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REVIEW

Current Prophylactic Medications for Migraine and Their Potential Mechanisms of Action

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Abstract

A relatively high number of different medications is currently used for migraine prevention in clinical practice. Although these compounds were initially developed for other indications and differ in their mechanisms of action, some general themes can be identified from the mechanisms at play. Efficacious preventive drugs seem to either suppress excitatory nervous signaling via sodium and/or calcium receptors, facilitate GABAergic inhibition, reduce neuronal sensitization, block cortical spreading depression and/or reduce circulating levels of CGRP. We here review such mechanisms for the different compounds.

Keywords Migraine prevention · Mechanism of actions · Cortical spreading depression · β blockers · Antiepileptic drugs · Antidepressants · Botulinum toxin

Introduction

Migraine is a disorder characterized by recurrent attacks of headache with moderate to severe intensity, often accompanied by photophobia, phonophobia, and nausea. The headache can aggravate with physical activity, is often unilateral, and may have a throbbing character. The underlying pathophysiology of migraine is only partly understood to date. Malfunctioning of brain areas and channels, which modulate the excitability of nociceptive brain circuits as well as central sensitization are thought to play a role [1], the latter especially in the transformation from episodic to chronic migraine [2]. Migraine aura is thought to relate to cortical spreading depression (CSD), a slow wave of depolarization propagating across the cortex, and some authors have suggested that CSD is also implicated in the pathogenesis of migraine headache [3], although this remains controversial [4]. Calcitonin gene-related peptide (CGRP) is a neuropeptide, which appears firmly connected to migraine pathogenesis. Systemic levels of this strong vasodilator rise during migraine attacks and while they fall thereafter, they appear to remain elevated even interictally as compared to healthy subjects [5]. Interestingly, endogenous CGRP release has been shown also during experimentally induced CSD in cortical rat slices. Intravenous injection of CGRP can trigger migraine attacks.

Patients affected by frequent attacks may need preventive treatment in order to reduce the frequency and severity of attacks. A number of mostly oral pharmacological treatments have been evaluated and are recommended for migraine prevention [6, 7]. Thereof, propranolol, metoprolol, flunarizine, topiramate, and valproate were considered first line treatments in the EFNS guideline for the prevention of migraine [7].

One can generally expect a 50% reduction in attack frequency in every second patient with these compounds, if they are taken regularly. Just as our understanding of migraine pathophysiology is limited in general, the mechanisms of action of such preventive compounds are also understood only in part and for the currently licensed compounds, the clinical development did typically not go from bench to bedside, but rather the opposite route. The majority of available treatments were repurposed for migraine prevention after initial development for other indications such as arterial hypertension, epilepsy, and depression.

In this review, we will discuss potential mechanisms of action of currently available treatment options for migraine prevention and cover agents for both episodic as well as

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chronic migraine. Because of space limitations, the focus will be on agents that are either licensed for migraine specifically or recommended in international treatment guidelines [7]. Novel compounds specifically targeting the CGRP pathway will be discussed in another dedicated article in this special issue (Reuter et al. Neurotherapeutics). Nonpharmacological migraine prevention strategies are very important in clinical practice [8, 9] but not covered in this article. We refer the interested reader to the article by Puledda and Shields in this issue (Puledda and Shields. Non-pharmacological approaches for migraine. Neurotherapeutics).

General Preventive Treatment Principles and Mechanisms of Action

The recommendations for when to use pharmacological migraine prevention vary greatly between published treatment guidelines. As a general principle, migraine prevention should be considered when attacks affect quality of life and is indicated in roughly one third of migraine patients [10]. Comorbidities should be taken into account when considering and selecting a migraine preventive.

Although the different compounds used for migraine prevention clearly act at different receptor sites or channels, it has been suggested that they may modulate common pathways or mechanisms implicated in migraine pathogenesis. For example, several migraine preventives such as propranolol, topiramate, valproate, amitriptyline [11], and flunarizine [12], but also CGRP antagonists [13] have been shown to suppress CSD. Other compounds have been suggested to reduce neuronal sensitization [14, 15]. Moreover, some of the available migraine preventives may reduce levels of circulating neuropeptides such as CGRP [16] and of "hyperalgesic" cytokines such as tumor necrosis factor α, interleukin-1β, and interleukin 6 [17], although it remains unclear whether such effects directly relate to the medication or indirectly relate to the reduction of attacks.

