Neuromodulators and its combinations for the preventive treatment of migraine

Neurotransmissores e suas combinações para o tratamento preventivo da migrânea

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ABSTRACT

Migraine is a chronic, debilitating neurological disorder. It affects nearly 15% of the adult population and it is characterized by a range of symptom profiles and degrees of disability. It is a disease generally believed to occur in consequence of a genetically hyper excitable brain state, in addition to a neurotransmitter dysfunction which results in susceptibility to the occurrence of intermittent attacks of headache with particular associated features. Pharmacotherapy remains the mainstay for the prevention of the attacks and despite the use of different classes of drugs, some older than 30 years and used by serendipity, some neuromodulators represent the most modern option and the better studied drugs for the prophylactic treatment of migraine. Supposedly acting by targeting one or more molecular sites in the brain, these drugs alter neurotransmission through effects on ion channels, on specific receptors and on neurotransmitter metabolism. Neuromodulators are considered the state of art in migraine therapeutic and its combination may represent an upcoming option for patients not responding well or presenting limiting tolerability issues with full-dose monotherapy. In this review, we explore the specificities of the different drugs belonging to this pharmacological class, the evidence available for its use in migraine as well as the fundamentals and potential for new approaches combining two neuromodulators, even in lower doses.

Keywords: Neuromodulators; Combination; Migraine; Preventive treatment

RESUMO

A enxaqueca é uma doença neurológica crônica e incapacitante. Afeta em torno de 15% da população adulta e é caracterizada por vários sintomas e graus diferentes de incapacidade funcional. A enxaqueca é considerada uma doença na qual há hiperexcitabilidade cerebral aliada à disfunção de sistemas de neurotransmissão originando susceptibilidade à ocorrência de crises intermitentes de cefaleia com características peculiares. A farmacoterapia preventiva é o eixo central do tratamento e, a despeito do uso de várias classes de drogas, algumas com mais de 30 anos e consideradas eficazes por acaso, alguns neuromoduladores representam a opção mais moderna e mais estudada para esse tratamento. Supostamente atuando em um ou mais sítios moleculares cerebrais, essas drogas alteram a neurotransmissão através da ação em canais iônicos, em receptores específicos ou no metabolismo de neurotransmissores. Os neuromoduladores são considerados o "estado da arte" no tratamento da enxaqueca e sua combinação pode representar uma opção nova para pacientes não responsivos ou que apresentam efeitos colaterais limitando o uso de doses plenas na monoterapia com esses fármacos. Nesta revisão, exploramos as especificidades das diferentes drogas pertencentes a essa classe, a evidência disponível para sua indicação e fundamentos para uma forma nova de utilizá-los através de sua combinação.

Palavras-chave: Neuromoduladores; Associação; Migrânia; Tratamento preventivo

INTRODUCTION

Migraine is a highly prevalent primary headache, which affects more women than men and may start during childhood or adolescence. Those affected may experience migraine throughout their lives.[1,2] Despite its life time prevalence of 12 to 15% and its disabling nature, migraine is an underdiagnosed and undertreated disease.[1] Migraine is a primary neurological disorder with a clear genetic basis.[3,4] During migraine attacks neural events result in the dilatation of meningeal blood vessels, which in turn, results in pain, further nerve activation, and inflammation.[5]

It probably results from dysfunction of brainstem involved in the modulation of craniovascular afferents.[3-6] Brainstem activation may also lead to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation. The resulting pain is felt as a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, as well as the activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve. Cortical spreading depression is a presumed substrate of migraine aura; spreading depression and central dysnociception may also occur in migraine without aura.[3-6]

Since the chemical cascade of migraine attacks is believed to occur, at least in part, consequent to a genetically hyper excitable brain state, neuromodulators that decrease neuronal excitability should be effective approach for the prevention of migrainous symptoms.[7-11]

NEUROMODULATORS IN MIGRAINE

Valproate (VLP) is simple, eight-carbon branched-chain fatty acid with antiepileptic properties, which was one of the first neuromodulators studied for migraine prevention. Divalproex (DVP) has also been extensively studied in controlled-studies. Studies have shown that DVP decreases migraine headache frequency by 50% or greater in 45%-50% of the patients after 3 months, *versus* 12%-15% among those receiving placebo.[13] Therefore, the therapeutic gain of DVP is lower than 35%.

