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CONSENSUS PAPER AND GUIDELINE

Diagnosis, pathophysiology and management of chronic migraine: a proposal of the Belgian Headache Society

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Abstract Chronic migraine (CM) is a disabling neurological condition affecting 0.5–2 % of the population. In the current third edition of the International Classification of Headache Disorders, medication overuse is no longer an exclusion criterion and CM is diagnosed in patients suffering from at least 15 headache days per month of which at least eight are related to migraine. CM is difficult to treat, and preventive treatment options are limited. We provide a pathogenetic model for CM, integrating the latest findings from neurophysiological and neuroimaging studies. On behalf of the Belgian Headache Society, we present a management algorithm for CM based on the international literature and adapted to the Belgian situation. Pharmacological treatment options are discussed, and recent data on transcranial and invasive neuromodulation studies in CM are reviewed. An integrated multimodal treatment programme may be beneficial to refractory patients, but at present, this approach is only supported by a limited number of observational studies and quite variable between centres.

Keywords Chronic migraine · Botulinum toxin · Topiramate · Neurostimulation · Pathophysiology · Algorithm

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Definition, clinical characteristics and comorbidities of chronic migraine

Chronic migraine (CM) is a disabling neurological condition that only recently gained separate classification status. In the International Classification of Headache Disorders second edition (ICHD-2) of 2004, CM was defined as a complication of episodic migraine (EM) with the patient suffering from at least 15 migraine days per month for at least 3 months in the absence of medication overuse [1]. In 2006, appendix criteria were published to broaden the concept of CM: the patient experiences at least 15 headache days per month, of which at least 8 days are migraine (migraine criteria are fulfilled or headache has been successfully treated with migraine-specific treatment), and there is no overuse of acute treatment [2]. In July 2013, the beta version of the ICHD-III was published, including adapted CM criteria: medication overuse is no longer an exclusion criterion (Table 1) [3].

Observational studies—including the International Burden of Migraine Study (IBMS) [4], the American Migraine Prevalence and Prevention (AMPP) study [5] and the German Headache Consortium study [6]—have provided data on differences in symptom and comorbidity profiles of CM versus EM. The relationship between EM

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Table 1 ICHD-III beta criteria for chronic migraine

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

and CM is complex and dynamic: approximately 2.5–3 % of EM patients per year evolve into a CM state, a process generally referred to as "progression" [7, 8]. However, CM can remit back to EM, with a 2-year remission rate of around 25 % in the AMPP [9].

The mean age of CM patients in the AMPP study and IBMS was similar to that of EM patients, both most common in females in their fourth decade of life [4, 10]. However, CM patients had longer attacks (both treated and untreated) than EM patients [4, 10], and CM patients are more likely to experience severe pain intensity [4]. CM patients are more disabled and have a lower quality of life than EM patients, as illustrated by a lower score on the Migraine-Specific Quality of Life (MSQ) questionnaire [4], and higher scores on the Headache Impact Test-6 (HIT-6) [5] or Migraine Disability Assessment (MIDAS) questionnaire [11].

CM is associated with a wide range of psychiatric and somatic comorbidities, more so than EM. Up to 25 % of migraineurs meet criteria for mood and/or anxiety disorders [12]. In the AMPP study, CM patients were almost twice as likely as EM patients to meet the criteria for depression, and similar results were seen in the IBMS [4, 5]. A similar distinction between EM and CM is seen with respect to anxiety disorders [12]. It has also been suggested that post-traumatic stress disorder occurs at a significantly higher rate in persons with CM than in EM [13], which may be explained in a subgroup of patients by childhood maltreatment [14]. CM patients tend to have a higher Body Mass Index than EM patients, and around 25 % of CM patients are obese [6]. CM patients suffer more than twice as frequent (around 30 % of patients) from chronic non-headache pain disorders as compared to EM patients [10]. Respiratory disorders and cardiac risk factors—including hypertension, diabetes mellitus and high cholesterol—were also significantly more reported by CM patients in the AMPP [10]. CM patients are less likely to be full-time employed and are more likely to be occupationally disabled [10].

A pattern thus emerges that EM and CM not only differ in the degree of headache frequency or severity, but diagnostic vigilance is warranted with respect to psychiatric and medical comorbidities which may further increase disability [11], reduce quality of life [15] and inflate healthcare costs [16].

Differential diagnosis of chronic migraine

CM has to be differentiated from secondary headaches as well as from other chronic primary headache syndromes such as hemicrania continua (HC), new daily persistent headache and chronic tension-type headache (CTTH). According to ICDH-III Beta, medication overuse headache (MOH) is considered as a supplementary and not as a differential diagnosis in patients with CM [3].

The list of secondary headaches that can mimic or resemble CM is large, and a detailed description is beyond the scope of this review. We should take them into consideration if there are atypical features, other neurological complaints or an abnormal clinical examination. In this case, a brain MRI is often needed, sometimes complemented by blood and CSF analysis or MR angiography.

A special attention should be given to cervicogenic headache and sinus headache for which CM is often misdiagnosed [17]. For the diagnosis of cervicogenic headache, evidence is needed that a disorder within the cervical spine or soft tissues of the neck, known to be able to cause headache, is present, as well as proof of a causal relation by temporal association, provocative manoeuvres or a diagnostic blockade [3]. Also for sinus headache, not only proof of presence but also proof of causality is needed. The presence or absence of purulent nasal discharge can be of help here to differentiate [3].

HC is a strictly unilateral, constant headache with short lasting superimposed attacks, accompanied by either autonomic signs or a sense of restlessness or agitation, or aggravation of the pain by movement. An absolute response to a therapeutic dose of indomethacin is mandatory [3]. So in case of doubt, a trial with indomethacin should be considered to exclude this entity [18]. The other trigeminal autonomic cephalalgias are less often a diagnostic problem because they mainly present with short lasting headaches of less than 4 h.

New daily persistent headache persists for more than 3 months and is daily from its onset that is in general clearly remembered. The pain lacks characteristic features and may be migraine-like or tension-type-like, or have elements of both [3].

CTTH is the only primary headache with prevalence as high as that of CM, which is around 2 % according to population-based studies [19]. Its defining criteria are mirrored in the sense that CTTH is defined as a headache that lacks migrainous features.

