufferers. The mechanisms underlying the effectiveness of CBT in treating primary headaches are complex and multifactorial, encompassing cognitive interventions, behavioural techniques, and improvements in self-management skills. Cognitive interventions aim to identify and modify maladaptive beliefs and attitudes about pain. For example, many patients with chronic headaches develop anticipatory fear of pain, believing that their headaches are uncontrollable and devastating. CBT helps to restructure these thoughts, replacing them with more adaptive and realistic beliefs. This change reduces anticipatory anxiety and improves the patient's coping capacity. Specifically, three main features and benefits of CBT applied to migraine include:

- *Enhanced Self-Efficacy*: CBT helps individuals develop a stronger belief in their ability to manage and cope with challenges, including pain and associated symptoms. By fostering self-efficacy, CBT empowers patients to take proactive steps in their treatment and daily life, which can lead to greater overall well-being [320–322].
- *Promotion of Internal Locus of Control*: CBT encourages individuals to recognize and harness their internal resources and capabilities in dealing with health issues. This shift from external factors to internal strengths empowers patients to feel more in control of their health outcomes and fosters a sense of empowerment and resilience [323, 324].
- *Reduction of Pain Catastrophizing*: CBT addresses maladaptive thought patterns that exaggerate the perceived threat of pain. By restructuring these catastrophic thoughts, CBT helps individuals develop more balanced and realistic perspectives on pain, which can alleviate emotional distress and improve coping strategies [325, 326].

Behavioural techniques help to reduce muscle tension, a common trigger for headaches, and by reducing muscle tension, the frequency and intensity of headaches also decrease. Among these, biofeedback is a technique that teaches patients to control physiological functions through visual or auditory feedback. Patients can learn to reduce muscle tension or regulate breathing and heart rate, so preventing or mitigating headaches. Powers et al. demonstrated that behavioural treatments are effective for managing migraines in children and adolescents. Youths aged 10 to 17 with CM received amitriptyline and

either 10 sessions of headache education or a tailored CBT program with biofeedback. After 12 months, 86% of those receiving CBT and medication had a 50% or greater reduction in headache days, and 88% showed significant reductions in disability, scoring below 20 on the Paediatric Migraine Disability Assessment [319]. Therefore, CBT combines cognitive and behavioural strategies to manage primary headaches, improving pain management, reducing muscle tension, and enhancing self-efficacy. It can be delivered individually, in groups, in person, or via telehealth, tailored to individual needs [327]. Integrating CBT with other treatments can enhance its effectiveness, though barriers like therapist availability and costs need addressing [328], but it might find solutions through digital health platforms [329].

Additionally, relaxation and meditation techniques, including progressive muscle relaxation, autogenic training and mindfulness, are effective methods for managing stress and pain by reducing stress responses and muscle tension [330, 331]. Progressive Muscle Relaxation (PMR) involves alternating between tensing and relaxing different muscle groups to achieve "extreme relaxation." Patients focus on the contrasting sensations of tension and relaxation in each muscle group. Once the basic technique is mastered, patients can learn advanced skills such as recalling relaxation, using relaxation on command, and maintaining relaxation in muscles that are not actively used. Initially practiced in a calm environment, these skills can be applied in everyday situations. PMR has been successfully used to treat anxiety and phobias, and online applications now offer guided exercises specifically for migraine treatment. Studies have shown a reduction of up to 41% in migraine attacks per month and up to 43% in the number of migraine days per month following PMR training [330, 331]. Autogenic training (AT) is a relaxation technique that involves focusing on bodily perceptions (such as the weight or warmth of legs and arms, heartbeat, or breathing) and using self-suggestion. Typically performed while sitting or lying down, patients concentrate on specific body parts or vital functions and repeat phrases like “my right arm is heavy” or “my forehead is cool.” The goal is to induce a deep state of relaxation, triggering a “relaxation response” characterized by slower breathing, a reduced heart rate, changes in brain wave activity, increased body temperature, and reduced muscle tension. This response helps to decrease anxiety and stress [330]. Regular practice of autogenic training has been found effective in improving the quality of life for individuals with chronic pain, including those with migraines, by enhancing stress management and reducing headache frequency. Dobos et al. found positive correlations (Spearman’s rho: 0.541, $p=0.085$) between the fMRI deactivation in the migraine-associated dorsal pons and the number of migraine attacks per month after a 16-week AT course [332].

Mindfulness is a form of meditation that focuses on being present with an intense awareness of sensations, without judgment. Practicing mindfulness involves various techniques, such as breathing methods, guided imagery, and other practices to relax the body and mind and help reduce stress [333]. Over the past 20 years, mindfulness-based interventions have gained popularity for treating various pain conditions, including migraines. From the mindfulness construct, different therapies have been developed under the umbrella term of Mindfulness-Based Interventions [334]. One of the most widely employed and researched is the Mindfulness-Based Stress Reduction (MBSR) protocol. Developed in 1979, MBSR helps individuals change their response to stressful thoughts and events, reducing emotional reactivity and improving cognitive appraisal [335, 336]. The standard MBSR program involves an 8-week course with weekly group sessions, totalling 26 h [337]. Another popular mindfulness-based intervention is the Acceptance and Commitment Therapy (ACT) [338]. This therapy uses metaphors, paradoxes, and mindfulness skills, along with various experiential practices. The aim of ACT is to improve patients’ quality of life by achieving emotional acceptance of physical pain and self-acceptance. ACT focuses on encouraging individuals to observe their experiences with openness and develop psychological flexibility [339, 340]. Recent Italian studies on mindfulness-based treatments combined with pharmacological treatment show greater improvements in several outcomes compared to pharmacological treatment alone, such as headache frequency, medication intake, headache impact, loss of productive time, disease cost, and better outcomes in disability and quality of life at 12 months from baseline. These results were found in a large sample of patients with CM and medication overuse headache ($N=177$) [341]. In these patients, mindfulness promoted an increase in salience network connectivity and in cingulate cortical thickness, which are deemed to improve body-awareness of painful sensation and the cognitive processing of nociceptive information [342].

Concluding remarks

In summary, the effectiveness of PMR, autogenic training, and mindfulness has been demonstrated in many studies, and a recent one showed a superior efficacy of a combined treatment in which mindfulness was added to treatment as usual in patient with CM associated to Medication Overuse Headache (MOH). However, the majority of studies are uncontrolled ones and it is therefore necessary to increase our understanding of behavioural

treatments efficacy by applying rigorous and homogeneous methodological criteria, and by including studies on CM during developmental age [343].

Non-pharmacological targets: diet and nutraceuticals

Overuse of medication for pain relief can lead to medication-overuse headaches and other adverse health effects. Therefore, strategies to reduce overuse and promote appropriate medication use are crucial. In this line, non-pharmacological and alternative therapies can be a suitable replacement for some patients, especially in children and adolescents [344–349]. In addition, recognizing and managing comorbid diseases and risk factors associated with headache disorders including migraine seems highly beneficial. Therefore, implementing a multi-modal management model that combines pharmacological and non-pharmacological treatments are encouraged. Here we present that dietary considerations and nutraceuticals, comprising vitamins, minerals, and herbal remedies can be considered as alternative approaches for managing migraine in adults, paediatrics, and pregnancy. While dietary factors and nutraceuticals offer potential benefits for migraine management, including migraine prophylaxis, it is essential to recognize the variability in study outcomes and potential adverse effects. Patients considering dietary alteration and the use of nutraceuticals should consult with healthcare professionals to assess their suitability and ensure appropriate monitoring.