At clinical relevant doses, both VLP and DVP attenuate plasma protein extravasion in migraine models of meningeal neurogenic inflammation, and this effect is reversed by $GABA_{-A}$, but not by $GABA_{-B}$ receptor antagonists.[14] Furthermore, the effect of VLP is mimicked by the $GABA_{-A}$ agonist, muscimol, but not by the $GABA_{-B}$ agonist baclofen, suggesting a $GABA_{-A}$ mediated mechanism. However, in higher doses it blocks the GABA degradation by GABA transaminase, thereby increasing GABA concentrations in both axon and in glial cells. The role of these pharmacological properties in migraine prevention is uncertain as it is the DVP action of blocking voltage-dependent sodium ion-channels, therefore modulating the release of excitatory amino acids, and of blocking low-threshold T-type calcium ion channels.[12]

Although VLP and DVP are more often used in the preventive treatment of migraine, at least VLP seem also to be effective for the acute treatment.[15] It is established that the substantia gelatinosa of the spinal cord receives descending 5-HT fibers from the rostroventral medulla (RVM) and these fibers connect with spinothalamic neurons.[16,17] Accordingly, VLP action in the acute treatment of migraine may be partially due to serotoninergic modulation.

Nowadays, DVP is much more commonly used than VLP for the preventive treatment of migraine. It is typically started at a dose of 250 mg bid, and can be brought up to a dose of 500 mg bid. For the acute treatment, typical doses range from 300 to 500 mg of intravenous VLP. Adverse effects limit the use of DVP and include weight gain, hair loss, potential liver dysfunction, teratogenicity, among others.[17]

Topiramate is the most recent medication approved by the FDA for migraine prevention. It is a sulfamate-substituted monosaccharide derived from D-fructose that is structurally distinct from other neuromodulators.([18] It has been proven to be an effective pharmacological agent at doses ranging from 50 mg to 200 mg/day[19-23] (Table 1) for the prevention of migraine and recently for the treatment of chronic migraine as well.

TPM has modulatory effects on voltage-sensitive L-type calcium channels.[12,18] However, the observation that TPM is more effective at 10 μM than at 50 μM in reducing the L-type Calcium currents suggests that TPM may have a different mode of action from traditional Calcium channel blockers. The biphasic concentration-response curve for the effect of TPM on L-type Calcium currents is similar to that for the modulatory effect of TPM on $GABA_{A}$ receptors.[24] Because TPM has no effect on ionic currents in the absence of GABA, its effect on $GABA_{A}$ receptors appears to be modulatory as well.[24] The effect of TPM is similar to that of the benzodiazepines (BDZs) in that TPM increases the frequency of channel activation. TPM has been reported to inhibit KA-evoked

Table 1 - Controlled double-blind placebo-controlled trials of Lamotrigine (LTG), Gabapentin (GBP) and Topiramate (TPM) in the prophylaxis of migraine

Drug dosage (mg)	Study design	Number of patients. Type of migraine	Treatment duration (weeks)	Main outcome
[57]LTG (200 mg)	Parallel groups	77 MA, MO	4 + 8 (adjustment +maintenance)	Mean attacks (4wk) LTG (3.2) > PL (3.0) (NS)
[37]GBP (2400 mg)	Parallel groups	143 MA, MO	4 + 8 (adjustment +maintenance)	Mean attacks (4wk)) GBP (2.7) < PL (3.5)
[20]TPM (125 mg)	Parallel groups	40 MA, MO	8+ 8 (adjustment +maintenance)	Mean attacks (28-day) TPM (3.31) < PL (3.83)

MA, migraine with aura; MO, migraine without aura.

whole-cell currents in hippocampal neurons and this is associated with decrease in neuronal excitability.[25]

TPM is one of the only neuromodulators associated with weight loss.[26,27] Adverse effects include paresthesias, cognitive deficits, nephrolithiasis, acute closed angle glaucoma, and non-anion gap metabolic acidosis-the latter three considered idiosyncratic in nature. A dose of 50 mg bid has been shown to be optimal, but effects have been shown at as little as 25 mg bid.[19,20]

