Chronic migraine: risk factors, mechanisms and treatment

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Abstract | Chronic migraine has a great detrimental influence on a patient's life, with a severe impact on socioeconomic functioning and quality of life. Chronic migraine affects 1–2% of the general population, and about 8% of patients with migraine; it usually develops from episodic migraine at an annual conversion rate of about 3%. The chronification is reversible: about 26% of patients with chronic migraine go into remission within 2 years of chronification. The most important modifiable risk factors for chronic migraine include overuse of acute migraine medication, ineffective acute treatment, obesity, depression and stressful life events. Moreover, age, female sex and low educational status increase the risk of chronic migraine. The pathophysiology of migraine chronification can be understood as a threshold problem: certain predisposing factors, combined with frequent headache pain, lower the threshold of migraine attacks, thereby increasing the risk of chronic migraine. Treatment options include oral medications, nerve blockade with local anaesthetics or corticoids, and neuromodulation. Well-defined diagnostic criteria are crucial for the identification of chronic migraine. The International Headache Society classification of chronic migraine was recently updated, and now allows co-diagnosis of chronic migraine and medication overuse headache. This Review provides an up-to-date overview of the classification of chronic migraine, basic mechanisms and risk factors of migraine chronification, and the currently established treatment options.

> *"Throbbing, pulsating, stabbing. On a bad day, I have difficulty leaving my bed, let alone my home. I cannot go to work on almost half of a month, cannot enjoy playing with my children or even meeting friends for a coffee. There are weeks during which I barely manage to keep my place in order. I feel nauseous almost all of the time and everyday odours make me want to throw up. Darkness and silence are my friends of late. I basically don't recognize myself anymore."* Anonymous migraine patient, describing her illness

Grave, disabling and receiving little attention, chronic migraine is a disease of great detrimental influence on a patient's life. Disability rates and burden of disease among individuals with chronic migraine are considerable[1–5], and chronic migraine has a more-severe impact on socioeconomic functioning and quality of life[1,2,5,6] than does episodic migraine. About 3% of patients with episodic migraine report a very severe headache-related disability, as defined by the Migraine Disability Assessment Scale (also known as MIDAS), whereas in chronic migraine, this figure is as high as 25%[2]. Moreover, the proportion of patients with chronic migraine who report reduced household productivity, missed family activities and missed household work is two to three times higher than that of patients with episodic migraine[3]. The annual per-person costs of chronic migraine[7,8] — consisting of direct costs caused by health care utilization and treatment expenses (~30%) and indirect costs attributable to absenteeism from work and loss of productivity (~70%)[8] — are about fourfold higher than those attributed to episodic migraine.

For neurologists, acknowledging the severe effect of chronic migraine on socioeconomic functioning and quality of life, and adequately treating the disorder — and even more importantly, preventing progression from episodic to chronic migraine — is thus of vast importance. In this Review, we will outline the mechanisms and risk factors for migraine chronification, and discuss the treatment options for patients suffering from chronic migraine.

Changes in classification

According to the current diagnostic criteria of the International Classification of Headache Disorders (ICHD-3 beta), chronic migraine is defined as headaches on at least 15 days per month for more than 3 months,

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Key points

- Chronic migraine is a clearly defined subtype of migraine affecting between 1–2% of the general population, yet it receives little attention
- Chronic migraine usually develops from episodic migraine at a conversion rate of about 3% a year; the chronification is reversible
- Risk factors for migraine chronification include overuse of acute migraine medication, ineffective acute treatment, obesity, depression, low educational status and stressful life events
- The pathophysiology of migraine chronification can be understood as a threshold problem: certain predisposing factors combined with frequent headache pain lower the threshold of migraine attacks, thereby increasing the risk of chronic migraine
- Treatment options include pharmacological and nonpharmacological options and neuromodulation
- Prevention of chronification is essential, and requires adequate treatment of individual migraine attacks, early initiation of preventive medication and avoiding analgesic overuse

with at least eight headache days per month fulfilling the criteria for migraine headaches[9] (BOX 1). The diagnostic criteria for chronic migraine have changed slightly with the latest edition of the ICHD[9]: in contrast to earlier editions[10], coexisting analgesic overuse is no longer an exclusion criterion for the diagnosis of chronic migraine, but is now seen as one of the several potential causes for migraine chronification. As a result, patients with medication overuse should be given two diagnoses: chronic migraine and medication overuse headache (MOH). Moreover, in the previous version of the ICHD criteria, ICHD-II, all the 15 headache days per month had to be migrainous, whereas in the current version, only eight of the 15 headache days have to be and the other headaches may follow the criteria for tension type headache (BOX 1; TABLE 1).