Diet

Diet plays a significant role in managing migraine, and understanding the potential triggers can help patients make informed dietary choices. Some key points have been extracted from recent reviews [344–346, 350–352] to consider for dietary lifestyle modification:

- *Preventing hunger and fasting:* Regular meals and avoiding long periods without eating can help stabilize blood sugar levels and prevent migraine attacks.
- *Sticking to frequent meals*: Eating smaller, more frequent meals throughout the day can help maintain steady energy levels and prevent hunger-related migraine triggers.
- *Avoiding specific food items*: Certain foods are common triggers for migraines, including alcohol, chocolate, caffeine-containing products (such as coffee, tea, cola), processed foods, seafood, fish, ice cream, foods containing nitrates (e.g., bacon, hot dog, ham, salami), foods containing tyramine (e.g., aged cheese, cheddar cheese, beans, smoked fish), citrus fruits, avocados, bananas, onions, and foods containing monosodium glutamate. However, it is important to note that triggers can vary from person to person, and keeping a food diary can help identify individual triggers. Patients can avoid or reintroduce potential trigger foods based on their own experiences [353].
- *Proper fluid intake and hydration*: Staying hydrated is important for overall health and may help prevent dehydration-related migraines.

Ketogenic Diet (KD) is a recently suggested treatment for migraine patients. KD is characterized by a severe depletion of carbohydrates' intake with a relative increase of fat assumption, leading metabolism to obtain energy from lipids through fatty acids oxidation and the formation of ketone bodies. In adults, KD can be effective, especially in patients requiring a hypocaloric diet [354, 355]. Although case reports have suggested a potential efficacy of KD even in childhood, compliance problems may raise due to the strict dietary regimen that is required [353].

Nutraceuticals

Various guidelines from organizations like the American Academy of Neurology/American Headache Society, Canadian Headache Society, and European Federation of Neurological Societies have addressed nutraceuticals with differing levels of detail, sometimes resulting in conflicting recommendations. A review [356] has summarized existing guidelines regarding the use of specific nutraceuticals, including riboflavin, coenzyme Q10, magnesium, butterbur, feverfew, and omega-3 polyunsaturated fatty acids.

- *Riboflavin*, a member of the vitamin B (B2) family, riboflavin acts as a cofactor for flavoprotein enzyme function in the electron transport chain of the Kreb's cycle, in addition to contributing to membrane stabilization and the maintenance of energy-related cellular functions. Schonen et al. [357] conducted a RCT showing significantly reduced attack frequency in adult patients treated with riboflavin compared to placebo, with a higher responder rate (56% vs. 19%).
- *Coenzyme Q10* (CoQ10) serves as an essential cofactor in the electron transport chain, safeguarding against mitochondrial collapse by maintaining proper energy output. While Sandor et al. [358] showed a significantly higher reduction in migraine attacks with CoQ10 than placebo, other RCTs did not reach the same positive results [359].
- *Magnesium* is thought to play a pivotal role in establishing a threshold for migraine attacks through various pathophysiological mechanisms, including

neuroinflammatory blockade and calcium channel blocking effects, among others. A review [360] of oral magnesium supplementation in migraine prevention suggests that low magnesium levels are associated with migraines, but due to limited evidence, increasing dietary magnesium intake may be advisable.

- *Butterbur*, scientifically known as Petasites hybridus, has proved useful in migraine prevention [361]. However, there have been reports of hepatotoxicity [362] associated with certain butterbur formulations, leading to regulatory actions in different countries.
- *Feverfew*, scientifically known as Tanacetum parthenium, has been investigated in several studies which showed contrasting results. A Cochrane Review [363] concluded that the evidence for feverfew's efficacy in preventing migraines is mixed.
- *Omega-3 polyunsaturated fatty acids (OPFAs).* While an early RCT involving 196 migraine patients found no significant difference in the mean number of attacks between those taking OPFAs and those on placebo over a 16-week period [364], there are two more recent RCTs suggesting OPFA efficacy in migraine prophylaxis [365, 366].
- *Palmitoylethanolamide* (PEA) and *Gingkolide B*. PEA is an endogenous fatty acid amide widely distributed in different tissues, including nervous tissues. The anti-inflammatory effects of PEA seem to be mainly related to its ability to modulate mast cell activation and degranulation. In a pilot study, involving adult patients with migraine with aura, administration of PEA resulted in a significant reduction in the frequency and intensity of migraine attacks [367]. An open-label study in paediatric patients showed that after 3 months of treatment headache frequency was reduced by > 50% in 63.9% of patients [368]. Gingkolide B is an herbal constituent extract from Ginkgo biloba tree leaves. In a prospective trial [369] involving young patients with migraine without aura, a combination therapy of gingkolide B, CoQ10, vitamin B2, and magnesium significantly reduced the number of monthly migraine attacks after three months of treatment.

Nutraceuticals in women during pregnancy

Due to the limited evidence supporting the use of medications during pregnancy, alternative treatment options are often considered. There are common misconceptions that all nutraceuticals are safe during pregnancy, which is not always true for those commonly used in non-pregnant migraine patients [370]. Magnesium has multiple indications during pregnancy, such as relieving muscle cramps, constipation, and pre-eclampsia. According to a Cochrane review [371], there was no significant difference in perinatal or postnatal mortality, small-for-gestational-age infants, or pre-eclampsia. Although the optimal dose of riboflavin for migraine prevention is 400 mg daily, during pregnancy, riboflavin is classified as category A within the recommended daily allowance of 1.4 mg per day and category C if intake exceeds this dosage [372]. CoQ10 is considered safe during pregnancy and has been shown to lower the risk of pre-eclampsia in women who are at risk for the condition [373]. Feverfew can induce uterine contractions and should not be recommended during pregnancy [374]. Due to its potential to cause congenital malformations, also butterbur should not be recommended during pregnancy [375].

Concluding remarks

In summary, nutraceuticals can be considered for migraine prevention in patients who prioritize efficacy, speed of onset, and absence of side effects when choosing a preventive treatment. Since there are no head-to-head trials comparing nutraceuticals to pharmacological agents for migraine prevention, patients should be counselled about the unknown relative efficacy of nutraceuticals compared to conventional medications. However, since most nutraceutical trials show low rates of adverse effects, patients concerned about side effects may consider consulting their physicians and trying nutraceuticals before pharmacological agents. The very low prevalence of serious adverse events makes nutraceuticals particularly appropriate for migraine prophylaxis in children and adolescents. However, when prescribing nutraceuticals, the clinician should be aware that RCTs supporting their efficacy in the paediatric populations are currently lacking [376].

Non-pharmacological targets: exercise and physical therapy

Still an important proportion of patients do not achieve sufficient improvement with preventive medication: indeed, more than 50% of migraine patients search also for non-pharmacological options, such as physiotherapy [377]. Due to the role of the trigeminocervical complex, problems such as neck pain and musculoskeletal impairments may be comorbid and have an influence on migraine characteristics [378, 379]. Therefore, a proper clinical examination and an assessment of pain characteristics are needed to understand the possible role of physiotherapy in migraine patients.

Physiotherapy includes exercises, manual therapy (MT), and educational interventions. A recent systematic review conducted by Onan et al., found that occipital transcutaneous electrical stimulation, acupressure, osteopathic manual therapy, soft tissue mobilization and occipital transcutaneous electrical stimulation complemented with home exercises, facial proprioceptive neuromuscular facilitation and connective tissue massage,

aerobic exercise, hydrotherapy approaches significantly improves headache intensity, frequency, duration, and quality-of-life. In the meta-analysis results, MT combined with medication treatment significantly improved headache intensity, and MT or aerobic exercise combined with medication treatment significantly improved the number of headache days per month [378].

Exercise

Exercise is widely used in the management of migraine patients, however different exercise modalities, and different dosages and parameters exist. According to the results of a systematic review and meta-analysis that included 21 studies mostly carried out on episodic migraine, on aerobic exercise versus strengthening exercises, strengthening exercises were found to have the highest effectiveness in improving migraine symptoms, followed by high-intensity aerobic exercise [380]. However, it is important to consider that only three of the included studies specifically focused on strengthening exercises, with a smaller participant pool compared to studies on aerobic exercise [381–383], and the last and largest of these studies targeting vestibular migraine [383] rather than general headache symptoms, which limits the possibility to generalize the effectiveness of strengthening exercise in migraine. A recently published guideline indicated evidence-based parameters for different exercise modalities [384] (Table 4).

