






























Consensus of the Brazilian Headache Society (SBCe) for prophylactic treatment of episodic migraine: part II

Consenso da Sociedade Brasileira de Cefaleia (SBCe) para o tratamento profilático da migrânea episódica: parte II

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Abstract

Background Migraine affects 1 billion people worldwide and > 30 million Brazilians; besides, it is an underdiagnosed and undertreated disorder.

Objective The need to disseminate knowledge about the prophylactic treatment of migraine is known, so the Brazilian Headache Society (SBCe, in the Portuguese acronym) appointed a committee of authors with the objective of establishing a consensus with recommendations on the prophylactic treatment of episodic migraine based on articles from the world literature as well as from personal experience.

Methods Meetings were held entirely online, with the participation of 12 groups that reviewed and wrote about the pharmacological categories of drugs and, at the end, met to read and finish the document. The drug classes studied in part II of this Consensus were: antihypertensives, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, calcium channel blockers, other drugs, and rational polytherapy.

Results From this list of drugs, only candesartan has been established as effective in controlling episodic migraine. Flunarizine, venlafaxine, duloxetine, and pizotifen were defined as likely to be effective, while lisinopril, enalapril, escitalopram, fluvoxamine, quetiapine, atorvastatin, simvastatin, cyproheptadine, and melatonin were possibly effective in prophylaxis of the disease.

Conclusions Despite an effort by the scientific community to find really effective drugs in the treatment of migraine, given the large number of drugs tested for this purpose, we still have few therapeutic options.

Palavras-chave

- ▶ Cefaleia Histamínica
- ▶ Enxaqueca Sem Aura
- ▶ Consenso
- ▶ Medicina Preventiva

Resumo

Antecedentes Migrânea afeta um bilhão de pessoas em todo o mundo e mais de 30 milhões de brasileiros; além disso, é um distúrbio subdiagnosticado e subtratado.

Objetivo Sabe-se sobre a necessidade de difundir o conhecimento sobre o tratamento profilático da migrânea; por isso, a Sociedade Brasileira de Cefaleias (SBCe) nomeou um comitê de autores com o objetivo de estabelecer um consenso com recomendações sobre o tratamento profilático da migrânea episódica com base em artigos da literatura mundial, assim como da experiência pessoal.

Métodos As reuniões foram realizadas inteiramente online, com a participação de 12 grupos que revisaram e escreveram sobre as categorias farmacológicas dos medicamentos e, ao final, reuniram-se para a leitura e conclusão do documento. As classes de medicamentos estudadas na parte II deste Consenso foram: anti-hipertensivos, inibidores seletivos de recaptção de serotonina, inibidores de recaptção de serotonina e noradrenalina, bloqueadores dos canais de cálcio, outros medicamentos e politerapia racional.

Resultados Desta lista de medicamentos, apenas o candesartan foi estabelecido como eficaz no controle da migrânea episódica. Flunarizina, venlafaxina, duloxetina e pizotifeno foram definidos como provavelmente eficazes, enquanto lisinopril, enalapril, escitalopram, fluvoxamina, quetiapina, atorvastatina, simvastatina, ciproheptadina e melatonina foram possivelmente eficazes na profilaxia da doença.

Conclusões Apesar do esforço da comunidade científica em encontrar medicamentos realmente eficazes no tratamento da migrânea, dado o grande número de medicamentos testados para este fim, ainda dispomos de poucas opções terapêuticas.

Keywords

- ▶ Cluster Headache
- ▶ Migraine Without Aura
- ▶ Consensus
- ▶ Preventive Medicine

INTRODUCTION

The Brazilian Headache Society (SBCe, in the Portuguese acronym) appointed a committee of authors with the objective of establishing a consensus with recommendations on the prophylactic

treatment of episodic migraine based on worldwide publications, as well as on personal experience. The detailed research methodology and involvement of the authors, along with an analysis of the therapeutic classes of beta-blockers,

anticonvulsants, tricyclic antidepressants, and monoclonal anti-CGRP antibodies are described in the first part of the present document.