This liberalization of the definition of chronic migraine has several important consequences. Firstly, the existence of migraine attacks of different severity is now acknowledged; lighter attacks can lack the vegetative hallmarks (accompanying photophobia, phonophobia, nausea, vomiting, headache exacerbation with physical exercise) and thus resemble tension-type headache. Secondly, the new definition increases the number of patients with the diagnosis of chronic migraine by up to threefold[11], which raises an important issue: studies in chronic migraine that use the new diagnostic criteria might well investigate a population that is clinically and pathophysiologically different from those investigated in older studies, not only because older studies by definition excluded patients with overuse of acute migraine medication, but also because the old criteria were more restrictive in terms of the type of attacks included as migrainous. The changes in migraine classification could lead to contradictory results between older and newer studies on chronic migraine; however, as criteria have only recently been changed, this does not yet affect many studies.

Epidemiology

Chronic headache with migrainous features accounts for about one-third of chronic headache (defined as headache on more than 180 days per year) in a general population[12]. The prevalence of chronic migraine is usually reported to be 1–2% in a general population[2,4,12,13], and about 8% among individuals with migraine[2]. Chronic migraine is almost three times more common in women than in men[2,4]. In women, the prevalence of chronic migraine peaks at the ages of 18–29 years and again at 40–49 years[2]. Primary chronic migraine is rare; most studies suggest that chronic migraine usually evolves from episodic migraine that gradually increases in attack frequency, with an annual progression rate of about 3%[14,15]. Age, female sex and low educational status are the most important nonmodifiable risk factors for migraine chronification[2,4,15,16]. People with chronic migraine are more likely to experience certain somatic and psychiatric comorbidities — such as depression, anxiety, and various respiratory and cardiovascular conditions — than are people with episodic migraine[17] (BOX 2).

Annually, about 3% of people with episodic migraine progress to chronic migraine[15]. The path to chronic migraine is obviously not a one-way-road — spontaneous or medically induced remission is possible and even common: about 26% of patients with chronic migraine remit within 2 years of the onset of chronic migraine[18].

Large-scale epidemiological studies have identified various factors associated with progression from episodic to chronic migraine, and also factors that promote migraine remission. Regarding the pathophysiological mechanisms underlying migraine chronification and remission, various studies point toward an understanding of migraine as a threshold problem. However, we are only beginning to understand the complex mechanisms leading to an increased migraine frequency and eventually to the development of chronic migraine.

Risk factors

Given that chronic migraine is a debilitating disorder and treatment response rates are rather low, identification and treatment or elimination of modifiable risk factors is of vast importance. The most important factors that confer increased risk of conversion from episodic to chronic migraine are overuse of acute migraine medication[15,19–26], ineffective acute treatment[27], obesity[28,29], depression[30], and stressful life events, such as divorce or being recently widowed[15].

Overuse of acute migraine medication

Probably the most important risk factor for migraine chronification is the overuse of acute migraine medication, defined as intake of analgesics on >15 days per month or triptans on >10 days per month[9]. Regular intake of acute migraine medication leads to an increasing headache frequency, which facilitates migraine progression[15,19–26]. Accordingly, discontinuation of acute medication overuse leads to substantial alleviation of headache and, in addition, facilitates effectiveness of prophylactic migraine medication[19].

Ineffective treatment of acute migraine

Ineffective acute treatment of migraine is a major risk factor for chronification. This fact cannot be stressed

Box 1 | **International Classification of Headache Disorders (ICHD) diagnostic criteria for episodic and chronic migraine**

ICHD-3: Episodic migraine

- A. At least five attacks fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity (for example, walking or climbing stairs)
- D. During headache at least one of the following:
  - nausea and/or vomiting
  - photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3: Chronic migraine

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

ICHD-II: Chronic migraine

- Headache fulfilling criteria C and D for '1.1 Migraine without aura' on ≥15 days/month for >3 months
- Not attributed to another disorder[1,2]
  - History and physical and neurological examinations do not suggest any of the disorders listed in groups 5–12,* or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such a disorder is present but headache does not occur for the first time in close temporal relation to the disorder.
  - When medication overuse is present and fulfils criterion B for any of the subforms of '8.2 Medication-overuse headache',* it is uncertain whether this criterion B is fulfilled until 2 months after medication has been withdrawn without improvement.