Another important issue that should be emphasized is that, according to ICHD-3 criteria, migraine can be triggered by physical activity (PA) [33]. It is stated that migraine may be triggered by PA and exercise due to dysfunction of the hypocretin neuropeptide produced by the hypothalamus [385], by lactate metabolism [386], and CGRP released during exercise [387]. Indeed, exercising during a migraine attack (ictal phase), may be a worsening factor, thus requiring modification of the exercise in a gradual and individualized exposure [384]. On the other hand, regular exercise can help patients for the management of migraine symptoms, and provides functional and psychological benefits [388]. The mechanisms behind the improvement, are increased in beta-endorphin levels in plasma after regular exercise, and the rearrangement of brain-derived neurotrophic factor levels [389] and endocannabinoid levels [390, 391]. Amin et al. stated that the trigger threshold of migraine may change in migraine patients who exercise regularly. Thus exercise may provide a prophylactic effect, if performed in the right phase of the migraine cycle [390]. Its efficacy is confirmed by the fact that several societies include exercise as part of the therapeutic option for migraine management, such as the French Headache Society [392], the Danish Headache Society [393], and the American Headache Society [394]. A recent Delphi study, highlighted how the exercise prescriptions should be individualized for every migraine patient, considering the just mentioned different exercise

Table 4 Evidence-based parameters for exercise

Exercise type	Exercise parameters	Migraine type	Improvements in symptoms	Recommendation (Grade)
Moderate-intensity continuous AE	Heart rate at an intensity between 12–16 on the Borg perceived exertion scale, a 64%-76% estimated HRmax, a 40%-59% HRR, or a 40%-59% VO_2R, performed over 8 weeks for 3 times per week	EM	HF, HI, possibly attack duration, disability, QoL	B
Yoga-mindfulness (breathing, relaxation, and meditation)	A 6-week intervention for 3 times per week	EM	HF, HI, disability, attack duration	B
Relaxation (progressive muscle relaxation, autogenic training, visual imagery)	At least for 6 weeks, from 1 to 7 times for week	EM	HF	C
	12 weeks, 3 times per week		HI	
High-intensity AE interval training	8 weeks, 3 times per week	EM	HF, HI, duration, disability	C
Low-intensity continuous AE	Intensity from 8–11 on the Borg perceived exertion scale, 50%-63% HRmax, 20%-39% HRR, or 20%-39% VO_2R; 6 weeks, 3 times per week	EM	HF, HI	C
Tai Chi (balance training)	Over a 12 weeks period, 5 times per week	EM	HF	C
Resistance strength exercise	Over 8 weeks, 3 times per week	EM	HF, HI, disability	C
Qi-Gong (slow movements, breathing, awareness)	Over a 3 months period with daily sessions	EM	HF and disability	D

AE Aerobic Exercise, *HRmax* Maximum Heart Rate, *HRR* Heart Rate Reserve, *VO_2R* Oxygen Uptake Reserve, *EM* Episodic Migraine, *HF* Headache Frequency, *HI* Headache Intensity, *QoL* Quality-of-Life

modalities, based on the patients' preferences, psychological aspects, level of PA, and possible adverse effects [395]. Indeed, the effect of exercise (acting as a migraine trigger or having a therapeutic effect) depends on migraine frequency (chronic or episodic), the type, the dosage, the duration, and the intensity of the exercise itself, but most importantly on the phase in which the exercise is performed. However, no specific exercise parameters emerge from these recommendations, with many studies referring to episodic migraine patients, representing a strong limitation when trying to apply in clinical practice exercises for migraine patients, and the role of exercise is still open to interpretation.

Manual therapy

MT is a commonly used non-pharmacological treatment, including soft tissue and articulatory techniques [396]. In a systematic review and meta-analysis of 6 studies on spinal manipulative therapy, with high heterogeneity, spinal manipulative therapy was shown to significantly reduce migraine days and headache intensity [397]. Results from a systematic review suggest that MT may be as effective as propranolol and topiramate for migraine [398]. Recent research confirmed that MT may be useful to decrease the frequency and intensity of migraine attacks [398, 399]. The mechanisms beyond MT interventions are based on the neurophysiological processes at both spinal and supraspinal level happening as consequences of the applied mechanical force, producing nociception modulation [400]. It has been reported that a combination of soft tissue and articulatory techniques yields larger improvements on headache intensity than the two approaches alone [401]. The main issues regarding MT include the heterogeneity of techniques, the number of sessions, and the duration of each session.

Neck pain (NP) and musculoskeletal impairment (MI) in the neck region are highly prevalent in migraine patients [402], and thus they should be properly assessed with a physical examination, to design a tailored treatment plan. The presence of NP in migraine patients is associated with worse headache characteristics, more severe MI, higher psychological burden, and enhanced signs and symptoms of sensitization [403]. A systematic review concluded that 4 out of 20 different assessment procedures (range of cervical motion, flexion-rotation test, pressure pain thresholds, and forward head posture) enable distinguishing migraine patients from controls. Manual joint testing and myofascial trigger points tests are usually positive in migraine patients, but they were not included in the meta-analyses because of heterogeneity of procedures [404]. If NP and MI are migraine comorbidities, i.e. the consequence of repetitive migraine episodes, or a sign of sensitization present only during the ictal phases ia matter of debate, but a recent study found that MI are present in all phases of the migraine cycle, independent on the presence of NP [405]. To further confirm the need for a proper physiotherapy assessment of migraine patients, a recent study found that more than 56% of migraine patients reported benefits from MT, and more than 90% expressed interest in MT to improve their migraine symptoms [406].

Pain neuroscience education

Pain Neuroscience Education (PNE) is a cognitive-educational approach, aiming at improving patients' knowledge about pain mechanisms, improve coping strategies, reduce fear, disability, catastrophizing, and avoidance [407]. This approach is helpful with strong-moderate evidence for intermediate-term effectiveness in migraine patients [408]. The combination of PNE with physiotherapy is more effective than physiotherapy alone, thus supporting the integration of different approaches, targeting together pain sensitivity and MI [409]. Alteration of pain sensitivity levels has been largely found in migraine patients [410], and increased pain sensitivity, together with MI, could be used as biomarkers to identify different subgroups of migraine patients with different needs. Recently, various clusters of migraine patients have been identified, according to pain sensitivity and MI [411]: in the ictal phase 81% of migraine patients exhibited increased pain sensitivity and MI, while in the interictal phase 45% only increased pain sensitivity, and 37% increased pain sensitivity and MI. This could be a first step in designing a more tailored treatment approach [412].

Concluding remarks

In summary, evidence exists that exercise, MT and PNE show effect on the improvement of migraine course, and are generally appreciated by patients. In the future high quality studies addressing aforementioned points, such as dosage, modalities, and frequency, should be designed, especially in exercise and MT. This will enable improving the knowledge behind physiotherapy in migraine patients, and possible have a role in international guidelines.

Pharmacovigilance

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problem" [413]. Information on the safety of different medications is typically published alongside clinical trials, real-world studies, and case reports, in addition to pharmacovigilance studies about databases

such as the WHO Safety Database (VigiBase®) [414] and the United States Food and Drug Administration Adverse Event Reporting System (FAERS) [415]. This chapter summarizes current evidence on the pharmacovigilance of acute and preventive migraine treatments.

Regarding acute medication, pharmacovigilance of triptans, lasmiditan, ubrogepant, and rimegepant have been investigated using VigiBase®, FAERS, and other reporting systems. According to the FAERS, triptans are associated with adverse events (AEs) such as ischemic cerebrovascular events, aneurysms, artery dissections, and pregnancy-related vascular events [416]. In terms of drug dependence, triptans have been found to be similar to ergot derivatives (10.9% and 9.3% of all reports of drug dependence for triptans and ergot derivatives, respectively), according to a French pharmacovigilance database [417]. Interestingly, these proportions were not significantly different from those of benzodiazepines. Additionally, whether triptans with higher lipophilicity (i.e., naratriptan and zolmitriptan) exacerbate depressive illness compared to those with lower lipophilicity (i.e., sumatriptan) has been questioned. A UK-based study using the West Midlands General Practice Research Database, comprising more than 20,000 patients with migraine, revealed that the rates of newly diagnosed depression after treatment were similar between patients prescribed triptans with higher lipophilicity and those with lower lipophilicity (3.9% versus 4.2%) [418]. Recently, the AEs of triptans in relation to breastfeeding have been evaluated based on four (inter)national pharmacovigilance databases. The 26 reports that were identified included breast and/or nipple pain, painful lactation, reflex, and decreased milk production [419].