Methods

The SBCe, through the current board, appointed an ad hoc committee with the purpose of creating the present Consensus on prophylactic treatment of episodic migraine (EM) and developing recommendations for the management of these patients in order to disseminate knowledge in the field of headache and assist medical professionals in their routine.

Twelve working groups were created, each dedicated to one or more classes of EM prophylactics.

The members were chosen by the Board of Directors of the SBCs according to the following criteria:

- Proactivity
- Ethics
- Practice with article writing
- Publication in journals and presented works
- Recognition

The coordinator of each group was chosen for their expertise in headache, curriculum, and practice in working with groups.

The participants in each group reviewed and discussed online the relevant topics, on which they wrote the initial text. These texts were reviewed by another group and returned to the original groups for corrections. The corrected texts were reviewed and standardized by the coordinators of the groups. At the last virtual meeting, all authors assessed and approved the final text of the Consensus.

The search for articles was carried out in the PubMed database, covering the period from the earliest articles recorded until articles published in 2020. The included studies ranged from case reports, case series, nonrandomized and/or non-controlled clinical trials and randomized and controlled clinical trials to systematic reviews and meta-analyses.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

General aspects

Actions mediated by the renin-angiotensin system (RAS) are recognized in extrarenal sites such as the lungs, blood vessels, and central and peripheral nervous systems. The presence of angiotensin 1 (AT1) and angiotensin 2 (AT2) receptors in regions like the anterior and prefrontal cingulate cortex, the thalamus, the periaqueductal gray matter, the tonsils, and the medulla emphasizes the idea that this system plays an important role in regulating inflammation and oxidative stress, which may be related to the pathophysiology of migraine.^{1,2}

A possible genetic association between RAS and migraine has been considered. Studies on angiotensin-converting enzyme (ACE) polymorphism in migraine patients have suggested that there is a higher prevalence and frequency of attacks of migraine without aura in people with the *DD-ACE* gene (homozygous for deletion).³

In addition, RAS interacts with neurotransmitters and endorphins acting on sympathetic modulation and synthesis of prostacyclin, bradykinin, enkephalin, and substance P, both centrally and peripherally, thus suggesting that substances that modulate this system may be relevant for the treatment of migraine.⁴

Lisinopril

Studies

A double-blind, randomized, crossover study comparing lisinopril with placebo in a population of 47 patients showed that this drug was superior to placebo regarding reducing the numbers of hours and days with headache, days with migraine, and the pain severity index, which were all ~ 20% lower after 12 weeks of follow-up.⁵

Enalapril

Studies

A single randomized double-blind study⁶ compared the use of enalapril with placebo for 2 months in 40 patients with episodic migraine. After a period of 1 month without prophylactic medication, the patients were randomized to receive enalapril 5 mg or placebo for 2 months. The group that used enalapril showed significant a reduction in duration, severity, and frequency of headache attacks per month, as measured on a visual analogue scale (VAS; from 1 to 10) when compared with the placebo group.

Captopril

Studies

Captopril has been evaluated in a single double-blind, randomized Class III study with 26 patients. Due to the small number of patients and to the high dropout rate from the study (23%) due to side effects and inefficacy, it was concluded that the data are insufficient to determine that captopril is not useful for the prophylaxis of migraine.⁷

Candesartan

Studies

A study by Tronvik et al. evaluated the efficacy of candesartan 16 mg as a preventative drug for migraine in 60 adult patients.⁸ This was a double-blind, randomized, placebo-controlled study with patients who had two to six migraine attacks per month. In the 1st month, the entire sample received only placebo, and then 30 patients were randomized to receive 16 mg of candesartan for 12 weeks and, subsequently, placebo for another 12 weeks. The other 30 patients were randomized to do the opposite (receiving placebo for 12 weeks and then receiving candesartan 16 mg for another 12 weeks).