Topiramate's efficacy is similar to the efficacy of DVP, and it has not been shown to be superior to beta-blockers or tryciclic anti-depressants, although recent studies have been suggesting that the combination of topiramate and other traditional pharmacological agents for migraine prevention promote better outcome figures for decreasing the frequency of migraine attacks.[28-31]

Gabapentin (GBP) is not approved by the FDA for migraine prevention, but is often used in the treatment of migraine. Its molecule is formed by the addition of a cyclohexyl group to GABA, allowing this form of GABA to cross the blood-brain barrier. It is not metabolized and does not induce or inhibit hepatic metabolism. Gabapentin has to be administered three times a day due to its half-life of 4 to 9 hours and drug-drug interactions are not an issue with GBP because of its pharmacokinetic profile of not binding to plasma proteins and its lack of interference with hepatic function. The mechanism of action of the gabapentinoids is not fully understood yet. Despite its structural similarity with GABA, it does not bind to GABA receptors in the CNS. It does interact with the alfa-2-delta subunit of voltage-gated ion calcium channels possibly modulating their currents as well as increases the rate of GABA synthesis in the brain. Gabapentin has also an antinociceptive effect. It inhibits monoamine neuro-transmitter release, including dopamine, serotonin and noradrenaline in addition to total cellular calcium content. At the spinal cord level, gabapentin alters N-methyl-D-aspartate (NMDA) receptor-mediated responses. These effects explain why GBP has been used in the treatment of neuropathic pain conditions.[32-36]

For the prevention of migraine, Gabapentin (1800-2400 mg/day) was found to be superior to placebo in reducing the frequency of migraine attacks in a controlled, double-blind trial, supporting the results of previous open trials. The responder rate was 36% for gabapentin and 14% for placebo[37] (Table 1). The most common adverse events were dizziness and drowsiness. Clinical experience does not corroborate the presumed efficacy of gabapentin and it is not considered one of the neuromodulators recommended for migraineurs.

Another gabapentinoid, pregabalin, which has a longer half-life and, therefore, may be used in two-daily dosages regimen, is also suggested as useful for migraine prevention despite of the lack of published controlled studies. Pregabalin is recommended for partial seizures, pain of post-herpetic neuralgia, pain of the diabetes mellitus neuropathy, fibromyalgia and generalized anxiety disorder.[38,39]

Levetiracetam (LCT) is a pyrrolidine, the racemically pure S-enantiomer of alfa-ethyl-2-oxo-1-pyrrolidineacetamide. It inhibits partial and secondarily generalized tonic-clonic seizures in the kindling model. The mechanisms by which it exerts this antiseizure effect are still unknown, but despite its lack of effect on Na^+ channels or either on GABA- or glutamate mediated synaptic transmission, LCT seems to act on a binding site at the synaptic vesicle protein SV2A, at least in rat brain membranes.[40] LCT is rapidly and nearly completely absorbed after oral administration and it is not bound to plasma proteins; peak serum concentrations are achieved within 2 hours, and daily doses are linearly related with plasma concentrations. An advantage of this neuromodulator is the fact that LCT

neither induces nor is a high-affinity substrate for CYP isoforms or glucuronidation enzymes and thus is devoid of known interactions with other antiseizure medications, oral contraceptives or anticoagulants.[41]

LCT was studied for migraine and chronic migraine prevention in few trials, mostly uncontrolled. Average dose was 1,000 mg and results were not impressive, but a better definition of effective doses in randomized controlled trials is warranted before this neuromodulator can be excluded from the migraine medication arsenal.[42-45] LCT was also studied for the prevention of migraine in children. In an open label prospective trial (n=20), levetiracetam was used in two daily dosages of 20 mg/kg after an initial daily dose of 20 mg/kg during one month. In a retrospective chart review of 19 children, who received 125-700 mg twice daily, migraine frequency was reduced and headaches attacks were eliminated in 52.6% of the treated patients.[46] Asthenia/somnolence, irritability, hostility and dizziness were associated with the use of LCT in this population.