For new classes of acute medication for migraine, a VigiBase® study comprising 826 and 47,433 reports on lasmiditan and triptans, respectively, found that the most commonly reported AEs for lasmiditan were dizziness (26.8%), feeling abnormal (13.0%), and somnolence (11.6%) [420]. Sedation, serotonin syndrome, euphoric mood, and autoscopy showed the strongest disproportionality signals for lasmiditan. While signals for cardiovascular adverse events were confirmed in triptans, lasmiditan did not show any such signals. Moreover, a recent analysis of 820 reports and 1,661 AEs associated with lasmiditan in the FAERS database focused on differences in AE signals according to demographic factors [421]. The analysis revealed that females were more likely to develop paraesthesia, whereas males tended to experience dizziness. The most common AEs were more likely to occur in older people and at higher doses.

Regarding gepants, 10 and 25 disproportionality signals were identified through the FAERS for ubrogepant and rimegepant, respectively, most of which were related to psychiatric, neurological, gastrointestinal, skin, vascular, and infectious AEs [422]. Another study on ubrogepant-related AEs based on the FAERS reported nausea, somnolence, oral paraesthesia, dizziness, hemiparesis, mental impairment, dysstasia, tinnitus, chest pain, cold sweats, and neck pain [423].

For preventive treatment, a recent systematic literature review on CM found that in real world studies that were published between January 2010 and February 2020, AEs have been reported mostly focusing on OnabotulinumtoxinA [424] and revealed that 0–25.1% of patients reported at least one treatment-related AE. Several studies have investigated AEs associated with CGRP-targeted medications. One of the most frequently reported AEs associated with CGRP mAbs is constipation, which has become more evident in the post-marketing period [425], especially with erenumab [426, 427]. Several vascular complications have also been identified with the use of CGRP-targeted medications, although conclusive evidence is yet to be reported [428]. A real-world database study showed a significant disproportionality signal of Raynaud's phenomenon with CGRP-targeted medications with an information component of 3.3 (95% confidence interval: 3.0–3.5), compared to triptans and beta-blockers [414]. In particular, erenumab has been associated with worsening blood pressure control irrespective of pre-treatment for hypertension [429]. In addition, myocardial infarction has been reported as a potential AE of erenumab [430]. These vascular AEs of CGRP-targeted medications could result from the potentially impaired vasodilation associated to CGRP. Furthermore, several post-marketing studies of CGRP-targeted medications have revealed that alopecia is a potential side effect of CGRP inhibitors [412]. In this context, it has been hypothesized that CGRP antagonism may impair the promotion of hair growth, the protective effect of hair follicles, and the blood flow supply to hair follicles. Given that many female patients with migraine are of childbearing age, the potential risks of using CGRP mAbs during the perinatal period have been investigated in recent years. Previous pharmacovigilance studies have found no major adverse effects on maternal health, birth defects, or spontaneous abortion; however, long-term data are still needed [431, 432].

Concluding remarks

In summary, several pharmacovigilance studies have investigated AEs associated with migraine treatment, focusing on triptans, OnabotulinumtoxinA, lasmiditan, gepants, and CGRP mAbs. When interpreting the above evidence, caution must be exercised, particularly regarding the following limitations. First, pharmacovigilance reporting systems often do not contain detailed

information on patients' backgrounds and would also pose the risk of underestimation. Second, AEs have been shown to be generally underreported due to a lack of knowledge among medical care providers and patients, with only 5–10% of all adverse drug reactions officially submitted to such systems [433]. Third, AEs of new classes of medication tend to be reported more frequently during the first years of marketing, peaking at the end of the second year after regulatory approval, a phenomenon called "Weber effect" [434]. Nevertheless, it is important to continue gathering information on AEs associated with migraine treatment and to provide patients with updated evidence when necessary, and to enable finding the most appropriate and safe therapy for each patient.

Migraine prognosis

The natural history of migraine can go through a phase of chronification, with a certain degree of variability of progression from EM to CM and it is often accompanied by acute drugs overuse [435]. CM is defined from ICHD-3 as the presence of headaches on ≥ 15 days/month for ≥ 3 months [436]. It has been estimated that Western countries suffer from headache on at least 15 days per month [437], and that CM prevalence has been estimated recently to be 4.6% of the global population [2]. CM prevalence is three times more common in women than men (18.9% vs. 9.8%) and presents two peaks between ages of 18–29 and 40–49 years-old [438]. The term CM has replaced the previously accepted definition of 'transformed migraine' which meant a type of headache with increase of the frequency and intensity, but this definition was not unequivocal on the meaning of chronicity of the disease, and includes also headaches with changes of clinical features which could underlie more severe disorders [439].

CM tends to be resistant to analgesics and can lead to the phenomenon of acute overuse of drugs, but should be differentiated from the MOH, which may complicate every headache type and can be caused by all medications used for treating headache [440]. The most effective way to prevent MOH is to identify patients at risk and to educate them about the use of acute medication. The risk is higher in patients with frequent headaches, use of opioids and comorbid anxiety and depression [441]. The burden of CM and MOH can be very high as can have a significant, negative impact on physical, social, and emotional functioning [442, 443].

A recent analysis of the Medication Overuse Treatment Strategy trial has demonstrated how an improvement of preventive medications for migraine can be associated with reduction of the disease burden, measured by a significant reduction of migraine-related physical impairment, anxiety, and symptoms of depression [444]. The best treatment options have been debated for long time, as they were found to be only temporarily effective in the majority of cases and did not guarantee long-term benefits. Topiramate and local injection of OnabotulinumtoxinA have shown efficacy as re-prophylaxis agents after CM detoxification, with a better tolerability profile of OnabotulinumtoxinA [435]. However, a high relapse rate has been observed especially in patients with overuse of opioids [445]. The new "era" of managing CM and MOH has been started from the introduction of monoclonal antibodies against CGRP or the CGRP-receptors. These new drugs have demonstrated to be effective in reducing monthly migraine days in CM and in MOH [446, 447].

Risk factors of migraine chronification and the measures that are effective for reducing the risk progression from EM to CM have been a challenge for several years. EM is defined by the occurrence of episodes of migraine for less of 15 days per month [448]. The recent updates of the GBD study confirms migraine as one of the leading causes of disability, particularly among women under 50 years [1, 2, 449]. Migraine prevalence is approximately 15% among the global population, and it is always more frequently observed in women than in men, in both chronic and episodic forms.

The rate of transformation from EM to CM has been estimated to be 2.5% approximately while only a limited proportion with CM revert back to EM [202]. Factors that increase the risk of progression are genetic predisposition, the occurrence of multiple comorbidities, chronic pain disorders, including fibromyalgia, back and neck pain, and unhealthy lifestyle. Also a high personal and societal burden, e.g. with a variety of psychological and personality traits, stressful life events, and major life changes has been considered as predominant risk factors [448]. Interestingly, also a lower education status, obesity, cutaneous allodynia, female sex and age increase the CM risk [450]. A systematic review and meta-analysis of 13 longitudinal cohort studies and 4 case-controlled studies has found that the most important modifiable risk factors for CM, which may provide important targets for intervention are depression, and medication overuse/high-frequency use, both in adults and adolescent/children [451]. This data confirms the importance of avoiding the drug abuse also in the earliest phases of the disease.