As mentioned, MOH has now to be understood as a supplementary diagnosis, so we should consider CM with

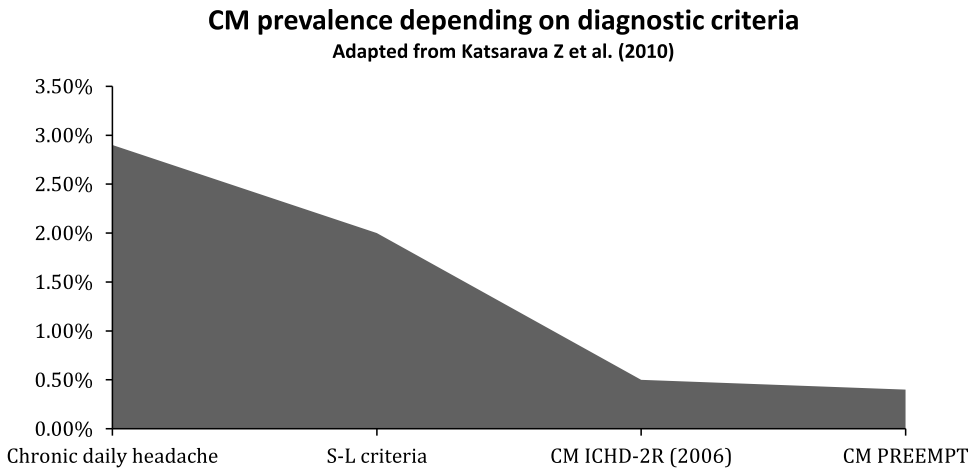

Fig. 1 CM prevalence depending on diagnostic criteria. Adapted from Katsarava et al. [6]

MOH and CM without MOH [3]. In earlier versions of the ICHD, a treatment of MOH by discontinuation of the overused substance was needed, before the diagnosis of CM could be retained. Now both can be diagnosed and also be treated in parallel [20].

Epidemiology of chronic migraine

A whole range of criteria…

Data about the prevalence and the incidence of CM depend on the criteria used in the population studies published during the last 20 years. As mentioned above, the definition and the criteria changed over this period. In the first edition of the International Classification of Headache Disorders (ICHD-1 1998), CM was not mentioned. The Silberstein–Lipton (S-L) criteria for transformed migraine (1994) provided a practical definition: daily or almost daily headache (≥15 days/month) for ≥1 month; history of EM and current headache still meeting ICHD-1 criteria for migraine. The S-L criteria did not exclude medication overuse, providing definitions of transformed migraine with and without medication overuse.

The ICHD-2 (2004) provided a definition of CM as a complication of migraine and required that migraine be present for ≥15 days per month in the absence of medication overuse [1]. Very few patients met these stringent diagnostic criteria. To address this, the International Headache Society published in 2006 revised criteria [2]. The ICHD-2R criteria define CM as headache occurring on ≥15 days per month with ≥8 days of migraine per month for at least 3 months, in the absence of medication overuse.

…still interesting results…

In seven studies using the S-L or almost equivalent criteria, the prevalence of CM ranged from 0.9 to 5.1 %. Three studies based on the stringent ICHD-2 resulted in a much lower prevalence of 0–0.7 %. At present there are no studies using solely the ICHD-2R criteria.

The German Headache Consortium study is a longitudinal cohort study (9665 people) of the prevalence and incidence of headaches within the general population (age 18–65 years) [6]. Three definitions of CM were used: with the CM definition (equivalent to the ICHD-3 beta criteria) used in the PREEMPT trials (see Sect. 5–management), prevalence was 0.4 %; according ICHD-2R criteria, it was 0.5 %; and using the S-L criteria of transformed migraine, it rose to 2 %. Coexistence of tension-type headache (21.6, 22.2 and 29.2 % of subjects) was different according the classification criteria (Fig. 1). Statistical analysis of demographic data demonstrated striking similarities between the 3 groups. All three populations were approximately 70 % women, average 44–46 years old, with a mean BMI of 26. Low level of education ranged between 70 and 78 % and 43–45 % were current smokers. In this population sample, 2.9 % of the adults suffered from chronic daily headache (≥15 days of headache per month) that encompasses CM and other chronic primary headaches, mainly CTTH, but also patients with medication overuse.

In the AMPP study on 162 756 people aged 12 years and older [21], the overall prevalence of CM (using S-L criteria) was 0.91, 1.29 % in females and 0.48 % in males. For both genders, the adjusted CM prevalence increased throughout adolescence, peaked in midlife and declined after age 50. Rates of CM were highest among females in midlife, ranging from 1.86 to 1.89 % from age 18–49 (Fig. 2). A similar pattern of increasing CM prevalence with age was observed in males. The prevalence of CM among adolescents (females 0.46 %, males 0.24 %) demonstrates that CM can start early in life (Silberstein S. 2007). Using the S-L criteria, EM sufferers develop transformed migraine at a rate of 2.5 % per year [7]. From 383 respondents with CM in 2005 follow-up, data were recorded in 2006 and 2007. After 2 years, 34 % ($n = 130$) had persistent CM while in 26 % ($n = 100$), CM

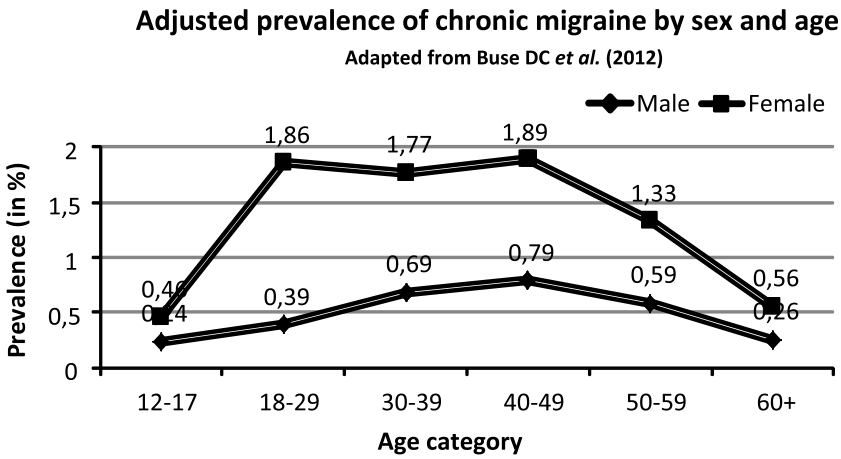

Fig. 2 Adjusted prevalence of chronic migraine by sex and age. Adapted from Buse et al. [5]

spontaneously remitted. Predictors of remission included lower baseline headache frequency (15–19 versus 25–31 headache days/month; odds ratio [OR] 0.29) and absence of allodynia (OR 0.45) [9, 22].

In a Taiwanese school cohort study of 3 342 adolescents aged 13–14 years, 63 subjects (21 boys/42 girls) developed incident chronic daily headache with an incidence rate of 1.13 per 100 PYs, including 37 with CM (0.66 per 100 PYs) and 22 with CTTH (0.39 per 100 PYs). A baseline diagnosis of migraine (52 %) and obesity were significant predictors for both CM and chronic daily headache. Female gender was a significant predictor for both CTTH and chronic daily headache [23].

…and important conclusions

From these epidemiological studies, we can conclude that CM is a relative frequent condition occurring in 0.5–2 % of the general population. The prevalence is 2.5 fold higher in females compared to males from age 18–55 years, with a less important gender difference in adolescents and after age 55 (Figs. 1, 2).

A baseline diagnosis of frequent migraine is a significant predictor for CM. CM patients frequently overuse triptans and/or analgesics, which favours headache chronification and leads to MOH. After cessation of medication overuse, remission from CM to EM occurs in about half of patients. In CM subjects without medication overuse, reversal to EM may also occur spontaneously.

