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TREATMENT

Migraine prophylaxis: what is new and what we need?

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Abstract A wide array of options are now available for migraine prophylaxis. Conventional treatments include beta-blockers, anticonvulsants, antidepressants, calcium antagonists and antiserotoninergic drugs. Emerging medications such as ACE inhibitors, sartans and nutritional supplements are gaining favour for migraine prophylaxis. Botulinum toxin type A is a promising therapeutic tool for chronic migraine. Tonabersat is likely to be a step forward for the treatment of migraine with aura. However, much work is needed to identify predictive clinical features of successful responsiveness and to better define the duration of prophylaxis.

Keywords Migraine · Prophylaxis · Disability

Introduction

Migraine is a chronic, disabling neurological condition characterized by recurrent episodes of headache associated with sensory and autonomic symptoms which affects up to 15% of adult population [1]. CNS dysfunction plays a pivotal role in migraine pathophysiology, with various parts of the trigeminal system necessary for expression of peripheral symptoms [2, 3]. Approximately 90% of migraineurs experience moderate or severe pain, 75% is highly disabled and 35% is bedridden during the attacks [4, 5].

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A preventive treatment should be considered for all migraineurs whose attacks have a critical impact on working productivity, social, familial and recreational activities despite appropriate use of acute medications. The primary goal of prophylaxis is to reduce the attack frequency of ≥50%. It may also reduce headache intensity, duration and disability and improve response to acute medications. Prophylaxis reduces the risk of medication overuse, migraine progression and, hypothetically, brain damage [6]. Patients with ≥3 disabling attacks per month who fail to adequately respond to acute medication should start a prophylactic treatment, possibly as a monotherapy, starting at low doses. Although epidemiological studies indicate that approximately 25% of migraine patients should require migraine prevention, preventive drug treatments are used by a small percentage of patients [5].

The present study will review conventional and emerging treatments and discuss the unmet needs in migraine prevention.

Conventional prophylactic drugs

Antiepileptics

Antiepileptics are very effective in migraine prophylaxis and reduce migraine frequency by 1.4 attacks/month [7].

Sodium valproate (800–1,500 mg/day) is among first-line treatments in prevention of episodic, chronic and refractory migraine. Its mode of action encompasses enhancement of GABA-mediated neurotransmission, attenuation of low threshold T-type $Ca2^{+}$ channels, blocking of voltage-dependent Na^{+} channels and attenuation of plasma extravasation [7]. Valproate reduces migraine frequency by ≥50% in significantly more patients

than placebo (OR: 2.74, 95% CI 1.48–5.08; $p = 0.001$; NNT = 3.1) [8, 9]. Side effects include nausea (NNH = 7), fatigue (NNH = 15), tremor (NNH = 12.5), weight gain (NNH = 18.8) and dizziness (NNH = 16.3) [8]. Birth defects occur in 10.7% of infant exposed in the first trimester as compared to 1.6% in controls (RR: 7.3, 95% CI 4.4–12.2) [10].

Topiramate is a $Ca2^{+}$ and Na^{+} channel blocker which blocks glutamate, inhibits carbonic anhydrase and stimulates GABA production. It modulates cortical hyperexcitability, inhibits glutamate signaling in trigeminal afferents and modulates nociceptive transmission through GABA-A receptors in the trigeminal nucleus caudalis and descending brainstem pathways [7]. A number of studies explored the efficacy of topiramate (50–200 mg/day) in the prevention of episodic, chronic, refractory and pediatric migraine. Topiramate is superior to placebo in reducing monthly migraine frequency by ≥50% (OR: 2.44, 95% CI 1.81–3.28, $p = 0.0001$; NNT = 3.9) [8, 9]. At the dose of 100 mg, the most frequent adverse events are parestesias (NNH = 2.4), weight loss (NNH = 11.1), anorexia (NNH = 11.7), taste disturbances (NNH = 15.3), memory problems (NNH = 16.6), nausea (NNH = 23.1) and fatigue (NNH = 31.2) [8].

Gabapentin enhances GABA turnover and release, and decreases the release of noradrenaline, dopamine and serotonin by binding to a subunit of voltage-gated $Ca2^{+}$ channels. [7]. Gabapentin (1,200–2,400 mg/day) is superior to placebo in reducing migraine frequency by ≥50% (OR: 4.51; 95% CI 1.51–13.43, $p = 0.007$; NNT = 3.3) [11]. It is considered a third-line treatment for migraine prevention [8].