Candesartan was superior to placebo when considering the mean number of days with headache in the 12-week period of treatment as the main outcome. Analysis according to intention to treat showed that during the 12 weeks of

treatment, the patients had an average of 13.6 ± 10.7 days with headache versus 18.5 ± 12.5 days during the 12 weeks of placebo ($p = 0.001$). There was no difference in adverse events between the two treatment groups.

In conclusion, candesartan 16 mg was superior to placebo in this 12-week crossover study, both in the primary and in all secondary outcomes, except regarding lost working days and the Health-Related Questionnaire SF-36, regarding quality of life.

In 2014, Stovner et al.⁹ conducted a triple-blind study comparing candesartan cilexetil 16 mg, slow-release propranolol 160 mg, and placebo. This was a placebo-controlled study, with a double crossover between groups, evaluating 72 adult subjects with episodic or chronic migraine. All patients received the 3 possible treatments for 12 weeks each. The primary outcome was the number of days with migraine for 4 weeks. In a modified intention-to-treat analysis, candesartan 16 mg was superior to placebo (2.95 versus 3.53 days) and was not worse than slow-release propranolol 160 mg (2.91 days).

Telmisartan

Studies

A randomized, double-blind, placebo-controlled study in parallel groups to study the effect of telmisartan 80 mg on migraine prevention showed that it was not superior to placebo.¹⁰ After 12 weeks, there was no statistically significant reduction in the number of days with migraine (telmisartan group 80 mg = 1.65 ± 3.46 days and placebo group = 1.14 ± 3.78 days; $p = 0.739$). The side effects observed were similar in the two groups.

Conclusion

Among angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), there is a consensus that candesartan is a good option for the preventive treatment of EM (grade A recommendation). Despite weak evidence of efficacy, lisinopril and enalapril can be used for the prophylaxis of EM, primarily as adjuvant therapy in patients with associated arterial hypertension (grade C recommendation for both). Captopril and telmisartan are not recommended for migraine prophylaxis (recommendation grades U and B, respectively).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

General aspects

Selective serotonin reuptake inhibitors (SSRIs) are drugs that increase the intrasynaptic serotonin levels through potent selective inhibition of serotonin reuptake,¹¹ with minimal effect on the reuptake of norepinephrine and dopamine.¹²⁻¹⁵

Citalopram/Escitalopram

Studies

For citalopram, two Class II studies with negative evidence have been conducted.¹⁶

Regarding escitalopram, there is only one Class III study, which compared it with venlafaxine. In the escitalopram group, frequency, duration, and intensity decreased significantly in the same proportions as with venlafaxine, but with a better safety profile for escitalopram.

Fluoxetine

Studies

Four double-blind, parallel controlled clinical trials¹⁷⁻²⁰ and subsequent reviews suggested that fluoxetine was ineffective for the prophylaxis of migraine attacks.^{21,22}

Sertraline

Studies

There is only one randomized prospective study (Class III), which revealed that sertraline was ineffective for migraine prophylaxis.²³

Fluvoxamine

Studies

In the study by Bánk,²⁴ with 70 participants, the individuals were randomly subdivided into 2 treatment groups: amitriptyline ($n = 32$; 24 women; with a dose of 25 mg/day) and fluvoxamine ($n = 32$; 23 women; with a dose of 50 mg/day). At the end of the study, there was an improvement in headache rates for both treatments.

Conclusion

There is insufficient evidence to indicate the use of citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, or mirtazapine for migraine prevention.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS

Venlafaxine

General aspects

Venlafaxine is a potent inhibitor of presynaptic reuptake of serotonin and norepinephrine and a weak dopamine reuptake inhibitor. Its metabolism is widely mediated by cytochrome P450. The half-life times of venlafaxine and its active metabolite are 5 and 11 hours, respectively, and their elimination occurs essentially through urine.²⁵

Studies

A parallel, randomized, double-blind, placebo-controlled study evaluated 60 patients in 3 groups for 10 weeks: venlafaxine 75 mg, 150 mg, or placebo. Significant reductions in migraine frequency and consumption of analgesics were observed for the active groups.²⁶ Bulut et al.²⁷ conducted a double-blind, randomized, crossover clinical trial in which they analyzed individuals with episodic migraine who used venlafaxine 150 mg/day and amitriptyline 75 mg/day. In both groups, there were significant reductions in the

frequency, duration, and intensity of migraine, with no statistical difference between them.