The recent COVID-19 pandemics has highlighted other potential risk factors of severe and persistent headache or chronification of migraine also after the acute infection. A prior history of headache, especially migraine, is an important risk factor of persistence of pain also in the chronic course (defined long COVID headache). Another predictive factor of persistence of headache after the

acute infection from SARS-CoV-2 is the resistance to common analgesics during the acute disease [452]. Also headache intensity (a more severe headache during the acute SARS-CoV-2 infection) seems to predict the persistence of pain in the long-term course. Other symptoms can accompany headache such as dizziness, cognitive dysfunction, insomnia/sleep disorders and fatigue [453, 454]. Older patients with multiple comorbidities and frailty might experience a more severe disease as compared to young subjects [455–457].

A small but still undetermined percentage of people with migraine experience disabling attacks that various therapeutic strategies are unable to control. Resistant and refractory migraine are new clinical definitions resulting primarily from the discovery of migraine-specific preventive treatments but also from a better understanding of the pathogenesis of this disease [458]. Characterized by ≥ 8 monthly days of debilitating headaches and inadequate response, intolerance or contraindication to ≥ 3 or all classes of preventive medications, respectively [459]. Resistant migraine is mainly due to drug failure and refractory migraine has complex and still unknown mechanisms that undermine the effectiveness of preventive treatment. Factors leading to or promoting resistance and refractoriness to preventative migraine drugs are as follows: psychiatric comorbidities and sleep disorders, poor diet, limited exercise, bad sleep habits, delayed or lack of access to medical care [451, 460, 461].

Concluding remarks

In summary, migraine prognosis is largely confounded by the presence of comorbidities, avoidable risk factors and, in particular, the possibility to get an accurate diagnosis and a specific treatment, with prophylaxis playing a specific role for reverting a chronic into an episodic course. Most likely, those who suffer from migraine will be subject to recurrent episodes of migraine headache during period of life in which migraine prevalence reaches its higher peaks. Considering the very good response rates or new specific therapies, i.e. the monoclonal antibodies against CGRP or CGRP-receptors, as well as those which will enter in the market soon, it is possible to presume that in the next forthcoming years the prognosis of migraine will be more favourable.

Psychosocial impact of migraine

The psychosocial impacts attributed to migraine include a broad variety of personal difficulties that contribute to the global disability faced by patients. Data concerning measures of global disability have been clearly reported and demonstrate that migraine is the 2nd leading cause of disability across the global population [462]. Additionally, migraine remains the leading cause of disability amongst women under the age of 35 years [462]. When considering the extreme psychosocial impact faced by individuals with migraine, the value of both defining and addressing common psychosocial difficulties (PSDs) and their role in the clinical course of an individual's diagnosis cannot be understated.

Measures that aim to estimate global disability experienced by a patient with migraine have been used in clinical practice for over 20 years. Currently, the most used scales of migraine disability are the Migraine Disability Assessment Test, the 6-items Headache Impact Test, and the Migraine Specific Quality of Life questionnaire [463–465]. While these scales remain frequently used due to their simple methodology, authors have voiced concerns regarding the accuracy, validity, and value of findings derived from such a general approach to a measure of disease related disability [466, 467]. Additionally, non-disease specific scales of disability such as the Patient Health Questionnaire-9, Visual Analog Scale, Work Productivity and Activity Impairment (WPAI), and WHO Disability Assessment Schedule 2.0 are frequently assessed in patients with migraine [468, 469].

While the burden of global disability attributed to migraine has been well reported, data defining specific psychosocial impacts and individual PSDs experienced by patients remain incompletely described. When attempting to interpret the PSDs experienced by a patient with migraine, it is crucial to assess the patient through a biopsychosocial model, as defined by the International Classification of Functioning, Disability and Health [470]. The classification defines PSDs as impairment of mental function, limitation of activity, restriction of participation in events that involve social interactions, such as in work, family life and leisure activities, as well as daily activities such as those connected to daily routing, homework or mobility [9]. Therefore, measuring disability with respect to all contributing PSDs is necessary to adequately define the true disability attributed to migraine.

A leading PSD reported by patients with migraine is related to impaired emotional function [471]. Individuals with migraine report significantly higher levels of comorbid mood disturbances such as depressed mood and anxiety when compared to the general population [472–474]. Strong evidence has demonstrated a correlation between headache frequency, global disability attributed to migraine, and worsening emotional function [471, 474–476]. In contrast, a recent study investigating the therapeutic role of CGRP mAbs in the preventative treatment of migraine concluded that CGRP mAbs therapy, regardless of patient response status, was associated with improved depressive symptoms [477]. While less thoroughly investigated, emotional disturbances including stress and anger are often reported by patients with migraine [471, 478, 479].

Another category of PSDs that are frequently reported by patients with migraine are factors associated with energy and drive functions including vitality, fatigue, and motivation [471]. Pathologic fatigue is reported by approximately 60% of patients with migraine and is highly associated with headache intensity and global disability [480]. Furthermore, it is proposed that impaired vitality and fatigue attributed to migraine are bidirectionally associated with mood disturbances and emotional functioning [471, 473, 481]. Further evidence of this relationship has been demonstrated in multiple studies reporting that patients treated with adequate acute and preventative migraine therapy report significantly lower burdens of fatigue and generally report improved vitality and motivation [475, 480, 481]. Furthermore, sleep disturbances are common in patients with migraine which is likely correlated with global migraine burden and mood symptoms [471, 482–484]. Assuring optimal migraine therapy is likely to lessen the burden of sleep disturbances and energy and drive functions amongst patients with migraine.

A leading economic PSD reported by patients with migraine are factors associated with work and school activities [485, 486]. Economic studies have consistently demonstrated that patients with migraine report a significantly higher burden in work related function secondary to increased workplace absenteeism and presenteeism, which is highly correlated with global disability [487–489]. While factors related to employment have been more thoroughly studied, data investigating school-related PSDs reported by students remain poorly outlined. It is generally acknowledged that school-age children with migraine are at an increased risk of school-related and learning difficulties secondary to absenteeism and presenteeism [490]. However, high-quality data providing definitive findings related to the PSDs faced by school-age children remain scarcely available.

PSDs associated with social functioning are often reported by patients with migraine, including feelings of isolation and loneliness [471, 491]. Available data supports a strong relationship between pain intensity, headache frequency, and social impairment [492, 493]. While poorly investigated, a therapeutic reduction in migraine pain intensity and a reduction in monthly headache burden is correlated with improved social function [471]. Somewhat related to social function, a final PSD attributed to migraine is the sequelae associated with substance abuse. While data defining the burden attributed to medication overuse headache is diffuse, limited data has investigated the multiple overlapping features between patients with CM associated to MOH and patients with substance use disorder [494]. While the relationship between habitual medication consumption as a precursor to substance abuse remains poorly elucidated, factors including increased headache pain intensity, increased consumption of acute medication, and impaired emotional function are all correlated with an increased risk of substance abuse [6, 440, 494]. Future studies are of utmost necessity to isolate contributing factors that lead to substance abuse amongst patients with migraine.

Concluding remarks

In summary, migraine has a considerable psychosocial impact, which can be detected at the level of individuals and of society. Individuals experience unpredictable effects of their conditions, which hampers their ability to interact with others, attend work or school activities, which can moreover be worsened by associated mood symptoms. The impact at societal level is mostly due to reduced workforce participation and productivity, which makes migraine one of the leading causes of health expenditure.

Occupational health consideration in migraine

Work-related stress is reported to predict new onset migraine in workers with no prior migraine history [495]. Stress has an impact on the incidence, chronification, and perceived burden of migraine [478]. However, occupational stress may be particularly difficult to avoid for those who are employed, and the extent of migraine-associated disability in the workplace may be influenced by psychosocial factors, such as job satisfaction which mediates the association between perceived disability and work productivity in workers with migraine [496].

Occupational factors may influence migraine prevalence. One example is the type of work performed. For instance, compared to the general population, the migraine risk appears to be increased in health care professionals, with notable differences among physicians of different specialties [497]. A recent study also found that among bank employees, those working in data analysis and information technology had higher migraine rates [498]. More work is needed to firmly establish which job factors may account for differences in migraine prevalence, and the extent to which they may be modifiable. There is additionally accumulating evidence in the literature regarding the association of shift work with migraine, and shift work may also act as a barrier to optimal migraine management [499, 500].