The side effects of LCT reported in initial clinical trials for epilepsy occurred in at least 3% of the patients and presented as fatigue or tiredness, somnolence, dizziness and infection (common cold or upper respiratory tract infection).[41,47]

Zonisamide (ZNS), a sulfonamide analog, is a neuromodulator recently approved as an adjunctive therapy for partial seizures in adults.[48] It has a high oral bioavailability and a long half-life (63 hours), allowing therapeutic regimens of once- or twice-daily dosages. Similarly to topiramate, zonisamide promotes blockade of voltage-gated sodium channels, inhibition of potassium-mediated release of glutamate, facilitation of serotonergic and dopaminergic neurotransmissions and enhancement of gamma-aminobutyric acid release. Additionally, it also seems to reduce ion flow through T-Type calcium channels. [49,50,51]

ZNS was primarily been tested for the treatment of refractory migraine. Thirty four patients reported statistically significant improvement of headache frequency, severity and duration with a daily dosage of 400 mg/day (initiation with 100 mg/day and titration till 400 mg/day) after three months of treatment. Four patients (11.8%) stopped the treatment due to adverse events, which include dysphoria and difficulty concentrating.[47,52]

In a retrospective chart review study of 33 patients (23 with transformed migraine and 10 with episodic migraine) who had failed over six preventive drugs prior to ZNS, an average daily dosage of 340 mg for 6 months of treatment, provided reduction in the number of headache days. Adverse events were reported by 14 patients (14.4%), being fatigue the most common.[53]

Recently, 34 patients with good response to the use of Topiramate, but interrupting it due to intolerable side effects, were evaluated after a one-month wash-out period. Zonisamide was used during 6 consecutive months in a dose up to 100 mg/day. The mean number of days with headache per month was reduced from 14,9 ± 5.3 during the wash-out period to 2,5 ± 0.6 after the treatment period. Headache severity and disability, as assessed by visual analog scale and migraine disability assessment scale, were also significantly reduced. The use of rescue medications at the end of the study was reduced as well. Four patients (12%) reported side effects not responsible for interrupting the treatment.[51]

Lamotrigine (LTG) is a neuromodulator of the phenyltriazine class chemically unrelated to existing neuromodulators. Its chemical structure is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine and has a molecular formula expressed as C9H7N5Cl2 with a molecular weight of 256.09. Lamotrigine is very slightly soluble in water and is well absorbed orally, with up to 98 percent bioavailability. Absorption is not affected by food. Approximately 55 percent of the drug is protein bound; therefore, clinical interaction with other protein-bound drugs is unlikely. Ninety percent of the drug undergoes glucuronic acid conjugation in the liver, with the conjugate and the remaining 10 percent of unmetabolized drug excreted in the urine.[54]

The Clearance of LTG is markedly increased by the co-administration of other antiepileptic drugs that induce hepatic enzymes. These include carbamazepine, phenobarbital, phenytoin and primidone. The half-life of lamotrigine may be reduced by about 50 percent with concomitant use of one or more of these medications (Table 2). However, when combined with valproic acid, its elimination is decreased, and its half-life may be more than doubled.[55]

LTG is used as adjunctive therapy or monotherapy in adults with partial seizures with or without secondary generalization. The mechanism of action is unknown, but it stabilizes neural membranes and inhibits the release of excitatory neural transmitters as glutamate release, possibly through modulation of voltage-sensitive sodium channels.[54]

A role for lamotrigine in the prophylactic treatment of migraine has been suggested mostly by small open trials, in which lamotrigine was suggested effective in

Table 2 - Effects of newer neuromodulators on drug levels of standard drugs of this class

	Newer anticonvulsants				
	Gabapentin	Lamotrigine	Felbamate	Topiramate	Fosphenytoin
Phenytoin	Ñ	Ñ	Increased 25%	Ñ or increased 25%	Ñ
Valproic acid	Ñ	Decreased 25%	Increased 40%	Decreased 11%	Ñ
Carbamazepine	Ñ	Ñ	Decreased 30%	Ñ	Ñ
Carbamazepine epoxide	Ñ	Ñ	Increased 55%	Ñ	Ñ
Phenobarbital	Ñ	Ñ	No data	Ñ	Ñ