Beta-blockers

Beta-blockers are first-line drugs in migraine prophylaxis. Blockade of β1-mediated effects and consequent inhibition of Na^{+} release and tyrosine hydroxylase activity are considered the main mechanisms of action. Beta-blockers reduce the neuronal firing rate of noradrenergic neurons of the locus coeruleus, regulate the firing rate of PAG neurons and probably interact with the serotonergic system by blocking 5-HT2C and 5-HT2B receptors. It has been hypothesized that beta-blockers exert some of their prophylactic effects in migraine through an action at the ventroposteromedial thalamic nucleus and inhibition of cortical spreading depression (CSD) [12]. Clinical findings support the efficacy of propranolol (80–240 mg/day), timolol (10–20 mg/day), metoprolol (50–200 mg/day), atenolol (50–100 mg/day), nadolol (80–120 mg/day) and nebivolol (5 mg/day). Propranolol is superior to placebo in reducing migraine frequency by ≥50% (OR: 1.94, 95% CI 1.61–2.35, $p < 0.00001$). Responders rate with propranolol is similar to metopropol but lower than nadolol (RR 0.60, 95% CI 0.37–0.97, $p = 0.04$) [13].

Antidepressants

Tricyclics potentiates 5-HTergic transmission and block activation of trigeminovascular system [12]. A metanalysis of 37 RCTs indicates that tricyclics (amitriptyline 25–150 mg/day, desipramine 150 mg/day, chlorimipramine 30–150 mg/day, nortriptyline 100 mg/day) are more effective than placebo in reducing the frequency of migraine attacks (average standardized mean difference −0.70, 95% CI −0.93 to −0.48) but not superior to SSRI (−0.22, 95% CI −0.75 to 0.31). Tricyclics increases their effect with longer duration of treatment ($\beta = -0.11$, 95% CI −0.63 to −0.15) and are more likely to reduce the intensity of migraine by ≥50% than either placebo (1.80, 95% CI 1.24–2.62) or SSRI (1.72, 95% CI 1.15–2.55). In addition, tricyclics cause more adverse effects than placebo (1.53, 95% CI 1.11–2.12) and SSRI (2.22, 95% CI 1.52–3.32) but do not increase dropout rates [14].

Venlafaxine 150 mg is superior to placebo for migraine prevention, with a median reduction of 4 days with migraine in the last 2 weeks of therapy as compared to the first 2 weeks [15].

Antiserotoninergic agents

Pizotifen blocks 5-HT2 and 5-HT1C receptors and weakly inhibits H1 histamine and muscarinic receptors. Five studies reported a beneficial effect of pizotifen (1.5–3 mg/day) over placebo for migraine prophylaxis. Osterman reported a 50% responder rate in 43% of patients with pizotifen, compared with 4% during placebo treatment in a crossover study. The main adverse effects are weight gain and sedation [16].

Methysergide, the first effective prophylactic migraine drug, is a semi-synthetic ergot alkaloid structurally related to methylergonovine which blocks 5-HT1 and 5-HT2 receptors and inhibits the release of histamine from mast cells. 11 RCTs compared methysergide (3–6 mg/day) to placebo or to active drug. In four trials, methysergide was superior to placebo for either severe headaches or attack frequency and in four trials was found to be comparable to pizotifen. Methysergide was also found to be comparable to lisuride, propranolol and flunarizine. Because of its side effects (fibrotic changes in the retroperitoneal, pleuropulmonary, cardiac, and other tissues), it should be reserved for severe cases in which other migraine preventive drugs are not effective. It should not be used continuously, but with a treatment-free interval of 1 or 2 months every 6 month in order to minimize the chronic side-effects of fibrosis [17].

Calcium antagonists

Flunarizine regulates neuronal excitability and attenuates dural vasodilatation probably by blocking L-type $Ca2^{+}$ and Na^{+} channels and reducing NO synthesis [12]. A meta-analysis on four RCTs showed a significant reduction in the frequency of attacks using flunarizine 10 mg versus placebo with a monthly difference of 0.55 attacks (95% CI 0.215–0.895; $p = 0.002$). Somnolence and weight gain are the most frequent adverse effect. Flunarizine should be avoided in the elderly because of the risk of parkinsonism [18].

Emerging prophylactic drugs

ACE inhibitors and sartans

Angiotensin converting enzyme inhibitors and angiotensin II type 1 receptor blockers modulate vasoreactivity, alter sympathetic tone, inhibit oxidative stress, promote degradation of proinflammatory factors such as substance P, enkephalin and bradykinin and probably modulate the endogenous opioid system [12].

Telmisartan (80 mg mg/day) induces a 38% reduction in migraine days versus 15% with placebo ($p = 0.03$) but a only bordeline difference in responders ($p = 0.07$) [19]. Candesartan (16 mg/day) provides effective migraine prophylaxis showing a significant reduction in days with headache as compared to placebo ($p > 0.001$) with a good tolerability profile [20]. Lisinopril (20 mg/day) reduces hours with headache, days with headache and days with migraine by 20, 17, 21, respectively, compared with placebo [21].