Chronic migraine pathophysiology

The Janus face of chronic migraine

The transformation of EM to CM is characterized by a marked increase in frequency of typical migraine attacks, but also by frequent interval headaches without obvious migrainous features. CM is thus a chronic pain disorder where migraine attacks coexist with almost daily head pain. In CM pathophysiology, one may thus expect to find features that belong to the migraine attack and acute head pain, in association with others more typically found in chronic pain disorders (Fig. 3). We will therefore briefly summarize present knowledge and hypotheses about EM before examining the abnormalities reported in CM and attempting to identify among the latter those that might be specific to CM.

Pathophysiology of Episodic Migraine, sesame to that of chronic migraine?

EM is characterized by the cyclic recurrence of attacks, separated by headache-free periods. It is generally accepted that the common forms of migraine with or without aura

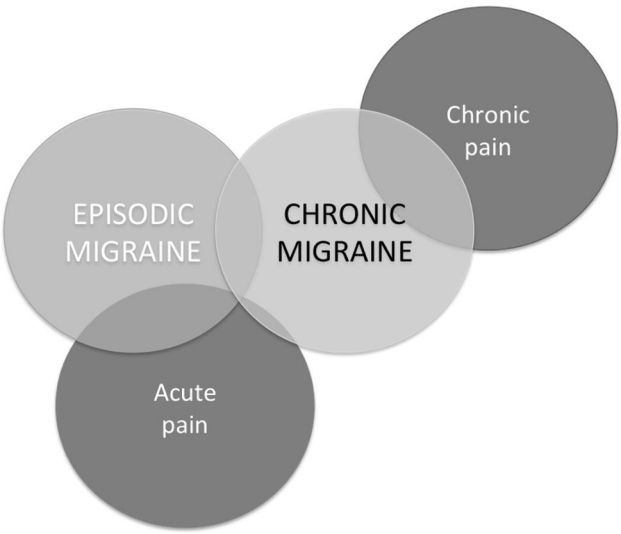

Fig. 3 Schematic representation of the interrelationship between Chronic Migraine, chronic pain disorders, Episodic Migraine and acute pain

Table 2 Brain changes in episodic migraine, chronic migraine and medication overuse headache (recent findings with electrophysiological and neuroimaging methods)

Episodic migraine (interictal)
↘ cortical sensitivity and ↗ responsivity to sensory stimuli [35, 36]
↗ fractional anisotropy thalamus (MR-DTI) [43]
↘ cortical thickness and activation S1, temporal lobe [26]
↗ cortical thickness and/or activation insula, cingulate, visual areas [24, 26]
↗ rs connectivity amygdala-insula [27]
↗ iron content PAG and globus pallidus [29–31]
↗ rs connectivity PAG-precuneus, visual [25]
↗ tissue density in PAG [129]
↘ olfaction-induced trigeminal nucleus activation
↗ pre-ictally [130]
↗ subclinical posterior circulation infarcts [30]
Chronic migraine
↗ cortical sensitivity and ↘ responsivity to sensory stimuli [26, 43, 44]
↗ cortical thickness and activation S1, temporal lobe
↘ insula, cingulate [26]
↗ rs connectivity limbic areas (Am, Ins, ACC)—thalamus, PAG, midtemporal, entorhinal, S1 [131]
↘ rs connectivity caudate-insula; ↗ putamen-insula [132]
↗ activation dorsolateral pons [47]
↗↗ iron content PAG and globus pallidus (T2) [29, 31]
↘ central pain modulation [133, 134]
no ↗ of posterior circulation infarcts [104]
Medication overuse headache
↘ metabolism and tissue density orbitofrontal cortex [48, 50]
↘ metabolism/activation of lateral pain system [50, 135]
↗↗ cortical sensitivity depending on drug overused [49]
precuneus connectivity: ↘ with DMN, ↗ with hippocampus [51]
↗ tissue density in PAG [48]

are complex genetic disorders where common genetic variants set a "migraine threshold" that is modulated by endogenous and exogenous factors. The brain in EM displays several functional and structural abnormalities between attacks (Table 2): abnormal thickness, connectivity and/or activation of certain cortical and subcortical areas [24–27], increased transmitter [28] or iron content [29–31], decreased ATP content [32, 33] and an abnormal pattern of sensory processing [34, 35]. The latter is characterized by low amplitude of initial responses and hyperresponsivity with lack of habituation of late responses during repeated sensory stimuli [36], and has been attributed to a thalamocortical dysrhythmia caused by deficient monoaminergic control by brain stem nuclei (review in [37]). It was hypothesized that the combination of cortical hyperresponsivity and reduced energy reserve may lead to rupture of metabolic homoeostasis and activation of the trigeminovascular system, the major pain-signalling neuronal pathway of the viscera brain, via subcortical chemosensitive neurons and/or via induction of cortical spreading depression waves at the cortical level [38] (see Fig. 4).

Interestingly, just before and during the attack of EM, the cortical response pattern to sensory stimuli normalizes [35] and activation occurs in the hypothalamus and dorsal upper brain stem comprising monoaminergic nuclei and periaqueductal grey matter [39–41].

Pathophysiology of chronic migraine: what is specific to migraine, and not common with chronic pain?

The major changes found in recent electrophysiological and imaging studies in CM are listed in Table 2. This table also shows, for comparison, those reported in EM and in MOH.

With electrophysiological methods, the sensory processing pattern of CM is similar to that of the migraine attack, as far as cortical responsivity is concerned, i.e. habituation normalizes and early high-frequency oscillations increase, reflecting thalamo-cortical activation. Hence, CM can be compared from an electrophysiological point of view to "a never-ending attack" [42, 43]. Both during an attack of EM and in CM (between typical migraine attacks), the amplitude of evoked potentials by low numbers of stimuli increases, which suggests that the sensory cortices become sensitized [43, 44]. Interestingly, the electrophysiological changes found in CM are reversible, as shown in a MEG study of CM patients reversing to EM [45].

A number of structural and metabolic changes have been reported at cortical and subcortical levels in CM (see Table 2). At present, it is not an easy task to distinguish changes that are specific to CM from those that can be found in other chronic pain disorders. For instance, the decrease in tissue density and activation found in areas belonging to the so-called pain matrix (the lateral pain system, thalamus, insula, cingulate…) is a well-known feature in chronic pain disorders. By contrast, connectivity changes of limbic areas and basal ganglia might be related more closely to CM, the more so that some of them have also been reported in EM but not in other cephalic pains [27]. Regarding the changes in limbic structures, one has to keep in mind, however, that depression is a major risk factor for CM [46].