Diagnostic criteria for chronic migraine according to ICHD-3 (REF. 9) and IHS Classification ICHD-II (http://ihs-classification.org/en/), and for episodic migraine according to ICHD-3. Of note, in the current classification system (ICHD-3), a diagnosis of medication overuse headache does not excluded a diagnosis of chronic migraine (in ICHD-II, medication overuse headache had to be excluded before the diagnosis of chronic migraine). *As defined in the ICHD-3.

enough, as it could be so easily avoided: recent data in over 5,000 patients with migraine in the American Migraine Prevalence and Prevention Study showed that ineffective acute treatment doubled the risk for migraine chronification compared with effective acute treatment[27].

Although the exact mechanisms that underlie this association are not clear, less-effective acute treatment of migraine leads to a more frequent intake of acute medication and/or increasing dosages, which in turn leads to headache progression. Moreover, longer exposure to headaches might promote sensitization processes and thereby promote headache chronification (FIG. 1). The clinicians should, therefore, make an effort to find an effective acute treatment regime for migraine attacks and/or initiate a preventive therapy early in the disease process to prevent migraine chronification.

Obesity and metabolic syndrome

Another long-known risk factor for migraine progression is obesity[17,31], which has been shown to be associated with a higher migraine prevalence[32], increased number of headache days per month[28], an elevated risk for developing chronic daily headache with migrainous features[15] and transformation from episodic to chronic headaches[29]. Insulin resistance in association with obesity substantially increases the risk of chronic migraine[31]; indeed, this combination is more prevalent in women with chronic migraine than in those with episodic migraine (odds ratio 13.2)[31]. In women, metabolic syndrome is associated with a higher risk of chronic migraine and an even higher risk of MOH, even after adjusting for age, BMI and waist-to-height ratio[33].

The mechanisms that link obesity with an increased frequency of migraine attacks and, eventually, to development of chronic migraine, are not entirely understood. It is noteworthy that hyperleptinaemia, a condition that is often associated with the metabolic syndrome, has been shown to increase the susceptibility to cortical spreading depression in rats[34].

Of note, some studies have found intracranial hypertension without papilloedema to be common in patients diagnosed with treatment-refractory chronic migraine[35–37], particularly in patients with high BMI[37]. Therefore, in approximately 10% of patients diagnosed with chronic migraine, the chronic headache might in fact be attributable to elevated intracranial pressure without papilloedema[38]. This finding suggests that a lumbar puncture with CSF pressure measurement should be considered in patients with refractory chronic migraine and obesity.

Other risk factors

Other risk factors for migraine chronification include the presence of craniomandibular disorders[39], as well as a variety of psychological and personality factors. Among the psychological factors, depression is probably the most important risk factor for migraine chronification[30], whereas stressful life events[15], posttraumatic symptoms[40,41] and certain personality profiles are mostly of prognostic significance[42]. Moreover, one study has reported that increased severity of depression led to an elevated risk of episodic to chronic migraine transformation, and that presence of depression preceded migraine progression, thus suggesting a causal relationship[30].

To conclude, effective acute treatment of migraine attacks and early intervention to mitigate risk factors such as obesity and depression are obvious and effective tools to prevent progression from episodic to chronic migraine.

Pathophysiology

Chronic migraine as a threshold disorder

Migraine is a cyclic disorder in which susceptibility to certain attack-triggering stimuli increases shortly before an attack[43–50]. During the interictal state, the sensory

Table 1 | **Differential diagnosis of chronic migraine**

Headache type	Duration	Localization	Accompanying symptoms
Chronic migraine	• Not strictly defined: hours to days (or continuous) • Headache present on at least 15 days per month	Unilateral or bilateral	• Nausea and/or vomiting on at least 8 days per month • Hypersensitivity to light, noise or odours • Physical activity exacerbates headache
Hemicrania continua	Daily continuous headache that is responsive to indomethacin	Always one-sided, changing sides is rare	Exacerbations can display migrainous or autonomic features
Chronic tension-type headache	• Not strictly defined: hours to days (or continuous) • Headache present on at least 15 days per month	Typically bilateral/ holocranial, but unilaterality is not an exclusion criterion	• No more than one of the following: photophobia, phonophobia, mild nausea • No moderate or severe nausea or vomiting
New daily persistent headache	Daily continuous headache with a distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours	Not strictly defined	Not strictly defined

threshold is normal and susceptibility to attack-inducing stimuli is relatively low. Oscillating changes, probably originating from the limbic system[43], drive periodical decreases in sensory thresholds that increase the susceptibility to attack-inducing stimuli. If the threshold sinks beneath a certain value, certain physiological changes, such as stressful events, hormonal changes or changes in sleep rhythms can lead to a full migraine attack[49,50].