Migraine has been associated with multiple chemical sensitivity (also known as idiopathic environmental intolerance) [501], a controversial condition that nevertheless can be extremely disabling, and may greatly interfere with work ability. Olfactory-induced migraine triggered by low-level chemical exposures should be

considered in the differential diagnosis for multiple chemical sensitivity syndrome. Distinguishing olfactory-induced migraine from multiple chemical sensitivity syndrome matters greatly in clinical practice, as the former can often be effectively treated or even prevented with pharmacotherapy, whereas such options do not exist for the latter.

Migraine may impact workplace productivity, as it peaks during peoples' most productive work years. A recent burden of disease analysis from the UK showed that being affected by migraine is associated with absence from work, unemployment, being disabled, and early retirement [502]. Another study found that 89% of migraine-related productivity loss is due to presenteeism, rather than absenteeism, and that migraine represents approximately 16% of total presenteeism in the United States [503]. Patients self-reported being only 46% effective while on the job with migraine symptoms [504]. Factors reportedly contributing to migraine-related productivity loss include migraine symptoms, and also the unpredictability of attacks, comorbidities, the emotional impact of migraine, the impact of underdiagnosis and under-management, and stigma associated with the condition [503]. Traditionally, the impact is measured in terms of lost workdays or days worked with reduced productivity, but in recent years questionnaire-based approaches have been implemented as well, e.g. the WPAI [505] and the HEADWORK questionnaire, which specifically addresses addressing the impact of migraine on work-related difficulties in terms of difficulties, and the factors contributing to these difficulties [506].

Workplace programs for headache education and evaluation are associated with significant productivity gains and cost savings for the employer [507]. Pharmacological therapy, notably rizatriptan, has also been studied along with workplace programming [508, 509] and appears to demonstrate benefits. The effect of workplace programming may be modified by the national context, in particular the integration of employment with health care insurance and/or provision of health services.

Migraine is widely acknowledged as a difficult condition to manage in the workplace, even by occupational physicians [510]. In addition to pain, associated cognitive symptoms, photo- and phonophobia are most highly associated with migraine-related disability [511] and must be considered when assessing fitness to work, particularly in safety-sensitive and decision-critical [512] positions. The approach to management of migraine in workers needs to take a number of factors into consideration, including the characteristics of the migraine and its triggers, the migraine treatments used and their adverse effects, the worker's other health issues, as well as the workplace and job characteristics. The accident risk may be increased in newly diagnosed patients with migraine, as road safety data from older drivers suggest [513]. Whether a prodrome exists prior to the onset of disabling symptoms and how long this prodrome lasts may help inform fitness to work decisions. As well, attendance expectations may need to be adjusted and backup personnel available to take over safety-sensitive or decision-critical roles. Other examples of workplace accommodations for migraine that have been described in the literature include flexible scheduling, the ability to work from home when possible, a scent-free work environment, optimization of desk ergonomics, and provision of tinted glasses to reduce light sensitivity [503].

Concluding remarks

In summary, migraine impacts on work productivity, in terms of reduction in ability to carry out work duties, and some work-related factors may negatively impact on migraine course which, in turn, might further on reduce productivity. Migraine is acknowledged to be a difficult to treat condition in the context of workplace: however, some initiatives to improve workplaces' inclusiveness, such as the "Migraine-Friendly Workplace" initiative led by the European Migraine and Headache Alliance exist (see: https://www.emhalliance.org/migraine-friendly-workplaces/).

Economic impact of migraine

The economic impact of migraine, covering both episodic migraine (EM) and chronic migraine (CM), is a significant concern. Migraine imposes direct costs on healthcare systems, including expenses for medication treatments, primary care visits, diagnostic tests, specialist consultations, emergency visits, and hospitalizations. These costs vary significantly across countries due to differences in healthcare systems and migraine management approaches. Additionally, migraine leads to substantial indirect costs, such as productivity losses, absenteeism, and reduced quality of life for individuals, families, employers, and societies. The economic impact extends to intangible costs, including pain, anxiety, and emotional distress, along with limitations in family and social activities. However, these intangible costs are difficult to quantify and are rarely accounted for. Understanding the economic impact of migraine is essential for health policymakers, providers, and stakeholders to develop effective and cost-efficient strategies for prevention, management, and resource allocation.

A narrative review by Leonardi on the burden of migraine from 1990 to 2018 identified 49 publications focusing on the burden or impact of migraine, including both EM and CM [5]. Among the identified main themes, impact on work or school activities, and disease

costs were included. The impact on work-related activities and daily life was a significant focus due to tangible consequences like costs, and 22 studies addressing this aspect. Findings indicated that migraine significantly affected productivity, leading to considerable losses due to reduced productivity at work ('presenteeism') or absence from work ('absenteeism'). On average, patients with migraine lost between 3.2 and 89.2 work-equivalent days per year, with presenteeism contributing significantly to productivity losses. Overall, indirect costs, including work loss and reduced productivity, outweigh direct medical expenses. For example, in Europe, 93% of the annual per-person cost of €1,177 for migraine is attributed to indirect costs [514].

Family life was also impacted by migraine, as evidenced by five studies in the review [5]. Results indicated that family burden increased with headache frequency, with caregivers facing challenges in caring for affected members, particularly children. Two studies highlighted the burden of caregiving for individuals with migraine, noting its impact on family life and workforce participation. Eleven studies from 2001 to 2017 provided data on the costs associated with both EM and CM [5]. Discrepancies in total costs were observed, likely due to variations in cost structures, such as focusing solely on direct costs versus including both direct and indirect costs, as well as differences in survey years. For example, a US-wide study reported the annual total cost of EM at $2,649 (€2,444) and CM at $8,243 (€7,606) [515]. In this study, direct medical costs accounted for 60–64% of migraine-related expenses. Conversely, a Europe-wide study found the average annual direct cost of EM to be €746 and CM to be €2,427 [515]. Generally, CM incurred higher costs compared to EM, with direct medical costs comprising a significant portion of total expenses. Studies consistently indicate that the costs associated with CM are three to four times higher than those of EM.

A subsequent review by Eltrafi et al. (2023) of thirteen studies on the economic impact of CM revealed significant variations in cost estimates, underscoring the substantial burden on patients and healthcare systems [516]. While direct costs like hospitalization and medication expenses were examined, indirect costs related to productivity losses were often underexplored. None of the studies quantified intangible costs, such as emotional and social impacts. Direct healthcare costs per patient ranged from £1,754 (€2,043) to £8,219 (€9,574) annually, with indirect costs ranging from £2,579 (€3,004) to £48,810 (€56,856) annually, influenced by methodological differences. The review highlights the need for comprehensive assessments of both direct and indirect costs to understand CM's economic impact fully.

While most economic evidence focuses on CM or high-frequency EM, leaving out many migraine sufferers with fewer monthly headache episodes, a recent study in Spain aimed to address this gap [488]. The study evaluated the societal and economic impact of migraine using monthly headache days (MHD) as a measure, comparing it to individuals without migraine. The yearly cost per migraine patient was calculated at €8,894, with €894 (10.1%) as direct costs and €8,000 (89.9%) as indirect costs related to absenteeism and presenteeism. The findings advocate for stratifying patients based on MHD rather than distinguishing between EM and CM. Individuals with 1–3 MHD incurred an additional annual cost of €2,724 per person compared to those without migraine, a 1.5-fold increase. For patients with ≥ 15 MHD, the cost doubled compared to individuals without migraine.

In linking migraine-related impairment (symptom burden) and reduced productivity, frequency (number of MHD) emerges as the primary factor, surpassing headache intensity and episode duration [517]. This finding has significant implications for current headache care practices, health policy decisions, and healthcare resource investments. Despite being underused, preventive medications have considerable potential for delivering economic benefits, possibly leading to cost savings. Economic benefits, particularly in males, are substantial, with preventing one migraine day per month resulting in a recovery of approximately 28% of lost productivity from paid work every three months, surpassing the previously estimated 20% threshold for structured headache services to be cost-saving.