The activation found in the upper brain stem is of particular interest for two reasons. It can be found during migraine attacks [40] as well as in CM patients in whom it persists despite occipital nerve stimulation [47]. The upper brain stem, probably the periaqueductal grey matter, is also the site where tissue density is increased in MOH [48]. Overuse of analgesics and/or migraine-specific acute medications is indeed by far the most frequent chronifying

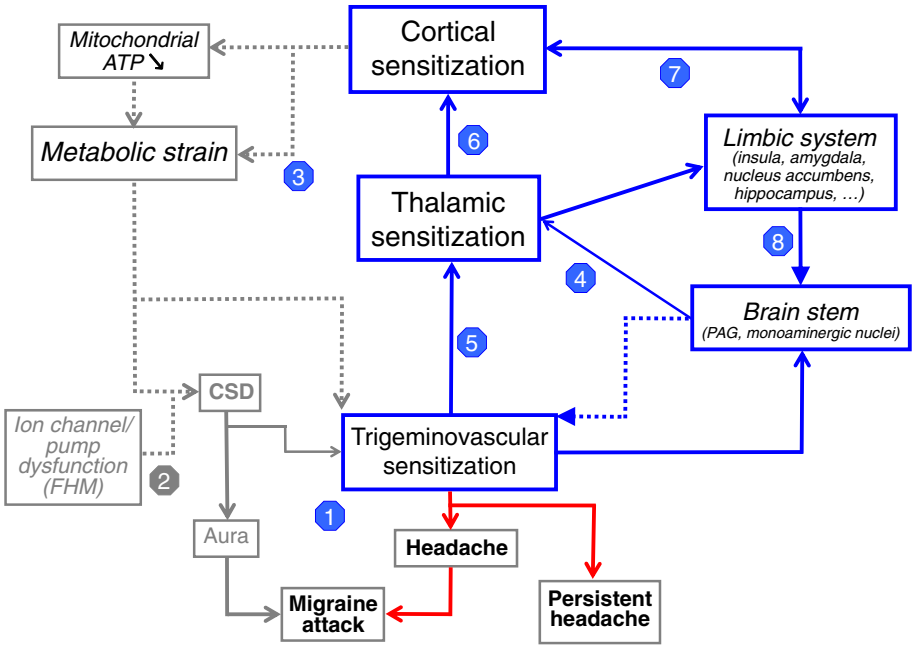

Fig. 4 A neurophysiological model of Chronic Migraine pathogenesis. The migraine headache (1) is due to activation of the trigeminovascular system (TVS), the major pain-signalling system in the brain. The migraine aura is caused by cortical spreading depression (CSD) that may or may not activate the trigeminovascular sytem. Genetic channelopathies (2) predispose to CSD in the rare familial/sporadic hemiplegic forms of migraine (FHM). Neurophysiological studies suggest that interictal abnormalities of sensory processing due to thalamocortical dysrhythmia combined with a decrease in the mitochondrial energy reserve may predispose the migrainous brain to an attack, i.e. to TVS activation (3) The interictal thalamocortical dysrhythmia favours hyperresponsivity of sensory cortices as well as abnormal pain processing, and may be induced by decreased control from brain stem monoaminergic nuclei. There is evidence for upper brain stem activation during migraine attacks. Whether this is due to collateral projections from the trigeminal nociceptive pathway, to chemosensing of the metabolic disequilibrium or to input from hypothalamus and the limbic system remains to be determined. Activation of the monoaminergic nuclei may explain why thalamo-cortical drive increases and cortical hyperresponsivity normalizes during an attack (4). The migraine attack is associated with sensitization of central nociceptive pathways (5), which can be detected by abnormalities of noxious evoked cortical and subcortical responses. The latter abnormalities amplify in CM, where the neurophysiological pattern is that of a « never-ending attack »; they spread in particular to thalamic and cortical levels (6). Because of the repeated pain attacks and possibly pre-existing comorbidities, connectivity of limbic areas with other cortical areas (7) and the descending pain control centres (8) is modified, which leads to abnormal central pain control and aggravates cortical abnormalities. *Full arrowheads indicate inhibition. Grey lines indicate connections that may not be relevant for migraine chronification*

factor of EM, together with high attack frequency. In MOH, sensory cortices become markedly sensitized depending on the drugs overused [49], the orbitofrontal cortex is hypometabolic [50] and atrophic [48], and connectivity of the precuneus is decreased with the default mode network, but increased with the hippocampus [51]. As in CM, some of these changes like the increase in tissue density of the PAG are reversible in patients who succeed in withdrawing from drugs and reverse to EM [48].

Considering the above findings and present knowledge in EM pathophysiology, a neurophysiological model of CM pathophysiology can be proposed (Fig. 4).

What are the implications for the management of chronic migraine?

As suggested by clinical experience and by the reversibility of several functional and structural brain changes, CM is not an irreversible condition, which must be taken into account in management decisions. CM is also not a progressive disorder in the sense that it would produce irreversible brain lesions, since posterior circulation subclinical "infarcts" that are somewhat more frequent in EM than in controls are not more prevalent in CM [52].

Since functional and structural changes are different in CM compared to EM and region-specific, neuromodulation treatments must be adapted accordingly (see 108).

In several studies, it has been shown that metabolic and morphological brain changes in EM increase with attack frequency [26, 29, 30]. Moreover, central sensitization that may occur during any migraine attack becomes persistent in CM and is thus likely to be a major chronifying factor, as suggested by a study of cutaneous allodynia [53].

Last but not least, because of the clinical and pathophysiological communalities between CM and chronic pain disorders, an integrated multidisciplinary management

approach, such as the one used in chronic pain disorders, is likely to be more effective in the most disabled patients than a single strategy [54].

Chronic migraine management

Table 3 summarizes the evidence for the various treatment modalities used in CM.

Pharmacological treatment

Topiramate

Topiramate is one of the best-studied medications for migraine, and its effectiveness in CM was confirmed in several studies. The encouraging results from a small randomized, placebo-controlled trial (RCT) of topiramate (50 mg daily) in 28 patients with CM and medication overuse paved the way for larger studies [58]. Two multicentre, parallel-group RCT in Europe (59 patients) and the USA (328 patients) showed that topiramate at a daily dose of 100 mg during 16 weeks was effective as a preventive therapy for CM [59, 60]. The effect size was overall modest, however, with a mean reduction in monthly migraine days of 3.5 (versus placebo −0.2) and a number-needed-to-treat of 12.5 [61]. Remarkably, the benefits of topiramate extended to the subgroup of patients who were overusing acute medications [62]. Topiramate use was also associated with a decreased number of monthly days of acute medication use (−3 days in the topiramate group versus −0.7 days in the placebo group), but this difference was not statistically significant. Adverse effects were mild to moderate in severity and consistent with those noted in previous clinical trials of topiramate: paraesthesia (number-needed-to-harm or NNH 2.4), dysgeusia (NNH 15.3), memory disturbances (NNH 16.6), nausea (NNH 23.1) and fatigue (NNH 31.2) [61]. No serious adverse effects were reported, but it is known from the pooled results of RCT in EM that one patient out of four drops out because of side effects [63].

Sodium valproate

Valproate was found effective for chronic daily headaches, transformed migraine or combined headaches in several open-label studies [55, 56]. In one RCT of 70 patients (29 CM, 71 CTTH patients) [57], sodium valproate (500 mg bid) for 3 months was superior to placebo for both general and maximum pain levels, and headache frequency, more so in CM than in CTTH. The number-needed-to-treat for reduction in headache frequency was 4, but this study is very atypical because of the complete absence of a placebo response. Up to now, its results have not been confirmed in a larger RCT.