According to the meta-analysis by Wang et al.,²⁸ the clinical trials with venlafaxine are not very robust, since most of them were considered to have a clear risk of bias. The mode of randomization was not reported in all studies; two of them were blind while two were open; and most had no published protocol. Despite these methodological limitations, venlafaxine promoted significant reductions in the frequency, duration, and intensity of migraine.

Duloxetine

General aspects

Duloxetine acts as a double inhibitor of serotonin and norepinephrine reuptake, but it weakly inhibits dopamine reuptake as well.²⁹

Studies

Two studies were included: a Class II study and a Class III study. Young et al.³⁰ published a prospective study on duloxetine among patients without depression who presented EM (on 4 to 10 days per month), and who were titrated for a final dose of 120 mg. In an intention-to-treat analysis, the subjects went from 9.2 ± 2.7 days to 4.5 ± 3.4 days of headache per month ($p < 0.001$). As a result, 52% of the patients had an improvement $\geq 50\%$ in the number of headache days. The authors concluded that duloxetine, at high doses, may be effective in individuals with episodic migraine, even without depression.

In 2019, Kisler et al.³¹ studied the preventive effect of duloxetine on EM through a prospective, placebo-controlled, double-blind clinical trial with 27 patients (25 women) without depression. The patients started at a dose of 30 mg/day of duloxetine in the 1st week and their dose was increased to 60 mg/day in the 2nd week, which was then continued until the end of 8 weeks of treatment. The authors concluded that duloxetine was more effective than placebo in preventing migraine, with improvements in the frequency of migraine attacks (2.0 versus 1.3), frequency of migraine days per month (3.3 versus 1.7), and other parameters (intensity and self-esteem) (3.3 versus 1.7).

Conclusion

There is a consensus that venlafaxine and duloxetine are probably effective for migraine prophylaxis, especially in individuals who also have psychiatric comorbidities, such as anxiety disorders and depression.

There is insufficient evidence to indicate the use of citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, or mirtazapine for migraine prevention.

CALCIUM CHANNEL BLOCKERS

General aspects

Calcium channel blockers (CCBs) form a heterogeneous group of medications that began to be studied for prophylactic migraine treatment in 1981.³²⁻⁴² The mechanism of

action of these drugs in migraine is debatable.^{43,44} It has been postulated that blockade of calcium channels inhibits the entry of extracellular calcium into the cells of the muscle layer of the brain vessels. However, direct blockade of 5-HT receptors has been considered essential for calcium channel blockers to be effective for migraine, especially regarding flunarizine^{45,46} and verapamil.⁴⁷

Flunarizine

General aspects

Flunarizine is the most widely used drug in this group. In addition to being a nonselective calcium channel antagonist,⁴³ it blocks the voltage-dependent sodium channels^{48,49} and can reduce the number of occurrences and the duration of cortical spreading depression (CSD). It may decrease mitochondrial injury induced by CSD⁵⁰ and has antagonistic action for the dopaminergic receptor D2, which can also contribute to the prophylactic migraine effect.⁵¹

Studies

Although there are 7 double-blind, randomized, placebo-controlled studies in which flunarizine, in a single nocturnal dose of 10 mg, was shown to reduce the frequency, the duration, and the intensity of migraine attacks, these studies do not present the necessary requirements to categorize this finding as Level A evidence due to various factors, especially the low number of subjects studied.^{32,52-57}

Three meta-analysis studies corroborate the positive results from primary outcomes,⁵⁸⁻⁶⁰ with the caveat in one of them⁶⁰ that the decrease in the frequency of headache attacks would take place at weeks 8, 12, 16, and 20, but not in week 4.