The process of migraine chronification can be seen as a threshold problem: general risk factors such as obesity, depression and stressful life events might lower the threshold for attack generation and thereby increase susceptibility to headache attacks. In addition, the increasing attack frequency shortens the interictal period so that the threshold might not restore to baseline level.

Box 2 | **Comorbidities of chronic migraine**

Somatic comorbidities

- Allergies
- Asthma
- Bronchitis, including chronic bronchitis
- Emphysema, chronic obstructive pulmonary disease
- Sinusitis
- Circulation problems
- Heart disease
- Hypertension
- Hypercholesterolaemia
- Stroke or cerebrovascular accident
- Ulcers
- Arthritis

Psychiatric comorbidities

- Anxiety
- Bipolar disorder
- Chronic pain (other than headache)
- Depression

The above mentioned diseases and symptoms are significantly more common in people with chronic migraine than in those with episodic migraine[17].

This theory is supported by the fact that high attack frequency itself is a risk factor for chronification[15,21]. Moreover, sensitization processes might increase the susceptibility to migraine-triggering factors and further lower the threshold (FIG. 1). Trigeminal cutaneous allodynia is more common in individuals with chronic migraine compared with those with episodic migraine[51], and indicates an increased risk of migraine chronification[52].

Of note, a high attack frequency and pain intensity are risk factors for the development of cutaneous allodynia in people with migraine[53] and might, thus, contribute to central sensitization. Patients whose acute headache medication is insufficient experience longer and more severe pain than do patients with effective acute medication[27]; this insufficient control of pain could lead to longer-lasting central sensitization and predisposes to migraine progression.

Pathophysiological mechanisms

Dysfunction of the descending pain-modulating network. The physiological mechanisms that underlie development of chronic migraine are not entirely understood. One commonly suggested explanation is that increased nociceptive processing leads to increased activity of the descending pain-modulating network, which results in elevated oxidative stress and subsequent dysfunction of pain modulation[54,55] that might further lower the threshold for developing new attacks. However, in a recent genetic study, no association could be found between chronic migraine and polymorphisms in genes associated with oxidative stress[56], and experimental evidence to support this theory is scarce: in fact, repetitive trigeminal nociceptive stimulation leads to activations in various parts of the descending pain-modulating system[57–59], including the periaqueductal grey (PAG). Moreover, neurons close to or within the PAG show increased activity during migraine attacks[43,46,60]. An increase in migraine attack frequency might, therefore, lead to more frequent activations within the PAG and ultimately to oxidative stress and dysfunction of the descending pain-modulating network[54]. Such dysfunction might, in turn, increase susceptibility towards

Cutaneous allodynia
In cutaneous allodynia, central sensitization to pain causes normally non-noxious tactile stimuli to skin (such as showering, shaving, brushing the hair or wearing tight clothing) to be experienced as painful.

Descending pain-modulating network
A top-down pain modulation system in which brain areas includingthe frontal lobe, hypothalamus and amygdala project on periaqueductal grey, which controls the transmission of nociceptive information in the spinal cord.

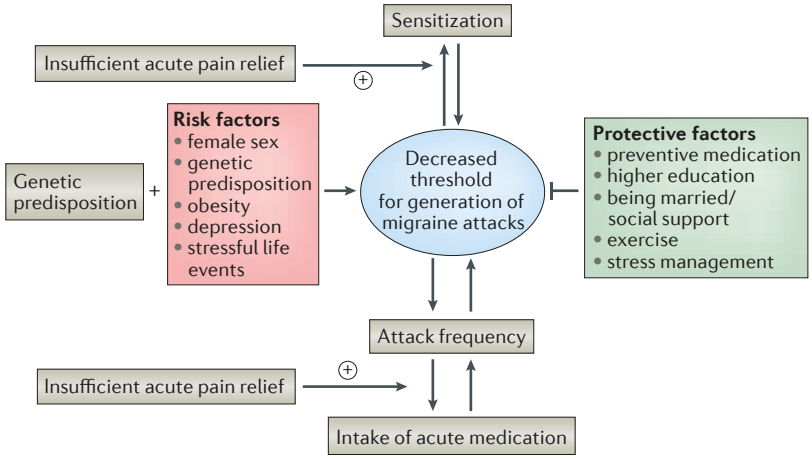

Figure 1 | **Multiple factors contribute to migraine chronification.** Genetic and nongenetic risk factors contribute to the threshold for the generation of migraine attack. Insufficient acute pain relief leads to sensitization, which can further lower migraine attack threshold. Increased migraine attack frequency itself also lowers attack threshold; moreover, it increases the intake of acute medication, which can decrease the efficacy of acute pain relief and further predispose to migraine chronification. By contrast, preventive medication and protective factors related to behaviour and lifestyle heighten the threshold and thereby inhibit migraine chronification.

physiological and environmental factors that precipitate migraine attacks, further lowering the threshold for attack generation.