Other agents

Beta blockers, methysergide, calcium antagonists, gabapentin, tizanidine, amitriptyline, fluoxetine and possibly memantine have been considered alternatives for the treatment of CM, but evidence for their efficacy is lacking [64].

Onabotulinum toxin type A (BoNT-A) in chronic migraine

Botulinum toxin injections were introduced as a potential treatment for primary headaches after the observation that its use for cosmetic reasons could be followed by headache improvement [65]. Although experimental studies in animals may suggest that BoNT-A is able to influence central sensitization and nociceptive trigeminal transmission, its precise mode of action in headaches remains unknown [66].

A large number of RCT were performed to test the effect of BoNT-A both in tension-type headache and migraine. In no trial of episodic or CTTH and EM, BoNT-A was found superior to placebo (reviewed in [67]). Post hoc analysis of some of those studies revealed, however, that patients with more frequent headaches might respond better to BoNT-A treatment.

By contrast, in CM, a meta-analysis of 5 RCT comprising a total of 1,508 patients (748 treated with verum, 760 with placebo) [68] shows that multiple pericranial injections of BoNT-A induce a significantly greater reduction of headache frequency than saline injections, although the latter also have a beneficial effect.

The two largest multicentre RCTs were those of the PREEMPT programme sponsored by Allergan [69] [70, 71]. PREEMPT 1 and 2 comprised 1,384 CM patients randomized either to BoNT-A ($n = 688$) or to saline injections ($n = 696$) and followed up for 24 weeks during which they received two injection cycles. The double-blind period lasted 24 weeks and was followed by an open period of 32 weeks during which all patients received BoNT-A. PREEMPT 1 showed no significant difference for the primary endpoint (mean reduction of headache episodes), but secondary endpoints like reduction of headache days were in favour of BoNT-A. Mean reduction of headache days was therefore chosen as primary endpoint for PREEMPT 2 and for the pooled results [69]. BoNT-A was significantly superior over saline in mean reduction of headache days at each time points (from week 4 to week 24 primary endpoint: −8.4 BoNT-A versus −6.6 placebo; $p < 0.001$; 95 % CI), in mean reduction of migraine days ($p < 0.001$),

Table 3 Available evidence for efficacy of treatment modalities in chronic migraine

Treatment	Trial evidence	Results and effect size	Adverse effects	Authors
Topiramate	2 RCT ($n = 59$; $n = 328$)	> placebo ↓ monthly migraine days NNT 12.5 Effective in MOH	paraesthesia (NNH 2.4), dysgeusia (NNH 15.3), memory problems (NNH 16.6), nausea (NNH 23.1), fatigue (NNH 31.2)	[59, 60, 62]
Valproate	1 RCT ($n = 29$)	> placebo ↓ pain intensity and frequency NNT 4 (but absent placebo response)	« rare » (no details)	[57]
OnabotulinumtoxinA	2 RCT (pooled $n = 1\ 384$)	> placebo mean ↓ headache days (−8.4 versus −6.6) Small effect size versus saline injections NNT 8	62.4 % Btx, 51.7 % saline 3.8 % discontinuation Btx; 1.2 % saline	[69–71]
Occipital nerve stimulation	3 RCT: ONSTIM ($n = 66$) PRISM ($n = 125$) St Jude ($n = 157$)	39 % of 50 % responders (headache frequency); underpowered negative negative 1° outcome (50 % reduction headache intensity) >sham: 30 % reduction headache intensity after 40-w open-label phase −6.7 monthly headache days	Frequent, non-serious: lead migration, battery replacement, local pain and infection, intolerance to local paraesthesia	[79–81]
Transcranial magnetic stimulation	1 RCT in EM with aura ($n = 164$) (2 pulses during aura) 1 sham-controlled trial ($n = 11$) (20 Hz rTMS over lDLPFC) 1 sham-controlled trial ($n = 13$) (10 Hz rTMS over LDLPFC)	Pain-free at 2 h 39 % (versus 22 % sham) Verum > sham Sham > verum	Minor Minor Minor	[101–103]
Transcranial direct current stimulation	1 sham-controlled trial ($n = 13$) (anode over 1° motor cortex; 10 sessions over 4 weeks)	Verum = sham (after 1 and 2 months) Verum > sham 4 months after therapy (pain intensity)	None	[109]
Cognitive-behavioural therapy	Cochrane meta-analysis in childhood and adolescence CM (21 studies) CBT + amitriptyline versus headache education + amitriptyline ($n = 135$; 10–17 years)	Reduction in headache intensity (risk ratio 2.9 for CBT) Little evidence for disability reduction CBT > education (66 versus 36, 50 % responder rate for headache days)	None Those of amitriptyline	[114, 115]
Multidisciplinary integrated care	2 observational prospective studies ($n = 841$; $n = 201$–1 years follow-up)	50 % responder rate for headache frequency reduction 36.4–62.7 %		[54, 118]

of moderate or severe headache days ($p < 0.001$), of cumulative hours of headache days ($p < 0.001$), of headache episodes ($p = 0.009$), of migraine episodes ($p = 0.004$) and of patients with a severe ($\geq$60) HIT-6 score ($p < 0.001$). At week 24, the 50 % responder rate (% of patients with $\geq$50 % decrease in the headache days) was 47.1 % in the BoNT-A group compared to 35.1 % in the placebo group (($p < 0.001$). The number-needed-to-treat for BoNT-A was estimated at eight for reduction in headache days [61]. Both groups were similar in reduction of acute medication intake ($p = 0.247$), but a post hoc analysis revealed significantly less triptan use at week 24 in the BoNT-A group than in the saline group ($p < 0.001$).

Adverse events occurred in 62.4 % of patients treated with BoNT-A compared to 51.7 % in those injected with saline, most of them being mild to moderate in severity. The discontinuation rate due to adverse events was low in both groups (3.8 % for BoNT-A, 1.2 % for saline).

The results of the PREEMPT studies appear promising for the most severely disabled population of migraine patients. However, they may not be transposable without reservation to clinical practice for the following reasons. Though statistically significant, the difference between BoNT-A and placebo outcomes is in fact modest. The high response to saline injections is a common observation in all BoNT-A studies. It could be due to the pericranial needling, the repetition of treatments, the direct observation of the procedure by the patients, their awareness that the drug is expensive and/or the cosmetic effect of clearing forehead wrinkles [72]. A recent review confirmed that physical treatments in general are associated with greater placebo effects than oral pharmacological treatments in migraine prevention [73]. In the PREEMPT studies, approximately 65 % of patients overused acute headache drugs at baseline. However, the treatment response was the same in patients without and with medication overuse, regarding primary and secondary endpoints. The patient population in the PREEMPT programme comprised about 40 % of subjects who never received a preventive drug treatment despite a CM history of almost 20 years and is therefore at odds with the usual phenotype of chronic migraineurs. It is surprising that in patients naïve to BoNT-A, the placebo response was higher and the reduction of headache days between placebo and BoNT-A groups was not significant (-9.2 versus -8.3; $p = 0.197$) while BoNT-A was superior in BoNT-A non-naïve patients (7.9 versus -5.6; $p < 0.001$) [74]. Unblinding of patients (and physicians) may thus be a confounding factor and may have decreased the placebo effect [73].