Headache disorders, including migraines, are highly prevalent in India, significantly impacting productivity and quality of life. In a door-to-door survey of 2,329 adults in Bangalore, 63.9% reported experiencing headaches in the past year. Migraine prevalence was 25.2%, with severe intensity and significant disability, reducing the functional capacity of the adult population by 0.46%. Despite the high burden, fewer than a quarter of sufferers sought medical help. Structured headache services in primary care are recommended as an efficient, effective, and equitable solution, highlighting the need for increased political awareness and will to address this issue [518].

A recent Australian study quantified the health and productivity burden of migraines in Australia using quality-adjusted life years (QALYs), productivity-adjusted life years (PALYs), and associated costs. A Markov model simulated outcomes for Australians aged 20–64 over 10 years, comparing current migraine prevalence to a hypothetical scenario without migraines. Results showed 8.5% of this population suffers from migraines, leading to a loss of 2.58 million QALYs and AU$1.67 billion in

health-care costs. Additionally, 384,740 PALYs were lost, costing AU$68.13 billion in GDP. These findings highlight the significant economic impact of migraines and the potential return on investment in effective interventions [519].

Concluding remarks

In summary, migraine has a significant economic impact on societies, measured both with mathematical models and with primary data, and the majority of the cost of migraine is associated to indirect costs, i.e. reduced productivity and loss of workdays. The advocacy by "Lifting The Burden", as part of its Global Campaign against Headache, for structured headache services [520] as an equitable and efficient healthcare solution for managing headaches is supported by evidence of cost-effectiveness derived from theoretical economic analytical modelling [12, 521]. Effective care, by reducing symptom burden, has the potential to restore lost productivity, suggesting that investment in care could yield cost-saving benefits.

Underserved populations

Migraine affects individuals across all socio-economic strata and can be particularly severe in those who are less privileged. This group of patients is often underdiagnosed, lacks access to specialized care, and rarely receives targeted treatments. Underserved populations have specific needs that should be addressed to improve migraine management and care. Underserved populations are not defined by a single criterion. Broadly speaking, they include individuals who face barriers to accessing healthcare due to socioeconomic status, geographical location, ethnicity, gender, or other factors. These barriers result in significant inequalities, providing these individuals with considerably fewer opportunities compared to others. The impact of these barriers on migraine care is herein discussed.

Socioeconomic status is a significant determinant of health outcomes, and this is also true for migraine sufferers. While the disease affects individuals from economic backgrounds, research has shown that socioeconomic status influences headache prevalence and burden, particularly when implicated in access to healthcare [522]. In the US, migraine is more prevalent in low-income households [523], and these patients visit emergency departments for headache treatment more frequently, which may imply suboptimal care [524]. Similarly, studies from Russia and Georgia have shown that poverty is associated with experiencing 15 or more headache days per month, also suggesting an unmet treatment need [525, 526]. In practice, advancements in migraine therapeutics that have improved migraine management for those who can afford them are often inaccessible to most patients worldwide. Notably, an evaluation in Latin America revealed that there are very few specialized headache training opportunities in the region, and most physicians with specific training primarily treat the wealthiest minorities in their countries [527].

Geographical Barriers exist as well. Access to healthcare services is often limited in rural and remote areas, where healthcare infrastructure is sparse. This is true not only for lower-income economies [528, 529] but also for countries like the United States, where only a few patients live in the same city where they receive treatment [530], and most patients have to travel more than one hundred miles on average to see a specialist [531].

Ethnic and racial minorities face unique challenges in migraine management. In the United States, American Indian and Alaskan Native populations, which are often neglected by society, have the highest migraine prevalence [523]. Blacks and Hispanics are significantly less likely to be diagnosed with migraine compared to whites. Specifically, African American patients are 25% less likely to receive a migraine diagnosis, and Hispanic patients are 50% less likely to receive a migraine diagnosis compared to White patients [523]. Furthermore, Black individuals are less likely to be prescribed acute migraine therapy compared to White individuals [523] and similarly, Hispanics are less likely to receive adequate prophylactic treatment in ambulatory settings [532, 533].

Gender differences have to be acknowledged too. Despite migraine is more prevalent and often more severe in women [534], women's pain is frequently underrecognized and under-treated, a phenomenon known as "gender bias" in pain management. This issue may be exacerbated in some countries where migraine is sometimes misunderstood as a conversion disorder, with its biological underpinnings being neglectfully overlooked [535, 536]. Additionally, while prevalence studies in gender minority groups are limited, available evidence suggests that migraine prevalence in these populations might be relatively high [537].

Finally, some consideration on research-related disparities have to be acknowledged. In both absolute terms and relative to its burden, migraine research is drastically underfunded [538, 539]. This scenario is particularly pronounced in low-income countries [527], which in addition are often excluded from most migraine clinical trials. This exclusion not only hampers the ability to generalize results to the majority of individuals living with migraine worldwide [540] but also reduces the chances of developing headache research in these countries.

Concluding remarks

In summary, addressing the needs of underserved populations in migraine care requires a multifaceted approach

that includes increasing access to healthcare, raising awareness, and implementing innovative strategies (Table 5). By focusing on the unique challenges faced by these groups, we can improve diagnosis, treatment, and quality of life for all individuals living with migraines. Ensuring equitable care and resources for underserved populations is not only a matter of social justice but also a critical step toward reducing the overall burden of migraine on society.

Conclusions

The most relevant hallmark of migraine is that it has common and individual features together. The most relevant commonality is connected to the clinical manifestation of migraine, i.e. unilateral location of headache, with pulsating quality, pain of moderate/severe intensity, which is aggravated by physical activity and associated to either nausea, photophobia or phonophobia [33]. Excluding this, the presentation is heterogeneous with regard to frequency of attacks, presence of aura, response to therapy, associated comorbidities or other symptoms. This likely reflects the heterogeneity of migraine with regard to its genetic and molecular basis. Several variants have been identified, which mostly underline vascular and neuronal tissues activity, and large evidence exist on the role of neuromodulators and neurotransmitters like 5HT, CGRP, amylin, PACAP and NO, which led to the development of migraine-specific therapies both for acute treatment and for prophylaxis, such as triptans or mAbs targeting GCRP.

The amount of therapies for treating migraine in acute and for prophylaxis is really wide, to the extent that one of the difficulties is with finding the best treatment for the single patient, considering its clinical features, comorbidity profile, but also by making considerations about non-response to treatment or presence of refractory migraine are needed [267, 541, 542]. Yet, this is not enough: patients have different lives, in which carry out different activities, and might show lifestyle habits which are not entirely adequate to manage migraine. These include, for example, skipping meals, being poorly hydrated, having insufficient sleep: therefore, patient education on lifestyle issues, as well as on ways to avoid triggers, should be part of the treatment [543]. Education will be more and more important in the future, as a strategy of brain health promotion [7, 11, 544], because this will enable reducing the amount of subjects who will need specialty care for migraine, thus leaving it to those who are in need in reason of refractory condition or presence of comorbidities.