There are comparative studies, among which the ones of greatest relevance are precisely those that demonstrated effects comparable with those from drugs of recognized efficacy such as propranolol^{60,61} and topiramate.^{62,63}

The primary outcomes from other comparative analyses showed that the efficacy of flunarizine was similar to that of metoprolol,⁶⁴ nifedipine,⁶⁵ valproate,⁶⁶ and topiramate.^{62,63}

Nicardipine

Studies

In a single Class II study, nicardipine, at a dose of 20 mg twice daily, was evaluated among 30 migraine patients. It was shown to have greater efficacy than placebo regarding decreased frequency, intensity, and duration of attacks. However, a reanalysis of this study⁶⁰ revealed, through the confidence interval (CI), that there was no statistical difference in the frequency of migraine attacks. Therefore, there are no studies showing an indication for use of nicardipine in prophylactic treatment of migraine. Nicardipine is no longer commercialized in Brazil.

Nifedipine

Studies

There are two Class III studies on nifedipine for prophylactic treatment of migraine. The first of these, with 24 patients,

using 30 mg per day, revealed that there was no difference in the primary outcome in relation to placebo.⁶⁷ The second, with 28 patients, using nifedipine at a dose of 5 mg, 3 times a day, demonstrated its efficacy in reducing the frequency of attacks.⁶⁸ A meta-analysis on these two studies showed that nifedipine was not superior to placebo.⁶⁰ In a comparative study with propranolol, the adverse events of nifedipine were the main factor responsible for the high rate of abandonment among patients, and it was concluded that this is not a drug of choice for prophylactic treatment of migraine.⁶⁹

Nimodipine

Studies

There are three class II and three class III studies, all of them double-blind, randomized and placebo-controlled, on the efficacy of nimodipine for migraine prophylaxis, with discordant results. A meta-analysis using the results from these studies and others concluded that there is no difference between nimodipine and placebo.⁶⁰

Verapamil

Studies

The prophylactic effect of verapamil for treating migraine patients was evaluated in two class III, double-blind, randomized, placebo-controlled studies, but with only 12 patients⁷⁰ and 14 patients.³⁹ The doses used were 240 mg per day³⁹ and 320 mg per day.⁷⁰ Although in both studies the results were considered positive, a subsequent reanalysis of the results did not identify any difference in reducing the frequency of attacks.⁶⁰

Conclusion

There is a consensus regarding the efficacy of flunarizine and its indication for prophylactic treatment of migraine, taking into consideration the absolute and relative contraindications. There is also a consensus that nifedipine, nimodipine, and verapamil should not be used in migraine prophylaxis.

OTHER DRUGS

Antihistamine (Cyproheptadine)

General aspects

Cyproheptadine is a first-generation antagonist of H1 histaminergic receptors, 5-HT₂ serotonergic receptors, and calcium channels. Cyproheptadine blocks the activity of 5-HT₂ receptors in the vascular wall and platelets, thereby reducing platelet aggregation.⁷¹

Studies

A small number of clinical trials have shown that cyproheptadine is effective for preventive treatment of migraine. In a double-blind, randomized crossover study involving 60 adult patients, cyproheptadine was shown to be safe and more effective than placebo after 12 weeks, although the groups were not adequately matched, thus reducing the study power

(Class III).⁷² A study by Rao et al.,⁷³ with a double-blind, randomized, placebo-controlled design, included 259 patients aged between 16 and 53 years old divided into 4 groups: placebo, cyproheptadine, propranolol, and cyproheptadine and propranolol for 12 months. It demonstrated that cyproheptadine and propranolol were significantly more effective than placebo. The highest efficacy was obtained when cyproheptadine and propranolol were used in combination (Class II).

Conclusion

Despite the small number of trials, cyproheptadine is a good choice for preventive treatment of migraine, in association with other prophylactic drugs and in thinner patients.

Serotonergic antagonist (Pizotifen)

General aspects

Pizotifen is a serotonergic antagonist that acts primarily on 5-HT_{2A} and 5-HT_{2C} receptors. It has mild antihistamine and anticholinergic action.