Only a subgroup of CM patients responds to BoNT-A injections, estimated at 30 % in tertiary headache clinic practice. Predictors for response to BoNT-A were not identified in the PREEMPT programme, and hence, a major challenge for the future is to try to identify responders on the basis of clinical and/or pathophysiological features. In a recent study of 81 CM patients, for instance, high plasma levels of CGRP (and VIP) correlated with a beneficial response to BoNT-A [75].

Meanwhile, it seems reasonable to propose BoNT-A therapy to patients who failed on several well-conducted preventive treatments, preferentially in a multidisciplinary setting and after withdrawal from medication overuse. Given the effect size in the PREEMPT studies, patients totally satisfied with the sole BoNT-A treatment are likely to be rare in clinical practice. The treatment is able, however, to reverse some of them from the chronic to the episodic form of migraine, in which case, other preventive therapies can become beneficial and be added. Drug withdrawal alone is able to achieve such reversal in $\pm$50 % of MOH patients. Despite the fact that in the PREEMPT trials, outcome was not different between patients with and without medication overuse, it seems therefore sound to detoxify before considering BoNT-A treatment.

When there is no improvement after one series of BoNT-A injections, a second series may recruit a proportion of responders, but new responders are scarce after a third series. One may therefore recommend abandoning BoNT-A treatment if there is no significant improvement of CM after the second series of injections. There is no consensus about the total duration of BoNT-A treatment. In the NICE guidelines—UK, it is recommended to stop BoNT-A if a patient is improved by less than 30 % after 2 cycles of injections and when a patient has returned to the episodic form of migraine for at least 3 months [76]. These recommendations, however, are based on headache frequency, and not intensity or duration.

Neuromodulation in chronic migraine

Due to the inefficiency of available and the lack of new preventive anti-migraine drugs, neurostimulation methods have raised great interest in recent years because of technological and scientific advances allowing a pathophysiologically based rationale in headache treatment. Neurostimulation can be applied to peripheral (pericranial) nerves or to central structures (the cerebral cortex). Evidence supporting efficacy of these approaches in migraine is scarce, and few RCTs are available.

Peripheral Neurostimulation (PNS)

PNS was used for a long time in neuropathic pain [77] before being studied in headaches, first in occipital neuralgia [78], and more recently in migraines.

Invasive PNS In migraine, like in other primary headaches, invasive PNS has been restricted to the most

disabled patients, i.e. those suffering from drug-resistant CM. The best-studied technique is percutaneous greater occipital nerve stimulation (ONS).

Occipital nerve stimulation: Besides some small and/or heterogeneous open studies, three short-term (i.e. 3 months each) RCT were performed in CM [79–81]. The ONSTIM study ($n = 66$ patients, [80]) showed a reduction of ≥50 % in headache frequency or a decrease of three points on the intensity scale in 39 % of patients treated with active ONS during 12 weeks, compared to no improvement in the "non-effectively" stimulated or medically treated groups. Unfortunately, ONSTIM was not powered to convincingly demonstrate effectiveness of ONS.

In the PRISM study ($n = 125$ patients [79]), available only in abstract form, ONS was not superior to sham stimulation within the 12-week assessment period.

Finally, in Silberstein et al.'s [81] ONS trial on 157 patients with CM, no difference was found between sham and verum at the end of the 3-month treatment period for the primary outcome measure: percentage of patients who had ≥50 % reduction in mean daily headache intensity. There was, however, a significant difference in favour of ONS in the percentage of patients with a 30 % reduction in mean number of headache days ($p < 0.05$) and a decrease of the MIDAS score ($p < 0.01$). After the 3-month randomized phase, the patients entered an open-label phase of 40 weeks [82] where after headache days had significantly decreased in the intention-to-treat group (−6.7 days) and in a subgroup with intractable CM refractory to preventive drugs (−7.7 days) ($p < 0.01$) This study has some serious methodological flaws, among which not the least is that only patients who underwent a successful trial of stimulation (defined as at least 50 % reduction in pain or adequate paraesthesia coverage in the painful areas) were permanently implanted and included, which likely favoured selection bias and unblinding.

ONS is minimally invasive, but adverse effects occur rather frequently: lead migration [83] and battery depletion requiring repeated surgery, local pain or infections, intolerance to local paraesthesia [83].

The precise mode of action of ONS in migraine is not known. Although the initial rationale for ONS was based on Kerr's principle, i.e. convergence of C2 and trigeminovascular efferents on the spinal trigeminal nucleus [84, 85], this is not supported by experimental studies in headache patients [86]. In chronic cluster headache, the therapeutic response to ONS is associated with activation of cortical pain control centres [87]. Whether this is also the case in CM remains to be determined. Like in chronic cluster headache where it does not modify hypothalamic activation, ONS probably acts as a symptomatic treatment in CM, since it is not able to normalize the activation in the dorsal rostral pons that characterizes both migraine attacks and CM [47]. The time to relief during ONS takes several months, suggesting that slow modulatory effects are involved, which contrasts with the rapid aggravation of headaches when the battery goes flat [47, 86]. The latter argues against a placebo effect or regression to the mean.

Combined PNS: In a retrospective study of 44 CM patients, the combination of ONS with supraorbital nerve stimulation (SNS) decreased headache frequency by 81 % and eliminated all headaches in 50 % of patients [88]. Transcutaneous cervical and auricular stimulators of the vagus nerve have been developed and are being tested in migraine.

Peripheral nerve decompression: A group from the Cleveland Clinic (USA) has proposed surgical decompression of multiple pericranial nerves as a treatment option for difficult to treat migraine patients. In a sham-controlled trial of 75 patients suffering from "frequent to severe migraine" and selected on the basis that they had a "trigger site" and ≥50 % amelioration after injection of 25U BoNT-A at this site, the therapeutic gain of surgical decompressions over sham operation was 26 % [89]. Because of major methodological flaws in study design, efficacy of migraine trigger site deactivation surgery in general is at best unclear at present [90]. Potential complications and high cost of the procedures further lead us to strongly discourage migraine trigger site deactivation surgery outside of the context of a clinical trial.

Non-invasive PNS The analgesic effects of TENS (transcutaneous electrical nerve stimulation) are known since a long time [77], and the potential benefit of TENS in headache therapy has been suggested previously [91]. Properly designed trials, however, are lacking as pointed out in a Cochrane review [92].

The effectiveness of a portable transcutaneous supraorbital nerve stimulator (tSNS) (Cefaly®) in EM prophylaxis was proven in a RCT [93] and is supported by the fact that among 2 313 subjects in the general population who rented the device for 60 days via internet, 53.7 % were satisfied and decided to buy it [94]. No data are available in CM. The modest effect size of tSNS with the Cefaly® device suggests, nonetheless, that in CM, it might at best be useful as an add-on treatment.

New devices thought to stimulate the vagus nerve transcutaneously (tVNS) were developed recently, and their efficacy as acute and preventive treatment of primary headaches is being evaluated. Preliminary results suggest that the cervical stimulator could help some CM patients [95].