Vitamins, minerals and herbal agents

Nutritional supplements acting on mitochondrial metabolism may antagonize energetic dysfunction in migraine by stabilizing neuronal function, restoring high-energy phosphate homeostasis and reducing brain oxidative stress.

Riboflavin (400 mg/day) and Coenzyme Q10 (300 mg/day) are more effective than placebo for a ≥50% reduction in migraine frequency (Riboflavin OR: 5.6, 95% CI 1.64–19.5, $p = 0.006$; Coenzyme Q10 OR: 5.45, 95% CI 1.23–24.26, $p = 0.03$) [22, 23]. Magnesium is the only preventive agent with a category-A pregnancy rating and is an appropriate choice for prophylaxis in women who are pregnant or trying to conceive. Magnesium citrate 600 mg/day showed a significantly higher reduction in migraine frequency in the final month of treatment as compared to baseline (−1.51) as compared to placebo (−0.58, $p = 0.03$) [24]. *Petasites Hybridus*, a herbaceous perennial plant in the family Asteraceae, showed an OR of 2.16 for a 50% reduction in migraine frequency when compared with placebo at the dose of 150 mg/day (95% CI 1.06–4.38, $p = 0.03$) [25]. A systematic review of 5 trials on *Tenacetum Partenium* concluded that there is insufficient evidence to suggest an effect over and above placebo for preventing migraine [26].

Botulinum toxin type A

In experimental models, Botulinum toxin type A (BTA) inhibits substance P release in the dorsal root ganglion and CGRP release from the trigeminal ganglion, showing also suppressive effects on the trigeminal/cervical nociceptive system. The rationale of its use in migraine is the inhibition of peripheral sensitization which would lead to an indirect reduction in central sensitization. Evidence from 8 RCTs does not support the efficacy of BTA for the prophylaxis of episodic migraine [27]. Two phase III studies of BTA in chronic migraine have been completed. In PREEMPT1 study, BTA was not different from placebo with regard to change in number of headache episodes from baseline [28]. In PREEMT2, BTA was reported to induce a significant reduction of headache days as compared to placebo (9.0 vs. 6.7 days, $p < 0.001$) [29]. A pooled analysis of data from PREEMPT1 and PREEMPT2 also showed a significant benefit of BTA over placebo with regard to headache days and headache episodes and BTA was also reported to be effective in a subgroup of patients with medication overuse. BTA was safe and well tolerated, with few treatment-related adverse events [30].

Tonabersat

Tonabersat (a novel benzopyran derivative) blocks CSD, associated nitric oxide synthase activation and cyclic GMP increase in the brain, possibly by binding to a connexin and modulating gap-junction function. Tonabersat (40 mg/day) showed a preventive effect on migraine with aura reducing median attacks of aura from 3.2 (1.0–5.0) per 12 weeks on placebo to 1.0 (0–3.0) on tonabersat ($p = 0.01$), but has no efficacy on non-aura attacks, challenging the view that silent CSD triggers migraine attacks without aura. Tonabersat is likely to be a useful option for the management of patients with aura [31].

Short-term prophylactic treatment

A short-term prevention may be indicated for women with menstrual-related migraine, whose attacks occur on day 2–3 of menstruation in at least two of three menstrual cycles. Drugs used in this way have included oestrogens, NSAIDs, ergots, magnesium and triptans. A systematic review of ten RCTs on short-term prevention (7 days) in

perimenstrual migraine suggests the use of transcutaneous estrogen 1.5 mg, frovatriptan 2.5 mg twice daily, and naratriptan 1 mg twice daily [32].

What we still need?

In spite of a bewildering array of options for migraine prophylaxis at least two crucial issues remain unresolved:

How to choose the preventive drug?

Current pharmacological prophylaxis is tailored on the disease, not on patient's phenotype. There is no characterization of specific subsets of migraineurs nor predictive clinical features to guide the choice among preventative agents. As a consequence, the therapeutic strategy is still based on non-specific criteria such as comorbidities and, above all, side effects of the drug.

How long should successful prophylaxis be continued?

In most cases, efficacy begins to wane after discontinuation on the drug. No scientific evidence exists as yet to suggest how long successful migraine prophylaxis should be prolonged. In clinical practice, preventive medication is usually stopped after 4–6 months of treatment to verify is still needed. However, a long-term treatment should be encouraged in those patients at risk for migraine chronification, with medication overuse or contraindication to acute therapies.

Conflict of interest The authors declare that there is no actual or potential conflict of interest in relation to this article.

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