Altered trigeminal and autonomic system function. Various biomarkers of functions of the trigeminal and autonomic systems differentiate the interictal state of chronic migraineurs from the interictal period of episodic migraineurs. In particular, interictal levels of calcitonine gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are higher in chronic than in episodic migraine[61,62], which suggests altered interictal activity of the trigeminal and cranial autonomic system in chronic migraineurs.

Thalamic contribution to central sensitization. Another brain structure that seems to be involved in the development of cutaneous allodynia in migraine[63], and might therefore contribute to migraine chronification, is the thalamus. That many preventive therapeutics in chronic migraine, such as topiramate[64], valproate[65] and CGRP-receptor antagonists[66], all modulate the thalamus further corroborates its role in migraine chronification. Research on animal models has shown that many preventive therapeutics in chronic migraine, such as topiramate[64], valproate[65] and CGRP-receptor antagonists[66], modulate thalamic activity as a response to trigeminal nociceptive input, further corroborating the role of thalamus in migraine chronification.

Medication-associated central sensitization. Apart from the effects of frequent exposure to pain within the trigeminal system, insufficient acute pain relief[27] and the resulting increased intake of acute headache medication might lead to migraine chronification via another mechanism. In animal experiments, daily intake of triptans led to central sensitization, as measured by increased cutaneous allodynia[67], increased susceptibility to cortical spreading depression[68,69] and disruption of brain networks, as assessed by resting-state functional MRI[69]. Frequent intake of acute migraine medication itself might, thus, lead to migraine chronification.

Protective factors. Various protective factors can heighten the threshold for migraine attacks. Such factors, including physical exercise, stress management, and preventive medication[70], might increase the threshold for attack generation and thereby counteract the chronification process and prevent development of chronic migraine.

Treatment

Once chronic migraine is established, finding an appropriate and beneficial treatment is challenging. The first step is the rigorous control of predisposing factors, of which the foremost is overuse of acute medication.

The best treatment for chronic migraine with acute medication overuse is subject to debate. The guideline of the European Federation of Neurological Sciences (EFNS) recommends early discontinuation of acute medication overuse (or tapering down the overused medication) combined with a prophylactic migraine treatment[71]. By contrast, some authors advocate — at least for patients with uncomplicated MOH (short duration of MOH, acute medication used at relatively modest doses, minimal psychiatric symptoms, no history of relapse after withdrawal[72]) — initial withdrawal of the overused medication alone before determining whether prophylactic treatment is still needed after 2–3 months of withdrawal [72]. Discussion between the two options continues, as independent trials[73–76] investigating preventive treatment in chronic migraine have shown that patients with and without MOH benefited from preventive medication without explicit detoxification. The lack of randomized controlled trials (RCTs) specifically designed for comparison of withdrawal alone, early prophylaxis alone, and withdrawal plus early prophylaxis means that making definite, evidence-based recommendation for MOH treatment is not possible.

According to a systematic review of available studies of MOH, published in 2016, there is currently more evidence for withdrawal or tapering in combination with early prophylaxis than there is for withdrawal alone[77]. Educating patients about the detrimental effects of acute medication overuse and the need for discontinuation of the overused substances is crucial to reduce the risk of relapse.

In addition to the strict control of predisposing factors, various other treatment options exist for chronic migraine, including the standard pharmacological treatment with migraine prophylactic drugs, injections with botulinum neurotoxin A, as well as invasive and noninvasive neuromodulation and neurostimulation therapies (TABLE 2).

Standard pharmacological treatment

The treatment of chronic migraine with only pain killers or specific headache medication taken after the attack