In the following, we will summarize the current understanding of mechanisms of action of specific agents or groups of agents (Table 1).

β-Blockers

Although all beta-adrenergic blockers (BABs) are competitive inhibitors of β-receptors, they may differ with regard to receptor binding (i.e., β1-selectivity and partial agonistic activity) and pharmacokinetic properties [18]. BABs with intrinsic sympathomimetic activity (e.g., acebutolol, alprenolol, oxprenolol, and pindolol) are not effective for migraine prevention [19]. Clinical studies support the efficacy of propranolol (80–240 mg/day), timolol (20–30 mg/day), bisoprolol (5 mg/day), and metoprolol (200 mg/ day) in migraine preventive treatment [20–22]. Atenolol and nadolol also have a moderate effect in reducing migraine attack frequency [19, 23].

The mechanisms of action of BABs in migraine prevention are not completely understood. Inhibition of β1-mediated effects could be considered the main mechanism of action. Indeed, blockade of β1 receptors could inhibit noradrenaline (NA) release and tyrosine hydroxylase activity, the rate-limiting step in NA synthesis [24]. Moreover, propranolol reduces the neuronal firing rate of noradrenergic neurons of the locus coeruleus [25]. Interestingly, BABs also regulate the firing rate of periaqueductal gray matter (PAG) neurons via a GABA-mediated action [26]. Both these effects may contribute to the antimigraine action of BABs. Recent findings in an animal model of trigeminovascular activation showed that propranolol exerts its prophylactic action, at least in part, by interfering with the chronic sensitization processes in the rostral ventromedial medulla and locus coeruleus, and by counteracting the facilitation of trigeminovascular transmission within the trigeminocervical complex [15].

Some BABs may also interact with the serotonergic system by blocking 5-HT_{2C} and 5-HT_{2B} receptors [27–29]. Since 5-HT plays a pivotal role in the pathophysiology of migraine, the BABs-induced effects on this neurotransmitter could account for their prophylactic action on migraine. Moreover, PET studies have supported the possibility that BABs also affect 5-HT synthesis, which is altered in migraine patients [30].

Propranolol inhibits nitric oxide production by blocking inducible nitric oxide synthase (NOS). Propranolol also inhibits kainite-induced currents and is synergistic with N-methyl-D-aspartate blockers, which reduce neuronal activity and have membrane-stabilizing properties [31].

In a double-blind randomized study, it was shown that propranolol and metoprolol decreased VEP amplitude in migraine patients. This action was associated with a better clinical response to the prophylactic treatment [32]. Therefore, it could be hypothesized that BABs have a significant effect on the excitability of the visual system (and probably more generally the cortex) in migraine patients. In migraine patients, the effect of BABs on auditory evoked cortical potentials was correlated with a reduction of migraine attack frequency [33]. This effect of BABs on auditory evoked cortical potential could be due to a modulatory action on serotonergic transmission [34].

Other neurophysiological studies analyzed the contingent negative variation, a slow event-related potential measuring cortical information processing. This potential is increased in amplitude, lacks habituation and is normalized by BABs in association with a clinical improvement in migraine [35]. All these clinical neurophysiological studies support the hypothesis that BABs exert their prophylactic action in migraine by influencing cortical information processing and cortical excitability possibly via NA and 5-HT systems [34, 36, 37].

Table 1 Preventive treatments used in migraine and their potential mechanisms of action