Studies

The efficacy and safety of pizotifen were compared against placebo in adults,^{74,75} showing good results for pizotifen. Randomized, double-blind comparative studies comparing pizotifen with other drugs have sometimes included a placebo arm or more than one arm with an active drug. In terms of efficacy, pizotifen was similar to the comparison drug (iprazochrome,^{75,76} flunarizine,⁷⁷⁻⁸⁰ metoprolol,⁸¹ prophylactic naproxen,⁸² nimodipine,⁸³ propranolol, and amitriptyline),⁸⁴ while one study showed that pizotifen was less effective than cyclandelate.⁸⁵

A double-blind, randomized, crossover dosing study was conducted to compare 2 schemes:⁸⁶ a single dose or 3 doses per day of pizotifen (equal total dose of 1.5 mg/day in these two schemes). Their efficacy was similar, but there was better tolerability of the single dose. Cleland et al.⁸⁷ conducted a partially open and partially double-blind study, both with crossover design, to compare prophylaxis for migraine using pizotifen with treatment using sumatriptan only in the attacks. Only when the patient had more than four migraine attacks per month was it better to use pizotifen. Unfortunately, a German study⁸⁸ could not be evaluated here since it did not contain an abstract and the authors of the present review were unable to obtain the original text. Level of evidence/recommendation: 3B.

Conclusion

Studies on pizotifen are typically old, sometimes designed before the criteria established by the International Headache Society had been defined. Nonetheless, it is a safe drug, even during pregnancy. Data are insufficient to determine the effectiveness of Pizotifen.

Melatonin

General aspects

The mechanism of action of melatonin is thought to involve anti-inflammatory effects, free radical elimination effects,

inhibition of dopamine release, reduction of positive regulation of proinflammatory cytokine, and protection of neurotoxicity through inhibiting glutamate release.^{89,90}

Studies

A randomized, double-blind, placebo-controlled study was conducted among 196 subjects with episodic migraine with aura or without aura. Melatonin 3 mg was compared with amitriptyline 25 mg and placebo for 3 months. Melatonin was better than amitriptyline and placebo, with a reduction > 50% in the frequency of migraine.⁹¹

Conclusion

There is a consensus that melatonin is possibly effective for prophylactic treatment of EM (Class II; Level C).

Alpha-Adrenergic blockers (Clonidine)

General aspects

Clonidine is an imidazole derivative that is an antagonist of the α_2 presynaptic receptors in the periphery and in the central nervous system (CNS). Peripherally, it inhibits the release of norepinephrine from sympathetic nerves and decreases the sympathetic tone by modulating vasodilation and constriction.^{92,93} Centrally, it inhibits the electrical currents of calcium ions, thus mediating analgesia in the spinal cord.⁹⁴

Studies

Clonidine has been evaluated through double-blind and placebo-controlled studies^{92,93,95–103} and in comparisons with propranolol¹⁰⁴ and metoprolol¹⁰⁵ in different age groups. Some studies have not shown any evidence in favor of clonidine. Other studies have presented conflicts, demonstrating some parameters of improvement and others of equality to placebo. In the study comparing clonidine with propranolol,¹⁰⁴ the two agents had similar prophylactic effects. Because of the divergence of the data, clonidine is not considered effective for prophylactic treatment of EM.

Conclusion

There is a consensus that clonidine is not effective for prophylactic treatment of EM.

Neuroleptics (Quetiapine, Aripiprazole, and Ziprasidone)

General aspects

Neuroleptics antagonize serotonin (5-HT_{1a} and 5-HT₂), dopamine (D₁ and D₂), histamine (H₁), and adrenergic receptors (alpha-1 and alpha-2).¹⁰⁶

Studies

Open case-control studies have evaluated quetiapine,^{107,108} a case-control study has evaluated aripiprazole,¹⁰⁹ and there is a case report on ziprasidone.¹¹⁰ All of these studies demonstrated that these agents were effective for controlling EM attacks. However, the levels of

evidence and recommendation were very low, which means that there is no indication for their use as prophylactics.