Table 2 | **Treatment of chronic migraine — evidence, benefits and limitations**

Treatment	Evidence*	Benefits	Limitations
Pharmacological and other preventative treatments			
Topiramate	>1 RCT	• Noninvasive • Cost-effective	In rare cases, rather severe psychological and cognitive adverse effects, such as aggravation of depressive symptoms
Candesartan, amitriptylin, valproate, gabapentin, tizanidin	≥1 RCT for each drug	• Noninvasive • Cost-effective	Drug-specific adverse effects and contraindications
Memantine, pregabalin, milnacipran, atenolol, zonisamide, duloxetine	Small, partly open- label studies and small case series	• Noninvasive • Cost-effective	• Drug-specific adverse effects and contraindications • Low level of evidence
Botulinum neurotoxin A	>1 RCT + a meta-analysis	Well tolerated; might be beneficial in specific patient subpopulations and in patients with pharmacologically intractable migraine	• Usual risks of intramuscular injections: pain, swelling, infection, bruising, ptosis, weakness of head posture • Only modest overall benefits • Expensive
Neuromodulation			
GON blockade	≥1 RCT	• Relatively well tolerated • Might be beneficial in patients with otherwise intractable migraine	• Adverse effects: pain, swelling, infection, bruising, alopecia areata (if corticosteroids are administered) • The two conducted RCTs had contradictory findings
ONS	≥1 RCT + a meta-analysis	Beneficial in patientswith otherwise intractable migraine	• The treatment is invasive and has severe long-term complications: infection, skin erosion, lead migration and/or breakage, chronic pain related to stimulator device or stimulation • Modest overall effect size
SONS	Small case series	Might enhance effects of ONS	• Severe complications similar to what is seen with ONS • Very low level of evidence • For chronic migraine, only data available is from combined invasive SONS + ONS
tVNS	≥1 RCT	Noninvasive	Currently no knowledge about long-term effects and consequences
High-frequency rTMS	One small open label study	Noninvasive	Very low level of evidence

*Evidence is rated specifically in the context of chronic migraine; although evidence for the efficacy in episodic migraine is high for many of these drugs, this is not usually the case for the efficacy in chronic migraine. GON, greater occipital nerve; ONS, occipital nerve stimulation; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SONS, supraorbital stimulation; tVNS, transcutaneous vagal nerve stimulation.

has begun is ineffective and should be avoided because it requires regular intake of acute medication, which predisposes to MOH. Instead, the aim of the treatment needs to be prevention of migraine attacks.

The standard preventive treatments include betablockers, topiramate or valproate. All of these substances have been shown to be superior to placebo in the prophylaxis of migraine in general[78–87], but only a few have been specifically investigated for their effectiveness in chronic migraine.

Topiramate is the only drug that has been investigated in this context in more than one double-blinded RCT. It reduces headache days effectively and is relatively well tolerated: paraesthesia and fatigue were the most common adverse effects[73,88–90]. Topiramate substantially improves various measures of quality of life[90,91] and reduces the frequency of migraine-accompanying photophobia, phonophobia and vomiting[90].

Furthermore, topiramate has been suggested to prevent progression from episodic to chronic migraine[92] and to possibly induce remission from chronic to episodic migraine[93], although in the topiramate intervention to prevent transformation of episodic migraine (INTREPID) trial, progression from high-frequency episodic migraine to chronic daily headache could not be prevented by 100 mg topiramate per day for 26 weeks[94]. Another open-label study suggested that combining topiramate with betablockers brings further benefit to patients with otherwise refractory migraine, including refractory chronic migraine[95]. By contrast, an RCT investigating the use of propranolol with topiramate for chronic migraine showed no benefit of the combination over topiramate alone[96]. Topiramate has also been reported to alleviate chronic migraine in patients with acute medication overuse without withdrawal of the overused medicine[73]. To date, topiramate is the only oral drug for which high-quality evidence indicates efficacy and safety specifically in chronic migraine. However, given the adverse effects of topiramate and the high comorbidity rates of chronic migraine and depression, it might not be the drug of choice in chronic migraine patients with comorbid depression.

Other preventive medications that have each been shown to be effective in chronic migraine in a single

RCT are candesartan[97], amitriptyline[98], sodium valproate[99], gabapentin[100] and tizanidine[101]. Smaller, mostly open-label studies provide support for the effectiveness of memantine[102], pregabalin[103], milnacipran[104], atenolol[105] and zonisamide[106]. In one small, open-label study, duloxetine improved the number of headache days per week and depressive symptoms in 30 patients with chronic daily headache and comorbid depressive disorder[107]. One possible mechanism of action of these drugs is the suppression of cortical spreading depression: chronic, but not the acute, use of topiramate, valproate or propranolol has been demonstrated to reduce cortical spreading depression in rats[108].

Some patients with chronic migraine do not show improvement with the above discussed oral preventive medications. For patients with pharmacologically intractable migraine, other well-established therapeutic options exist and emerging therapies such as antibodies against CGRP or its receptor are promising, although not yet approved for clinical use[109]. Among the established therapies, injections with botulinum neurotoxin A and neuromodulatory methods can offer help to patients with otherwise intractable migraine.