Drug	Dose	Potential mechanisms of action
β-Blocker		
Propranolol	40 mg to 120 mg b.d.	Inhibition of nitric oxide synthase Interaction with the serotonergic system
Metoprolol	25-100 mg twice daily	Inhibition of thalamic relay neurons Block of central sensitization
Anticonvulsants		
Valproate	400-600 mg twice daily	Block of voltage-dependent sodium channels Block of low-threshold T-type calcium ion channels Suppression of proteinkinase C (glumatatergic neurotransmission) Inhibition of the NF-κB pathway (in an animal Downregulation of CGRP expression
Topiramate	50-200 mg/day	Block of voltage-dependent sodium channels and high-voltage-activated L-type calcium channels Inhibition of glutamate-mediated excitatory neurotransmission Facilitation of GABA-A-mediated inhibition. Inhibition of carbonic anhydrase activity Reduction of CGRP secretion from trigeminal neurons
Calcium channel blocker		
Flunarizine	5-15 mg daily	Block of voltage-gated sodium channels Reduction of neuronal excitability and normalization cortical hyperexcitability D2 antagonism
Antidepressants		
Amitriptyline	25 mg to 75 mg nocte (typically start with 10 mg)	Inhibition of serotonin/noradrenaline reuptake pump Facilitation of endogenous pain control mechanisms
Fluoxetine	20 mg daily	Block of serotonin reuptake reversible 5-HT2C receptor blocker
Onabotulinumtoxin A	155 units at fixed sites (+ additional units "follow the pain")	Block of peripheral and central sensitization Relaxation of head and neck muscles
Renin angiotensin system (RAS) modulating compounds		
Lisinopril	20 mg daily	Modulation of vasoreactivity, alteration of sympathetic tone, and promotion of degradation of proinflammatory factors Modulation of endogenous opioid system Reduction of angiotensin-mediated
Candasartan	16 mg daily	Vasoconstriction Increase of sympathetic discharge Release of adrenal catecholamines Modulation of cerebral RAS influencing neuronal, astrocytic, and endothelial cell activity
Nutraceuticals		
Riboflavin	400 mg daily	Effect on mitochondria?
Coenzyme Q10	100 mg three times daily or 75 mg twice daily	Effect on mitochondria?
Butterbur	50 to 75 mg twice daily	Anti-inflammatory action through inhibition of cyclooxygenase-2 and
Feverfew	6.25 mg three times daily	Vasodilatory effects through inhibition of L-type voltage-gated calcium channels Inhibition of Fos-induced activation of trigeminal nucleus caudalis Partial agonist activity at TRPA1 channels Antinociceptive and anti-inflammatory effects
Magnesium	600 mg	Effect on enzymatic function/mitochondria?

Cortical spreading depression (CSD) could also represent a target for BABs in migraine. In an experimental model, it was observed that treatment with propranolol suppressed retinal spreading depression [38]. Moreover, treatment with propranolol blocked CSD in rats, without altering regional cerebral blood flow and systemic arterial blood pressure [39].

Finally, it has also been hypothesized that BABs exert some of their therapeutic effects in migraine through an action at the ventroposteromedial thalamic nucleus, which represents a relay of trigeminal sensory input to the primary somatosensory cortex. Considering the complex and widespread nature of the sensory disturbance in migraine, and neurophysiological findings, a possible thalamic involvement in the mechanisms of action of BABs represents a fascinating hypothesis [40, 41].

Antiepileptics

Several antiepileptic drugs (AEDs) acting at different pre- and post-synaptic sites have been studied and proven effective for migraine prevention with the best clinical trial evidence in terms of migraine preventive action being available for topiramate and valproate [7]. However, clearly not all antiepileptics are similarly efficacious in migraine as in epilepsy. Those compounds that possess a rather specific/narrow mechanism of action typically seem to be less efficacious in migraine. As an example, oxcarbazepine was not superior to placebo in reducing the number of migraine attacks in a double-blind trial [42]. Interestingly, oxcarbazepine did also not reduce the frequency of CSD in animal experiments [43], while topiramate and valproate (and also other effective migraine preventives) did [11], suggesting this might be useful as a predictive model for evaluating novel migraine treatments.

Topiramate has been proven efficacious both in episodic as well as chronic migraine and is licensed for migraine prophylaxis in many countries. Topiramate is a "dirty drug" and blocks multiple channels such as voltage-dependent sodium channels and high-voltage-activated L-type calcium channels [44]. It has also been shown to inhibit glutamate-mediated excitatory neurotransmission and facilitate GABA-A-mediated inhibition. Topiramate also inhibits carbonic anhydrase activity [45]. Moreover, it has been shown that topiramate can reduce CGRP secretion from trigeminal neurons in response to depolarizing stimuli [46]. It is currently unclear which of the noted mechanisms is key for topiramate's effect in migraine prevention. Interestingly, CGRP plasma levels were shown to be unaltered by low-dose (50 mg per day) topiramate treatment in a small migraine trial, providing some preliminary evidence that topiramate effect may be independent from the CGRP pathway in humans [47].