Ñ: No effect

reducing the frequency of migraine with aura and aura symptoms.[56] However, a larger double-blind randomized study demonstrated that lamotrigine was ineffective in migraine prophylaxis, even after three months of drug use and more adverse effects were recorded in the lamotrigine-treated group compared with placebo[57] (Table 1). In more recent small, open-label studies, in which smaller doses were included, lamotrigine was effective in reducing the frequency of migraine auras and the monthly rate of migraine with aura attacks.[58,59,60] It does corroborate the importance of larger controlled trials investigating the true role of lamotrigine in migraine.

Lamotrigine does not impair cognition and the main contraindication to its use is hypersensitivity to the drug. The need for monitoring drug levels has not been established. The most frequently encountered adverse reactions include dizziness, ataxia, somnolence, headache, blurred vision, nausea, vomiting and skin rash, which is seen in approximately 10% of the patients. The risk of more serious reactions, such as the Stevens-Johnson syndrome, may be minimized by initializing the drug at a low dose, escalating it slowly, and avoiding concomitant use of divalproex or valproate sodium.[47]

The adamantane derivative memantine (1-amino-3,5-dimethylaminoadamantane, D-145, Akatinol) (MEM) is a neuromodulator representing the first in a novel class of Alzheimer's disease medications acting on the glutamatergic system. MEM is a moderate-affinity voltage-dependent noncompetitive antagonist at glutamatergic N-methyl-D-aspartate (NMDA) receptors.[61] By binding to the NMDA receptor with a higher affinity than magnesium Magnesium ions, MEM is able to inhibit the prolonged influx of calcium Calcium ions associated with neuronal excitotoxicity. In addition, biochemical, pharmacological, and electrophysiological studies show that memantine interferes with the metabolism of the neurotransmitters dopamine, noradrenaline, and serotonin and modulates synaptic transmission.[62]

MEM was studied for refractory migraineurs. Subjects with migraine (episodic migraine with 8-14 days of headache per month or transformed migraine, who had previously failed at least 2 trials of adequate preventive therapy) were included. Other preventive drugs were allowed if the patient had been on a stable dose for more than 30 days. MEM dose ranged from 10 mg to 20 mg per day and the treatment phase lasted 3 months. The primary endpoint was number of days with headache at month 3. In the ITT population ($n = 28$), monthly headache frequency was reduced from 21.8 days at baseline to 16.1 at 3 months ($P < .01$). The mean number of days with severe pain was also reduced from 7.8 to 3.2 at 3 months ($P < .01$) and mean disability scores were significantly reduced at 3 months as well, when compared with baseline (36.6 vs 54.9, $P < .01$). Side effects were present in 37.5% of the patients; 5.5% dropped out the study because of poor tolerability. Most adverse events were mild. The study, although not double-blind, posted preliminary evidence that MEM could be useful for preventing refractory migraine.[62]

EXPERT COMMENTARY

Combining neuromodulators in migraine?

Managing the migraine patient is sometimes difficult, especially when they are referred to tertiary centers. Guidelines recommendations suggest that the goal of preventive treatment is to reduce headache frequency by at least 50%, based on the assumption that this reduction is likely clinically meaningful.[63-65]

When patients fail to respond as expected to appropriate therapy, or announces at the first consultation that he or she has already tried everything and nothing will work, it is important to identify the reason or reasons that treatment has failed. Accordingly, although

monotherapy is usually recommended, rational combination therapy is sometimes necessary.[66,67]

In clinical practice, the use of the neuromodulators TPM and DVP may be limited by tolerability issues and optimal doses may not be achieved despite improvement of headache. Phrases like "This drug helped me with the headache but I was unable to function" or "I prefer to keep my headaches and remain thin or with my hair" are common complaints brought to the health provider prescribing full doses of these pharmacological agents.[68,69]