Botulinum-neurotoxin A

Efficacy in chronic migraine with or without MOH. Botulinum neurotoxin A (BoNT-A) is, to date, the only treatment that is approved specifically for chronic but not episodic migraine. In two large-scale phase III RCTs, called Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2, BoNT-A at a minimum dose of 155 U was shown to effectively reduce total headache days in chronic migraine patients with or without acute medication overuse[74–76] when injected every 12 weeks in frontal, temporal, occipital and neck muscles in a standardised, so-called PREEMPT-scheme. Treatment effects were observed at 24 weeks[74–76] and 56 weeks[110]. These results have since been replicated in further studies[111–113]. A systematic review and meta-analysis revealed small to modest benefits of treatment with BoNT-A in chronic daily headache and chronic migraine[114]. Subsequent comparisons with prophylactic standard medication showed BoNT-A to prevent the development of chronic migraine with efficacy similar to that of topiramate and amitriptyline[98,115]. Interestingly, BoNT-A was also effective for chronic migraine patients with chronic medication overuse[116,117], and reduced depressive symptoms in patients with chronic migraine and comorbid depression[118,119]. However, in one RCT, BoNT-A as a prophylactic treatment in MOH without withdrawal of the overused medicine failed to reduce headache days per 28 days[120].

Long-term data on safety, efficacy and tolerability of BoNT-A do not yet exist, but ongoing studies, such as the Chronic migraine OnabotulinuMtoxinA Prolonged Efficacy open Label (COMPEL) study, aim to investigate the long-term safety, efficacy and tolerability of nine cycles of repetitive BoNT-A injections administered every 12 weeks[121].

Recent studies have shed some light on the potential actions through which BoNT-A alleviates headache. Given that sensitization of central and peripheral nociceptors is assumed to be one of the key mechanisms of migraine chronification, the effect of BoNT-A on sensitized nociceptive afferents is of particular interest. BoNT-A was shown to reverse sensitization effects on nociceptive meningeal C-fibres in rats[122,123], possibly owing to uptake and axonal transport of BoNT-A by peripheral nociceptors and consecutive transcytosis to dural afferents, where it might inhibit CGRP release[123]. In line with this hypothesis, BoNT-A decreased interictal CGRP levels in individuals with chronic migraine[124,125] and alleviated cranial allodynia, indicating reduced central sensitization[126]. BoNT-A also reduced the expression of proinflammatory proteins in cultures of the rat trigeminal ganglion, and might thereby suppress neurogenic inflammation[127]. These findings suggest that BoNT-A might have benefits that are not explained by its very well understood neuromuscular effects and that might make it particularly effective in reversing the state of central sensitization.

Neuromodulation

Although the first-line treatment in chronic headache is pharmacological, the above discussed drugs have limited efficacy in relieving headache and can produce adverse effects[128]. Nonpharmacological therapies and management, such as biofeedback[129], exercise[130,131], cognitive therapies[132], stress management[133], manual therapy[134] and electrical stimulation techniques (so-called electroceutics)[135] have also been used to treat chronic migraine, but few well-controlled clinical trials have evaluated their efficacy.

Neuromodulatory methods used for the therapy of chronic migraine can be divided into methods that modulate peripheral nerves and methods that modulate parts of the CNS. Peripheral neuromodulation methods include pharmacological blockade of the greater occipital nerve (GON)[136] and electrical stimulation of occipital nerves[137–141], supraorbital nerves[142–144] or the vagal nerve[145–150]. Central neuromodulation methods include transcranial magnetic stimulation (TMS)[48,151,152] and transcranial direct current stimulation (tDCS)[153].

Pharmacological blockade of the greater occipital nerve. In contrast with the more invasive neurostimulation techniques, pharmacological blockade of the greater occipital nerve (GON) is a relatively well-tolerated treatment[136]. Data on its effectiveness as preventive treatment for chronic migraine, however, are inconclusive: a double-blinded RCT in a group of patients with either episodic or chronic migraine did not find significant differences between active and placebo treatment[154], whereas another double-blinded RCT suggests that GON blockade with bupivacaine is effective for prophylaxis of chronic migraine[155].

Occipital nerve stimulation. In contrast with pharmacological GON blockade, electric occipital nerve stimulation (ONS) is an effective therapy often recommended for pharmacologically intractable chronic migraine, and has been in clinical use for over 10 years[139,156]. Safety and

Biofeedback
Monitoring of bodily function and responses with biofeedback, such as electromyogram, can help relieve muscle tension and thereby alleviate headache.