Conclusion

The neuroleptics quetiapine and aripiprazole have been shown to be effective for treating migraine in open case-control studies. Ziprasidone was not evaluated at all. For these reasons, there is a consensus that although quetiapine and aripiprazole were effective in open studies, they cannot be considered prophylactic due to lack of data from controlled studies.

Vitamin K inhibitor (Warfarin)

General aspects

Warfarin is a vitamin K antagonist that acts by inhibiting platelet aggregation and secretion of 5-hydroxytryptamine (5-HT),¹¹¹ acting in the coagulation cascade of intrinsic factors (factors II, VII, IX, X).¹¹²

Studies

Nine case reports^{112–120} and two open studies have evaluated the use of warfarin.^{111,121} The doses used were 5 to 10 mg in a single dose. However, most studies have reported on the use of warfarin for maintaining INR between 2 and 3. The studies have suggested that warfarin is effective for controlling EM attacks. In most studies, the improvement of migraine was detected serendipically when using warfarin in associated clinical situations such as pulmonary thromboembolism, peripheral venous thrombosis, and atrial fibrillation. The clinical response seems to be more marked in cases of migraine with aura.

Conclusion

Warfarin is possibly effective for prophylaxis of EM, especially in patients with migraine with aura. There is a consensus that, due to the risk-benefit balance, warfarin should not be used in migraine prophylaxis.

Leukotriene receptor antagonist (Montelukast)

General aspects

Leukotriene receptor agonists produce a reduction in proinflammatory mediators, specifically in the production of leukotriene (LTB₄) in leukocytes, thus altering platelet aggregability.^{122–125}

Studies

Montelukast has been evaluated through a multicenter, double-blind placebo-controlled study,¹²⁶ two case-control studies,^{127,128} and four case reports.^{129–132} The multicenter, double-blind, placebo-controlled study showed that this drug was not more effective than placebo. The open case studies demonstrated drug effectiveness and there was also a therapeutic response in the case reports. Montelukast is considered a possibly ineffective drug for prophylactic treatment of migraine.

Conclusion

There is a consensus that montelukast should not be indicated for prophylactic treatment of episodic migraine.

Statins (Simvastatin and Atorvastatin)

General aspects

Statins have anti-inflammatory properties,^{133,134} vasomotor effects,¹³⁵ and effects on platelet coagulation,¹³⁶ in addition to central action on the trigeminal caudal nucleus.¹³⁷

Studies

Atorvastatin 40 mg/day ($n = 46$) was compared in a double-blind study with sodium valproate 500 mg/day ($n = 36$) for prophylaxis of high-frequency migraine (6 to 15 days/month). After 3 months of treatment, it was shown to be able to reduce the number of days with pain, the duration and intensity of attacks, and the consumption of analgesics.¹³⁸

In an open study, 20 mg simvastatin ($n = 29$ women with dyslipidemia) was compared with propranolol 60 mg ($n = 25$ women) for treatment of EM over a 90-day treatment period. Both groups reduced the number of days with headache by > 50%.¹³⁹ In another study, use of simvastatin 20 mg + vitamin D 1,000 units twice daily was compared with a placebo group for treatment of EM over a 24-week follow-up period. In the simvastatin group, 25% of the patients reduced the number of migraine days by > 50% with 12 weeks of treatment and 29% achieved this after 24 weeks of treatment.¹⁴⁰

Conclusion

There is a consensus that atorvastatin and simvastatin are possibly effective for prophylactic treatment of EM. However, they should be used primarily as adjuvant therapy for patients with dyslipidemia (– **Table 1**).