Clinical experience suggests that patients with good therapeutic response but poor tolerability may often benefit from combining medications at smaller doses.[29,70] Combining low doses of TPM and DVP may be of interest also because of their sometimes opposite adverse events profile (e.g. increase vs. decrease in weight). In addition, thinking about the fundamentals, specifically regarding TPM and DVP, one can speculate that a synergistic effect occurs. Since Valproate increases GABA levels and potentiates GABA-mediated responses possibly blocking its degradation by GABA transaminase, and blocks low-threshold T-type calcium ion channels,[12,13,17] whereas TPM enhances GABA neurotransmission by facilitating $GABA_A$ receptor action increasing the opening frequency of the chloride ion channels in $GABA_A$ receptors, in addition to the reduction of the L-type Ca channels activity, it is reasonable to think that these combined effects could result in better efficacy on migraine prevention. Additionally, TPM negatively modulates the excitatory neurotransmitter glutamate thru binding to the non-NMDA kainate/AMPA receptors, thereby decreasing the flow of sodium and calcium ions across the postsynaptic membrane.[20,24-26]

In fact, a recent open label trial with a small number of patients suggested that TPM and DVP, combined in smaller doses than usually used, was an interesting option for patients that benefited from therapeutic doses of these medications but would be otherwise discontinued due to tolerability issues.[31]

Another possible approach is the combination of the modulatory effects of a gabapentinoid, which acts on alfa-2-delta subunit of voltage-gated ion calcium channels, modulating their currents and increasing the rate of GABA synthesis in the brain in addition to alter N-methyl-D-aspartate (NMDA) receptor-mediated responses, with TPM, which aims its action also on calcium channels and glutamatergic system, but in different receptors.[12,26,32,33]

Finally, perhaps the potential advantages of obtaining a modulatory effect of TPM on Kainate/AMPA receptors with the modulation on NMDA receptors promoted by memantine also in the excitatory glutamatergic system may represent an interesting option.[70]

Although these combinations or any other involving two neuromodulators have never been tested in randomized controlled trials, one might speculate on whether this could be useful for those patients failing the adequate trials of individual options of this class for migraine prevention, especially if they needed higher doses for obtaining efficacy.

Although not every neuromodulator can be combined with each other due to metabolism interactions and inductions mediated by inhibition of different types of CYP enzymes, most of the more recent members of neuromodulators could be considered as ad on therapies, for patients not responding or doing so, but with tolerability issues, when using full doses of a specific agent (Table 2).

Until it cannot be proved by the rigors of large controlled studies, the option of combining neuro-modulators, even in smaller doses, may only be speculated.

Five-year view

There have been exciting developments in understanding the molecular biology and involved mechanisms of migraine in the past years. Since migraine may involve an unbalance between the excitatory glutamatergic and inhibitory gabaergic systems as well as a calcium "channelopathy" directly affecting the regulation of neurotransmitter release, drugs aiming at stabilizing the neurochemical synchronization of central circuits, probably involved in migraine, through actions on various mechanisms, may, indeed represent powerful components of the migraine treatment arsenal. However, as presented, a ceiling effect of 50-60% headache frequency reduction is the only achieved outcome for most patients. Additionally, tolerability issues may limit treatment success due to the impossibility of using full-dose schemes. Trials on combination therapies for migraine are just beginning, mostly due to previous lack of funding interest. Although nothing has been proved yet, especially for the prevention of migraine, the next few years may represent a changing paradigm, reasoned by the better outcome figures obtained with combination of drugs for migraine acute attacks. The expectations for more efficacious and

better tolerated migraine preventive treatments are anxiously expected. Until then, exciting results on combining available drugs may fulfill the upcoming horizon for relieving the burden of migraine.

Key issues

– Migraine is a genetically inherited disease, which involves a brain hiper excitable state

– Neurotransmitter dysfunction, probably related to a calcium channelopathy, is also involved in migraine

– The neurotransmitter dysfunction probably results in a state of central dysnociception and/or dysmodulation

– Neuromodulators are effective migraine preventive pharmacological agents through the decreasing of neuronal excitability

– Some neuromodulators are proven effective. Others may be used, but further evidence of their efficacy is still lacking

– The combination of two neuromodulators may useful for some patients who don't tolerate full doses of individual drugs or need better efficacy outcomes

– The future of migraine preventive treatment may involve two or more drugs aiming at different mechanisms of action and/or brain circuits

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