The information herein presented is not intended to be systematic or entirely exhaustive. The approach was narrative and each of the authors, in preparing the section assigned to them, included the most updated, comprehensive and precise evidence possible addressing migraine specific features, from genetic and molecular basis up to the impact at societal level. The most relevant

Table 5 Main issues and possible solutions for addressing migraine in underserved populations

Barriers to diagnosis and treatment	1. **Lack of Awareness and Education**: Both patients and healthcare providers may lack awareness about the latest migraine treatments and management strategies. Educational programs are essential to improve understanding and recognition of migraines in these communities. 2. **Stigma and Misconceptions**: Migraine is often stigmatized as a minor or psychosomatic condition. This stigma can prevent individuals from seeking help or adhering to treatment plans. Addressing misconceptions through public health campaigns can help reduce stigma and encourage people to seek appropriate care. 3. **Limited Healthcare Resources**: Underserved areas often lack headache specialists, neurologists, and advanced diagnostic facilities. Enhancing healthcare infrastructure and training primary care providers in migraine management can improve access to care. 4. **Cultural and Linguistic Barriers**: Cultural beliefs and language differences can hinder effective communication between patients and healthcare providers. Culturally competent care and multilingual resources are necessary to ensure that all patients receive appropriate guidance and treatment.
Innovative solutions and strategies	1. **Telemedicine**: Expanding telemedicine services can provide remote consultations with headache specialists, overcoming geographical barriers. Telemedicine can offer timely diagnosis, follow-up care, and patient education, particularly in rural and underserved urban areas. 2. **Community Outreach Programs**: Establishing community-based health programs can raise awareness about migraines, provide education on management strategies, and offer screening services. Collaborations with local organizations and leaders can enhance the reach and effectiveness of these programs. **3. Patient Education and Self-Management**: Empowering patients with knowledge about migraine triggers, lifestyle modifications, and self-management techniques can improve their ability to manage the condition. Educational materials should be culturally appropriate and available in multiple languages. 4. **Integrated Care Models**: Developing integrated care models that address both migraines and comorbid conditions can improve overall health outcomes. Coordinated care between primary care providers, specialists, and mental health professionals is crucial for comprehensive management 5. **Policy Advocacy**: Advocating for policy changes to improve access to migraine care, increase funding for headache research, and ensure insurance coverage for effective treatments is essential. Policymakers should be informed about the impact of migraines on underserved populations and the need for equitable healthcare solutions.

consequence of this is that the contents represent the opinions of the authors, and not the results of a systematic review of the available evidence. Nevertheless, the cultural worth, especially for non-migraine experts, represents a relevant strength of this paper.

Recognizing the hallmarks of migraine and the features of patients' daily lives thus enables not only to prescribe specific pharmacological treatments, but also non-pharmacological ones, such as physical therapies, non-invasive neuromodulation, nutraceuticals, and behavioural treatments. Providing the best possible treatment, considering social and cultural peculiarities [7, 11], will be more and more of importance to reduce the impact of a heterogeneous condition which affects approximately 1.16 billion people worldwide [1] and is the second cause of health loss among young adults, accounting for 7% of all-cause YLDs (7.5% among females) [545].

Medical research on headaches today particularly suffers from the syndrome of single-disease niche sub-specialties, epitomizing a poor propensity for comparison among different disciplines, thus emitting a monolithic type of scientific light [546–548]. This leads to a limitation of results that are brilliant yet lack a systematic project articulation. This is evident in the widespread vagueness of the discussion in many contemporary original research papers, with little to no interpretative vision, resulting in a reduced attractiveness of funding [549].

Without resorting to the now imaginative, old-fashioned holistic vision of the able generalist physician, it is more necessary than ever today for researchers to have a cross-sectional and joint vision with other niche disease specialties and stop relegating themselves to the role of fine technicians in the service of an organ or a function. This is one of the goals of this trilogy of *Hallmarks of Primary Headaches*, like a *fil rouge* that can lead from one end to the other, from the extreme, distal one dedicated to researchers, to the proximal, practical one dedicated to clinicians.

Let's start with migraine.

Abbreviations

5-HT	Serotonin
ACT	Acceptance and Commitment Therapy
AEs	Adverse Events
AMY1	Amylin 1
BBB	Blood–Brain Barrier
BKCa	Calcium-Activated Potassium
BOLD	Blood Oxygenation Level Dependent
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
cAMP	Cyclic Adenosine Monophosphate
CBF	Cerebral Blood Flow
CBT	Cognitive Behavioral Therapy
cGMP	Cyclic Guanosine Monophosphate
CGRP	Calcitonin Gene-Related Peptide
CLR	Calcitonin-Like Receptor
CM	Chronic Migraine
CNS	Central Nervous System
CoQ10	Coenzyme Q10
CPM	Conditioned Pain Modulation
CSD	Cortical Spreading Depression
CTR	Calcitonin Receptor
EM	Episodic Migraine
FAERS	Food and Drug Administration Adverse Event Reporting System
FHM	Familial Hemiplegic Migraine
fMRI	Functional Magnetic Resonance Imaging
GABA	γ-Aminobutyric Acid
GBD	Global Burden of Disease Study
GPCR	G-Protein Coupled Receptor
GWAS	Genome-Wide Association Studies
HM	Hemiplegic Migraine
HRV	Heart Rate Variability
KD	Ketogenic Diet
Kir	Inward rectifier potassium
mAbs	Monoclonal Antibodies
MBSR	Mindfulness-Based Stress Reduction
MHD	Monthly Headache Days
MI	Musculoskeletal Impairment
MMD	Monthly Migraine Days
MOH	Medication Overuse Headache
MRS	MR Spectroscopy
MT	Manual Therapy
NO	Nitric Oxide
NP	Neck Pain
ONS	Occipital Nerve Stimulation
OPFAs	Omega-3 polyunsaturated fatty acids
PA	Physical Activity
PACAP	Pituitary Adenylate Cyclase Activating Polypeptide
PALYs	Productivity-Adjusted Life Years
PDEs	Phosphodiesterases
PEA	Palmitoylethanolamide
PKC	Protein Kinase C
PMR	Progressive Muscle Relaxation
PNE	Pain Neuroscience Education
PNS	Peripheral Nervous System
PRS	Polygenic Risk Score
PSDs	Psychosocial Difficulties
QALYs	Quality-Adjusted Life Years
RAMP1	Receptor Activity-Modifying Protein 1
RCT	Randomized Clinical Trial
SNPs	Single Nucleotide Polymorphisms
SNS	Supraorbital Nerve Stimulation
SUR	Sulfonylurea Receptor
tACS	Transcranial Alternate Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TG	Trigeminal Ganglion
TMS	Transcranial Magnetic Stimulation
TNC	Trigeminal Subnucleus Caudalis
TRP	Transient Receptor Potential
TVS	Trigeminovascular System
VIP	Vasoactive Intestinal Peptide
VNS	Vagus Nerve Stimulation
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
YLDs	Years Lived with Disability

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Authors' contributions

Alberto Raggi planned the study, drafted the introduction and discussion sections of the manuscript, and collected the entire body of the manuscript.

Paolo Martelletti planned the study and supervised the whole manuscript. The remaining authors drafted sections of the manuscript, in detail: Lou Grangeon and Kristin Sophie Lange, genetic basis; Adriana Della Pietra and Eloisa Rubio-Beltran, molecular pathways; Wei Wang and David Garcia-Azorin, central nervous system (CNS) and peripheral nervous system (PNS) implications; Igor Petrusic and Yonggang Wang, neuroimaging in migraine; Gianluca Coppola and Fu-Jung Hsiao, neurophysiological aspects of migraine; Valeria Caponnetto and Andreas Straube, cardiovascular, cerebrovascular and psychiatric comorbidities of migraine; Marco Arruda and Danilo Antonio Montisano, the migraine cycle: prodromes, ictal phase, and postdromes; Bianca Raffaelli and Alejandro Labastida-Ramirez, pharmacological targets for acute treatment: serotonin and CGRP; Lanfranco Pellesi and Doga Vuralli, pharmacological targets for prophylaxis: CGRP and PACAP; Licia Grazzi and Simone Vigneri, non-pharmacological targets: neuromodulation; Agnese Onofri and Alessia Marcassoli, non-pharmacological targets: cognitive behavioral therapy, relaxation and mindfulness; Parisa Gazerani and Massimiliano Valeriani, non-pharmacological targets: diet and nutraceuticals; Dilara Onan and Matteo Castaldo, non-pharmacological targets: exercise and physical therapy; Keiko Ihara and Tsubasa Takizawa, pharmacovigilance; Marta Waliszewska-Prosół and Claudio Tana, migraine prognosis; William Wells-Gatnik and Matilde Leonardi, psychosocial impact of migraine; Sebastian Straube and Xiangning Fan, occupational health consideration in migraine; Michela Tinelli and Tissa Wijeratne, economic impact of migraine; Marco Lisicki and Mario Peres, underserved populations.

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