Just like topiramate, there are multiple mechanisms at play by which valproate may improve migraine frequency. Similar to topiramate, valproate also enhances GABAergic inhibition and blocks excitatory ion channels [44]. The exact mechanisms by which this is achieved differ between the two drugs, though. Valproate blocks the degradation of GABA, hence increasing GABA levels in axons and glia cells. It blocks voltage-dependent sodium and low-threshold T-type calcium ion channels [44]. Furthermore, valproate can suppress proteinkinase C, a regulator of the glutamatergic neurotransmission [48]. A more recent study identified the inhibition of the NF-κB pathway (in an animal model of migraine using nitroglycerin triggering) as an additional potential mechanism of action in migraine [49]. In the same preclinical study, valproate also downregulated the expression of CGRP in brain tissue.

Calcium Antagonists

Several calcium antagonists have been used for migraine prevention since the 1980s [50]. In this regard, flunarizine (usually used at daily doses of 5–10 mg [15]) is the best studied compound and licensed for this indication in many countries (although not available in the USA). Verapamil and the antihistaminergic drug cinnarizine are alternatives (e.g., in refractory migraine cases or when flunarizine is not available) that also act at calcium channels. However, both latter drugs are off-label for migraine treatment and the evidence in terms of efficacy is much more scarce than for flunarizine.

Flunarizine is a nonselective calcium antagonist, which has also been shown to block voltage-gated sodium channels [51, 52]. Action at these two sites may reduce neuronal excitability and normalize cortical hyperexcitability in migraine. Furthermore, flunarizine acts as a D2 dopamine antagonist and has in this regard been shown to possess (at high doses) comparable antipsychotic efficacy as haloperidol [53]. It has also been shown that flunarizine can reduce the number and duration of CSD waves [12]. Furthermore, it has been suggested that flunarizine can alleviate CSD-induced mitochondrial injury [12]. Finally, flunarizine has also been shown to increase leptin levels [17], which have been suggested to reflect leptin resistance, which may potentially explain the treatment-related weight gain [54].

Antidepressants

There are more than three placebo-controlled trials each supporting the superiority of the tricyclic antidepressant amitriptyline and of the selective serotonin reuptake inhibitor (SSRI) fluoxetine over placebo for migraine prevention [55]. This effect occurs in the absence of depression and antimigraine effects are typically observed at doses lower than in depression. Less evidence is available for other antidepressants, although at least other tricyclics and the selective

serotonin-norepinephrine reuptake inhibitor venlafaxine [56] are probably also effective for migraine prophylaxis.

Amitriptyline is a mixed serotonin-norepinephrine reuptake pump inhibitor and thereby thought to facilitate descending noxious inhibition, i.e., endogenous pain control mechanisms descending from the brainstem to the trigeminal nucleus caudalis and the spinal cord. Alpha2-adrenoceptor blockade has been shown to block the antinociceptive effect of amitriptyline [57] and hence at least part of amitriptyline's efficacy is thought to be mediated by α2-agonism, but multiple other channel and receptor effects of amitriptyline are known. As such, amitriptyline is thought to act as a sodium channel blocker and also has antimuscarinic and antihistaminic effects. There is also an interaction with the endogenous adenosine system and it has also been shown to suppress cortical spreading depression [11]. As with other preventive migraine medications, it remains unclear which mechanism is key and probably the multiplicity of synergistic effects in multiple pathways explains the clinical efficacy (as well as the broad side-effect profile).

Fluoxetine is a more targeted substance that (relatively) selectively blocks serotonin reuptake from the synaptic cleft leading to increased serotonin levels. Noradrenaline reuptake is inhibited only at higher doses. Furthermore, fluoxetine is a competitive, reversible 5-HT2C receptor blocker [58]. The 5-HT2C mechanism is shared with the old antiheadache drug methysergide and a receptor gene polymorphisms of 5-HT2C has been shown to modulate migraine susceptibility (in a Turkish population) [59]. Hence this receptor blockade may explain (part) of the efficacy of fluoxetine.