Manual therapy
In patients with headache, manual therapy, also known as manipulative therapy — including massage therapy, physiotherapy and spinal manipulative therapy — aims to alleviate headache by relieving muscle tension and increasing mobility of the cervical spine.

Electrical stimulation
Therapeutic options using electrical current, voltage or induction of currents by magnetic fields to influence nerve or muscular functioning.

efficacy of this treatment have been confirmed in several trials[137–141,157], although it should be noted that two RCTs investigating ONS efficacy in migraine (including chronic migraine) failed to meet their primary endpoints[138,158], defined as a difference in percentage of responders (a minimum of 50% reduction in mean daily visual analogue scale scores)[138] or the change in headache days per month at 12 weeks after implantation[158]. A 2015 systematic review and meta-analysis revealed a modest overall effect size of ONS in chronic migraine[159]. Despite promising efficacy rates in otherwise intractable chronic migraine, rather severe long-term complications, such as infection, skin erosion, lead migration and/or breakage and chronic pain related to the stimulator or stimulation are a significant problem of this approach[137,138,140,141]. Electrical stimulation of the occipital nerve should certainly only be used after careful consideration of possible risks and benefits.

Supraorbital stimulation. Recently, electric supraorbital stimulation (SONS) has been shown to significantly reduce headache days per month compared with sham stimulation in a trial that included patients with both episodic and chronic migraine[142]. The combination of invasive SONS with ONS has been reported to prevent attacks in chronic migraine more effectively than ONS alone[143,144].

Vagal nerve stimulation. On the basis of small case series reporting notable headache relief after invasive vagal nerve stimulation (VNS)[147–149], different devices for noninvasive transcutaneous VNS (tVNS) have been developed. A double-blinded RCT showed auricular transcutaneous stimulation of the vagal nerve at 1 Hz to be effective in reducing headache days per 28 days in chronic migraine[145]. In addition, an open-label study of cervical tVNS found a substantial reduction in frequency, intensity and duration of migraine attacks in both episodic and chronic migraine[146]. tVNS is, therefore, a promising tool in the acute treatment of migraine attacks that occur with a high frequency, and possibly also in chronic migraine[150]. Although both invasive and noninvasive VNS have been shown to inhibit cortical spreading depression in rats[160], the mechanism by which VNS ameliorates migraine are not entirely understood.

Central neuromodulatory techniques. The efficacy of central stimulation methods, such as TMS and tDCS, in migraine have yet not been investigated in larger-scale, double-blinded RCTs. A small unblinded pilot study of 11 patients suggested that high-frequency repetitive TMS (rTMS) of the dorsolateral prefrontal cortex (DLPFC) ameliorates chronic migraine (attack frequency, headache index and acute medication intake)[161], whereas low-frequency rTMS was no more effective in migraine attack prophylaxis than placebo[162]. Single-pulse TMS has only been used to treat acute migraine attacks in episodic migraine[151]; its possible benefits in chronic migraine[152] remain unknown. A study assessing the efficacy of tDCS in migraine did not show tDCS to have a significant effect on headache frequency compared with placebo[153]. Central stimulation methods have not yet been studied sufficiently to support efficacy and make treatment recommendations for chronic migraine.

Conclusions and future perspectives

Chronic migraine is a rare but disabling disorder with grave socioeconomic consequences. Various risk factors for migraine chronification have been identified, but the pathophysiological mechanisms remain poorly understood. Understanding the pathophysiological mechanisms that lead to the conversion from low-frequency episodic migraine attacks to high-frequency attacks and ultimately to chronic migraine is mandatory for the development of new treatments that could prevent or reverse the chronification process. Although several therapeutic options are available, their efficacy is still far from sufficient. Important data are still lacking: most importantly, drugs used as standard treatment for episodic migraine should be systematically investigated for their effectiveness in chronic migraine. Moreover, although some studies support the use of peripheral neurostimulation methods in chronic migraine, the majority of the neurostimulation-based and neuromodulatory treatment options need further investigation. The next years will be inspiring for the field, as current research areas are being extended and novel areas are covered, ultimately broadening our understanding of the complex syndrome of chronic migraine.

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Both authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.

Competing interests statement
The authors declare no competing interests.

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ToC blurb

000 **Chronic migraine: risk factors, mechanisms and treatment**

Arne May and Laura H. Schulte

About 2% of the general population and 8% of people with migraine have chronic migraine, defined as ≥15 headache days per month. The condition can be disabling and has a severe impact on quality of life, yet it receives little attention. This Review summarizes the current understanding of the risk factors and pathophysiological mechanisms of migraine chronification, and discusses strategies to prevent and treat the disorder.