Central neurostimulation

Only non-invasive central neurostimulation has been used in migraine. Mainly two methods, both able to modify activity of the underlying cortex, are currently explored in

CM: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [83].

Transcranial magnetic stimulation While single TMS pulses momentarily interrupt cortical activity and, in animal models, cortical spreading depression [96], rTMS induces long-lasting changes: low stimulation frequencies (i.e. 1 Hz) have an inhibitory effect [97], whereas high frequencies (≥10 Hz) are excitatory [98]. In healthy volunteers and migraine patients, rTMS is able to durably modify excitability of the visual cortex and hence to reverse the abnormalities of evoked potentials found in many migraineurs [99, 100].

In patients suffering from EM with aura, two single TMS pulses over the visual cortex within an hour after aura onset resulted in a pain-free response rate at 2 h of 39 %, compared to 22 % for the sham stimulation [101]. It is not known whether such a portable TMS device can be useful as symptomatic treatment in CM.

The efficacy of rTMS for CM prevention was investigated only in a few small studies. Based on the hypothesis that the left dorsolateral prefrontal cortex (LDLPFC) is hypoactive in chronic pain disorders, Brighina et al. [102] studied the effect of excitatory high-frequency (20 Hz) rTMS over the LDLPFC in 11 chronic migraineurs. After 12 sessions of rTMS, attack frequency, headache index and acute medication intake were reduced for up to 2 months, while there was no significant improvement in five patients receiving the sham stimulation. These results were not confirmed by another study where high-frequency (10 Hz) rTMS over the LDLPFC in 13 CM patients turned out to be less effective than placebo [103].

As mentioned in the pathophysiology section, cortical responsivity differs between interictal EM and CM. There is thus a rationale for a pathophysiologically guided selection of neurostimulation procedures and protocols depending on the migraine cycle. Using this approach, inhibitory quadripulse rTMS were applied over the visual cortex in 16 CM patients during a 4-week proof-of-concept trial (two rTMS sessions/week as add-on therapy) [104] and found that monthly migraine days decreased by 41 % ($p < 0.05$) and severe attacks by 25 % ($p < 0.05$). The 50 % responder rate was 38 % and half of the patients reversed from chronic to the EM. Clinical improvement remained stable at least 1 month after the end of the treatment sessions. There were no adverse events, and, interestingly, medication overuse did not modify the response to the rTMS therapy. These results paved the way for an ongoing sham-controlled trial.

Transcranial direct current stimulation tDCS uses weak currents to modify the cell's resting membrane potential, leading to focal modulation of cortical excitability. Like in rTMS, two opposite effects can be obtained: cathodal stimulation inhibits neuronal firing, whereas anodal stimulation increases it. In healthy volunteers, tDCS is able to modulate resting EEG and event-related potentials [105], and functional connectivity of corticostriatal and thalamocortical circuits [106], which is of particular interest for migraine that may be associated with thalamocortical dysrhythmia (see Sect. 4) [107].

In EM, anodal tDCS over the visual cortex (2 weekly sessions for 8 weeks) significantly reduces attack frequency and duration [108]. In 13 CM patients, anodal tDCS over the primary motor cortex for 4 weeks produced a beneficial delayed effect on pain intensity and duration (120 days after stimulation) that was attributed to slow modulation of central pain-related structures [109].

Conclusions

From the results presented above, the following provisional conclusions can be drawn.

First, invasive ONS still awaits definitive proof of efficacy and should only be envisaged in CM sufferers after failure or intolerance of several preventive anti-migraine drugs and of BoNT-A injections. In medication overuse headache patients, it is recommended to detoxify before considering any invasive neurostimulation, as drug overuse seems to be associated with a less favourable outcome with ONS [110]. More trials are clearly needed to identify responders. Meanwhile, potential candidate patients for ONS must be informed that outcome is uncertain, improvement moderate, adverse effects inevitable and price high, unless they accept to enter a RCT. A proportion of chronic cluster headache patients may go into remission while being on a waiting list for surgical intervention [83]. Assuming that this might also be the case in CM patients, it may be wise to leave them on a waiting list for several months before the operation.

Second, pericranial transcutaneous nerve stimulations are unlikely to be of great benefit to CM patients because of their modest effect size in EM. It remains to be seen whether multisite TENS has greater effects. Among the non-invasive neurostimulation methods, rTMS and tDCS are the most promising for CM, and probably more so tDCS because of its easy use and low price. Future studies should try to adjust the stimulation protocol and site to the migraine cycle and to the patients' pathophysiological profile. Large RCT is clearly needed, and they will have to find a satisfactory way of handling the control/sham stimulation and the possibility of unblinding due to the sensations generated by the neurostimulation [83, 93, 95].

Cognitive-behavioural therapy

Cognitive-behavioural therapy (CBT) defined as various combinations of pain education, stress management,

relaxation with or without biofeedback is widely used in chronic pain disorders where it has a significant beneficial effect. The effect size, however, is modest. In fibromyalgia for instance, a Cochrane meta-analysis of RCT found at a follow-up of 6 months a mean reduction of 0.6 points in pain, 1.3 in negative mood and 1.2 in disability, all on a 0–10 scale [111].

In chronic headaches, few studies have been performed since the report by Martin et al. [112] in 1998 showing that a CBT designed to treat depression is more effective in patients with high chronicity while self-management has a better outcome when depression is low. In high-frequency migraine (mean 5.5 migraine days/month), addition of behavioural management alone to optimized acute treatment had no significant effect, whereas the combination of behavioural therapy with a beta blocker significantly improved outcome at 16 months [113].

The most convincing data favouring an effect of CBT on CM comes from trials in children and adolescents (<18 years). A Cochrane meta-analysis of RCT (21 studies) concluded that CBT is effective in reducing headache intensity in this patient population (mean risk ratio: 2.9 in favour of CBT) and also improves pain and disability for children with non-headache pain. There was limited evidence, however, to estimate the effects on disability in children [114]. A recent RCT compared the benefits of CBT combined with amitriptyline (1 mg/kg/d) to those of headache education with amitriptyline in 135 children and adolescents (10–17 years old) suffering from CM. After the 20-week randomized period, the rate of 50 % responders for headache days was 66 % in the CBT plus amitriptyline group versus 36 % in the other group; corresponding values after 12 months of follow-up were 86 % and 69 % [115]. It is not known at present whether such favourable results can be obtained in adult patients with CM.

Integrated headache care

CM patients are notoriously difficult to treat. From the review of available therapies above, it is obvious that no single treatment modality is beneficial in more than ±30 % of adult patients. Moreover, as mentioned, CM patients have pathophysiological features in common with chronic pain patients, including cognitive-behavioural patterns. In particular, depression and anxiety, though frequently pre-existing, usually worsen with the duration of the chronic phase and treatment failures.