Onabotulinumtoxin A

Trials investigating the efficacy of onabotulinumtoxin A in episodic migraine and chronic daily headache have yielded inconclusive results, partly because of methodological limitations regarding the injection paradigm and the dose [60–64]. The efficacy of onabotulinumtoxin A has been demonstrated for chronic migraine in the clinical programme called REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) [65–67]. In the two phase III trials of the PREEMPT program (PREEMPT1 and 2), a minimum dose of 155 U (up to a maximum allowed dose of 195 U) of onabotulinumtoxin A was injected into head and neck muscles of each patient. Nowadays, onabotulinumtoxin A is marketed in several countries with an indication for chronic migraine.

Onabotulinum toxin A (BoNT-A) is a protein complex produced by the gram-positive, anaerobic bacterium *Clostridium botulinum* [68]. There are seven serotypes of botulinum toxin [68], the serotype A has been used in human therapy since 1980 when Scott proposed BoNT-A injection into extraocular muscles as an alternative to strabismus surgery [69]. The first evidence for an effect of BoNT on migraine was the serendipitous observation of an improvement of migraine in patients treated with BoNT for hyperfunctional lines of the face made in the late 1990s by a plastic surgeon [70]. In the subsequent years, several exploratory studies with BoNT-A using heterogeneous doses and injection paradigms were carried out in migraine and tension-type headache and chronic daily headache with inconclusive and mostly negative results [62, 63, 71–74]. A subgroup analysis of 228 CDH patients enrolled in the randomized placebo-controlled study by Mathew et al. showed that the patients without prophylactic medication at the date of study enrolment experienced a significant reduction in the number of headaches in a 30-day period. So the authors concluded that onabotulinumtoxin A was effective in the treatment of patients with CDH, who do not receive other prophylactic medication [75].

Based on these preliminary studies, a series of studies called the Placebo-controlled phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT), treated patients with chronic migraine who would receive BoNT-A at fixed sites (procerus, corrugator, frontalis, temporalis, occipitalis, cervical paraspinal muscles and trapezius) in fixed doses (5 units per site for a total of 155 units), including those with or without medication overuse. The studies revealed a significant reduction in headache and migraine days, moderate/severe headache days and cumulative headache hours on headache days as well as in patients' functioning, vitality, psychological distress, and overall health-related quality of life [65–67].

The exact mechanism by which BoNT-A reduces migraine days in chronic migraineurs is not yet fully understood, although an increasing body of evidence suggests the dominant hypothesis that the toxin exerts its antinociceptive action via peripheral mechanisms [76]. While it was initially thought that BoNT-A may exert positive effects in primary headache disorders simply by the relaxation of muscles in the head and neck region, it turned out that BoNT-A is rather ineffective in disorders, where muscle tension may play a key role such as tension-type headache. It is today believed that BoNT-A acts in migraine by directly inhibiting peripheral sensitization by attenuating neuropeptide and neurotransmitter exocytosis from peripheral sensory neurons, thereby indirectly reducing central sensitization, the hallmark of chronic migraine [76]. The effectiveness of BoNT-A in chronic migraine, as opposed to negative findings in episodic migraine, may relate to the fact that sensitization phenomena play a more important role in chronic versus episodic migraine.

Neuronal stimulation initiates a series of intracellular events that leads to the fusion of a neuropeptide and/or neurotransmitter containing vesicle with the nerve cell membrane. This process is facilitated by interaction between proteins on the vesicle, the so-called vesicle-associated membrane protein (VAMP/synaptobrevin) and on the internal membrane surface, the synaptosomal associated protein (SNAP-25), which together form the soluble N-ethylmaleimide–sensitive factor