Integrated headache care is therefore proposed to the most disabled patients in certain tertiary headache centres [116]. It is based on a multidisciplinary and, in some cases multimodality approach, where patients receive in various combinations neurological care, psycho-educational information, cognitive-behavioural relaxation therapy, sport therapy, psychotherapy and sometimes neurostimulation treatment. Most programmes are performed on an outpatient basis; inpatient care is offered to some patients but is rarely necessary. There is at present no uniform format, and the modalities vary largely between centres [116]. There is also no RCT in CM providing evidence that integrated care is superior to other treatment modalities. One prospective randomized trial found that a multidisciplinary intervention programme in episodic migraineurs had a better outcome than standard therapy. The benefit remained significant after a 3-month follow-up, but there was no change in medication use or work status [117].

Two German groups have published observational prospective or cross-sectional studies of headache-specific multidisciplinary treatment programmes in recent years. The patients included in these studies are qualified as "difficult-to-treat" and most of them are migraineurs, but not all of them fulfil the criteria for CM. Overall there is a decrease in headache frequency and headache-related disability in all studies [54, 118–120]. The 50 % responder rate after a follow-up of 12 months varies between 36.4 % in the largest survey of 841 patients [54] to 62.7 % in the study by Wallasch et al. [118] of 201 patients. Interestingly, in the Gaul et al. report [120], adherence varied between treatment modalities: 35 % for drug treatment, 61 % for relaxation and 72 % for aerobic exercise. Aerobic exercise was evaluated as such against topiramate and relaxation in a randomized trial of EM; it achieved a 50 % responder rate of 30 % compared to 26 and 23 %, respectively, for the two other modalities [121].

Consensus proposal of a management algorithm for chronic migraine

Figure 5 shows a tentative algorithm for the management of CM. Items in bold are those for which strong evidence is available.

The first preoccupation of clinicians taking care of migraine patients should be to prevent chronification. This includes optimized prophylactic treatment in patients with frequent migraine, but also counselling on risk factors such as excessive caffeine intake, oestrogen therapies or stress management. To treat the acute attack of mild or moderate severity, preference should be given to NSAIDs rather than to analgesics because they are less prone to induce medication overuse headache [122]. It is also of uttermost importance to manage comorbid disorders, mainly depression and anxiety, in order to prevent an aggravating effect on migraine and to favour the reversal from CM to EM. This can be achieved by optimizing therapy taking into account the effects and side effects of the respective drugs used for migraine and the comorbid disorder [123].

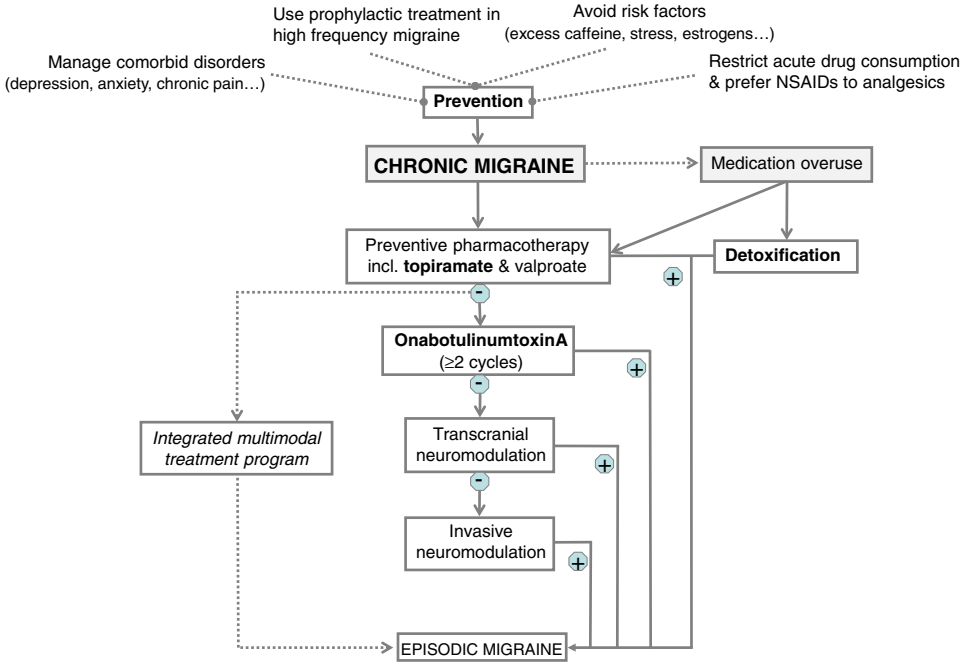

Fig. 5 Chronic migraine management algorithm

The major objective in the management of patients with established CM is to reverse them to EM, which decreases their disability and increases their responsiveness to prophylactic therapies. Detoxification is mandatory in patients with acute medication overuse, should be combined ab initio with an adequate preventive treatment and suffices in ±60 % of overusers. Detoxification may be achieved through simple advice in many patients [124, 125], but in refractory patients, specific withdrawal strategies should be employed [20, 126].

It is common thinking that CM patients are (or have become) resistant to available preventive treatments. This, however, may not be assumed without reservation in many of them because they never received (>40 % in the PREEMPT trials) or never took at a sufficient dose or for a sufficient time an established preventive drug. There is no agreement on the number of drugs a patient should have received before being considered refractory, but it is common consensus that at least three or four drugs belonging to the four most effective pharmacological classes (beta blockers, anticonvulsants, calcium antagonists, tricyclic antidepressants) should have been adequately tested [127]. Among these drugs, topiramate has the strongest evidence of efficacy in CM, but the effect size is modest (see above) and other drugs may not have been properly studied.

Methysergide, for instance, the pioneer prophylactic drug used in migraine prevention on the basis of the serotonin theory, has not undergone RCT in severe or CM because it is an old drug with a limited market. There is, nonetheless, a consensus among the authors that methysergide can be very useful in frequent and CM patients refractory to the other preventives. The European Medicines Agency (EMA), though banning all ergot derivatives because of poor risk/benefit ratio, has recently shared this opinion by making an exception for methysergide and considering that it may have "a clinically relevant effect in severe migraine and cluster headache". Its recommendations for the future use of methysergide are as follows: restrict the drug to adult patients resistant to standard medicines; treatment started and supervised by specialized physicians with experience in treating migraine; patients screened for fibrosis at baseline and every 6 months thereafter; allow a methysergide-free period of ≥4 weeks every 6 months [128]. These recommendations have been forwarded to the European Commission, which will issue a final legally binding decision in due course [128].

In patients who do not respond or are intolerant to several preventives, alternative therapies must be considered. Among them, BoNT-A injections have at present the best risk/benefit ratio, but, as mentioned, only a subgroup of patients will respond. Unfortunately, no evidence-based alternatives can be offered to those non-responders. Neurostimulation methods are promising, but RCTs are needed. For obvious reasons, non-invasive methods should be tried before invasive ones.

There is evidence from other chronic pain disorders and some indication from observational studies in CM that patients who are not improved by preventive drugs and adequate management of risk and aggravating factors do better with integrated multimodal treatment programmes.

Such programmes, however, are available only in specialized headache centres, and more trials are needed to determine which are the most effective programmes and whether they should be customized to individual patients or patients subgroups.

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