attachment protein receptor (SNARE) complex [77–79]. The SNARE complex is instrumental to vesicular trafficking and to vesicle fusion with the membrane. BoNT-A adheres to the nerve cells and enters inside through the endocytosis mechanism and inhibits fusion of intracellular vesicles with the nerve membrane [80] by cleaving SNAP-25 [81]. Once intraneuronal vesicular fusion is impaired because of BONT-A, neuropeptide release is inhibited and receptors are downregulated [77, 79]. A large number of experiments *in vitro* and *in vivo* showed that [82] botulinum toxin could also inhibit the release of a variety of neurotransmitters, including glutamate, GABA, aspartate, catecholamines, dopamine, and monoamine neurotransmitters [83–85]. All these neurotransmitters and neuropeptides are key signaling molecules in chronic migraine and it is therefore likely that, altogether, these mechanisms are important in the current notion of migraine prevention because they are capable of disrupting the cascade of events that leads to peripheral and central sensitization, mainly via the block of release of inflammatory neuropeptides from stimulated trigeminal sensory neurons [76–78, 86]. This mechanism of action is supported by clinical studies demonstrating suppression of cutaneous allodynia, an indicator of central sensitization, after onabotulinumtoxin A injection in the periorbital skin [87, 88].

In this framework, it is relevant to note that, in an animal model, administration of BoNT-A in close proximity of sensory fibers that bifurcate from parent axons of intracranial meningeal nociceptors and reach extracranial tissues by crossing the calvarial bones through the sutures [89–91] proved more effective in inhibiting the responses of nociceptors to topical capsaicin than when it was injected into muscles and sutures [92].

Other Compounds

ACE and ARB Agents

There are two randomized controlled studies suggesting an effect of candesartan at a dose of 16 mg per day in migraine prevention with comparable efficacy to propranolol. Candesartan is an angiotensin II receptor, type 1 blocking (ARB) agent and thus it reduces the effect of angiotensin, which has several effects that may be relevant to migraine, such as increased sympathetic discharge, and adrenal medullary catecholamine release. Molecular biology confirmed the components of the cerebral renin–angiotensin system (RAS) and their location in the brain [93]. RAS may play a role also in migraine pathogenesis. Brain RAS could act independently of the peripheral RAS, influencing neuronal, astrocytic, and endothelial cell activity [94].

Lisinopril, an angiotensin-converting enzyme inhibitor (ACEI), has been shown to be prophylactically effective at a dose of 10 mg twice daily in a small, double-blind, placebo-controlled crossover trial [95]. ACEIs modulate vasoreactivity, alter sympathetic tone, and promote degradation of proinflammatory factors, such as substance P, enkephalin, and bradykinin [95, 96]. An additional mechanism of action for ACEI in migraine could be modulation of the endogenous opioid system. As a matter of fact, the effect of this class of drugs has been reported to be blocked by antagonizing opioid receptors [97]. In addition to its traditional role as a circulating hormone, angiotensin is also involved in local functions through activity of tissue renin-angiotensin system that occur in many organs, including the brain (both systemic and presumptive neurally derived angiotensin) [98]. Angiotensin II receptors are located on neurones, astrocytes, and endothelium, and the hormonal effect is mainly mediated through the angiotensin II type 1 receptor. Brain angiotensin II type 2 receptors are located in areas predominantly involved in sensory processing, but their function remains to be clarified [99]. The RAS modulates cerebrovascular flow [100], and influences fluid and electrolyte homeostasis, autonomic pathways, and neuroendocrine systems. Angiotensin II modulates potassium channels and calcium activity in cells [98], increases the concentration of dopamine and of the main serotonin metabolite, 5-hydroxyindoleacetic acid, and activates nuclear factor kB, which is associated with increased expression of inducible nitric oxide synthase [101, 102].

Feverfew (*Tanacetum parthenium* L.)

Double-blind placebo-controlled studies suggested efficacy of feverfew in migraine prophylaxis, although it is usually not considered first choice as antimigraine preventive drug for tolerability (and safety) reasons [103–105]. The most frequent adverse events reported were sore mouth and tongue for the presence of ulcers, swollen lips, loss of taste, abdominal pain, and gastrointestinal disturbances [105]. Moreover, the safety of long-term use of feverfew needs to be established [106].

Feverfew is a member of the Asteracee family, empirically used as herbal remedy for migraine. Parthenolide, a sesquiterpene lactone, appears to be feverfew's active ingredient and has multiple actions in the central nervous system. Several of its properties suggest a potential mechanism of action in migraine prevention, including evidence to suggest that parthenolide inhibits Fos-induced activation of the nucleus trigeminalis caudalis [107], a nucleus central to migraine pathogenesis, and evidence for partial agonist activity of parthenolide at TRPA1 channels [108], which have been implicated in migraine pathogenesis [109]. It has also been demonstrated that oral administration of feverfew extract leads to significant antinociceptive and anti-inflammatory effects in experimental models [110]. This action could be explained by the regulation of degradation of the inhibitory protein of NF-kB and of expression of inducible NOS by parthenolide, the active constituent of feverfew [101].

Moreover, there is evidence that feverfew inhibits human blood platelet aggregation *in vitro*, probably through the protein kinase C pathway [111]. Feverfew could also exert modulation of 5-HT neurotransmission, antagonizing the effects mediated by 5-HT2B and 5-HT2A receptors implicated in the plasticity changes underlying chronic headache [112–114].

Butterbur (*Petasites hybridus*)

Some promising results support the efficacy of this extract in reducing migraine attacks [115–117]. Nevertheless, a recent systematic review shows that there is only moderate evidence for its effectiveness as an antimigraine drug [118].

Butterbur is a shrub with a long history of use for medicinal purposes. It demonstrates a variety of properties that render it a candidate for migraine prophylaxis, including anti-inflammatory action through inhibition of cyclooxygenase-2 [119]. Moreover, the co-active ingredients *petasins* could exert a block of Ca2+ channels [120–123].

Riboflavin (Vitamin B2)

A placebo-controlled, double-blind trial showed that a high dose of riboflavin can be effective in migraine prophylaxis [124]. This positive result was confirmed by an open-label study [125]. Riboflavin was comparable to propranolol after 3 and 6 months of administration in an RCT assessing its efficacy for adult migraine prophylaxis [126].

Riboflavin is a vitamin that plays an important role in cellular energy production through its two active coenzyme forms that are involved in oxidation-reduction reactions during a variety of cellular processes [127]. Brain energy metabolism has been found to be abnormal in migraine headache [128]. Riboflavin catalyzes the activity of flavoenzymes in the mitochondrial respiratory chain and improves the clinical and biochemical abnormalities in patients with inborn errors of mitochondrial metabolism [129, 130]. As mitochondrial deficits are suspected in some patients with migraine headache, this could reflect a mechanism of action in migraine prevention.

Magnesium

While a role for magnesium-related mechanisms can be hypothesized in migraine pathogenesis, limited evidence has indicated efficacy in migraine prophylaxis. In fact, several studies suggested a deficiency of Mg2+ in the central nervous system of migraineurs [131–133]. A Mg2+ deficit in migraine was also described at a peripheral level, in serum and blood cells [134, 135].

Clinical trials evaluated the potential usefulness of oral Mg2+ in migraine prevention, showing conflicting results [136, 137]. Three separate RCTs with varying methodologies, magnesium dosages, and formulations have found oral magnesium to be effective for migraine prophylaxis in adults [138–140]. Another RCT contradicted these findings and found oral magnesium to be no different than placebo on interim analysis in a sample of refractory migraine patients and therefore halted recruitment prior to achieving the planned sample size [141]. A possible effect of Mg2+ supplementation was demonstrated for short-term prophylaxis of menstrual migraine [142].

Magnesium is found ubiquitous in the human body and is an essential cofactor for more than 350 enzymes. It plays an important role in a multitude of biological processes, some of which might be linked to migraine pathogenesis [143]. It could modulate mitochondrial oxidative phosphorylation, 5-HT neurotransmission, and the NO system [144]. Moreover, it could regulate the uptake of glutamate into astrocytes and interfere with NMDA receptor function [144] and thereby improve migraine.

Conclusions

Several compounds with heterogenous mechanisms of action have been studied for the prevention of migraine during the past decades with some of them being licensed for this indication. Potential mechanisms of action include a reduction of excitatory glutamatergic neurotransmission by inhibition of sodium and calcium channels, facilitation of inhibitory GABAergic neurotransmission, reduction of central sensitization, and suppression of cortical spreading depression, but a number of other mechanism may be at play. While the migraine preventive properties of the available compounds were mostly discovered post hoc by circumstantial evidence, the advent of CGRP antibodies will for the first time allow a treatment tailored to the disease after systematic drug development from bench to bedside (Reuter et al. Neurotherapeutics, in this issue).

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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