RATIONAL POLYOTHERAPY

True polytherapy and false polytherapy

Polytherapy can be divided into two subtypes: 1) true polytherapy; and 2) false polytherapy. The first consists of prescribing two or more drugs for treating migraine and the second is a situation in which at least one drug is directed to treating comorbidity.¹⁴¹

Evidence and Justifications for rational polytherapy

Rational polytherapy in migraine is a topic that has been discussed for a long time.¹⁴² Preventive treatment of episodic migraine always begins with monotherapy, but if attacks become more frequent and refractory to monotherapy, the natural tendency is to use associations of drugs in an add-on system.¹⁴³ Although this is a common practice in the offices of headache specialists, only a small number of clinical trials have been conducted on polytherapy within migraine prophylaxis.^{143–145} – **Table 2** briefly describes the studies that have supported the use of polytherapy.

Conclusion

Monotherapy is the rule for the initial treatment of EM. In some situations, polytherapy may be indicated. There is no consensus on when to indicate it. There is a consensus that polytherapy should not be started until after at least 2 drugs with recommendation level A and/or B have been tried, at appropriate doses and for a minimum of 6 weeks.

Authors' Contributions

PSFS: Discussion, group coordinator, writing, reviewing, conceptualization; EMM, PAK: discussion, group coordinator, writing, reviewing, conceptualization, editing, data collection; AOK, ATNMC, CAPR, EMS, GOMT, IF, LCC, LMB, MFPP, PMP, RPSN, HCC: writing, reviewing, discussion, conceptualization; EJP, JJFC: writing, reviewing, editing, group coordinator, discussion; JAS, LPQ, MNPS: writing, reviewing, editing, discussion; JAJM, JBAS, MENMC: writing, reviewing, discussion; JGS: writing; MRCFF, MEJ, PFMF, YDF: writing, reviewing; PFMRF: conceptualization, data collection, writing, reviewing, editing.

Conflict of Interest

AOK: Speaker for Allergan, Ipsen Pharma, Merz, and Onyxann Cantera; AT: Lilly, Teva, Ache, Supera, Allergan, and Novartis; CAPR: Teva, Novartis, Eli Lilly, Lundbeck, Aché, Apsen, and EJPC: Speaker for Novartis, Allergan, Libbs, and Lilly; EMS: Speaker for Libbs, Allergan, Novartis, Lilly, Lundbeck, and Teva. Advisory board: Allergan, Libbs, Teva, and Lundbeck; EMM: Speaker for Teva, Novartis, Eli Lilly, and Allergan; Advisory board: Libbs and Eli Lilly; GOMT: Speaker for Eli Lilly; HCC: Speaker for Allergan and Eli Lilly; ID, JAMJ, BAJ, MRCFF, MEJ, PFMF, RPSN, YDF: No conflict of interests to declare; AJS: Speaker for Eli Lilly, Novartis, and Teva; JJC: Speaker for Eli Lilly, Novartis, Teva, and Libbs; Advisory board: Teva, Novartis, and Eli Lilly; JCS: Speaker for Teva, Novartis, and Allergan, Lilly; LCC: Speaker for Allergan, Novartis, and Sanofi; Advisory board: Allergan; LMB: Speaker for Novartis; LPQ: Speaker for Eli Lilly and Allergan; Advisory board: Eli Lilly and Teva; MNPS: Speaker for Eli Lilly, Novartis, Teva, Allergan, and Libbs; Advisory board: Sanofi, Eli Lilly, and Libbs; MENMC: Speaker for Eli Lilly, Novartis, Teva, and Allergan; Advisory board: Eli Lilly; MFPP: Grants from Fapesp and CNPq; personal fees from Allergan, Eurofarma, Eli Lilly, Libbs, Novartis, Pfizer, and Teva, during studies; PMP: Speaker for Novartis, Teva, Eli Lilly, and Libbs; Advisory board: Libbs; PSFS: Speaker for Teva, Novartis, Allergan, EMS, and Politec; Advisory board: Libbs and Eli Lilly; PAK: Fees for services from Libbs, Novartis, Allergan, Livanova, and Teva; PASRF: Speaker for Eli Lilly, Novartis, Allergan, and Libbs; Advisory board: Novartis, and Eli Lilly.

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Table 1 Drugs, dosages, adverse effects, evidence level, recommendation level, and risks in pregnancy and breastfeeding

Drug	Frequency of dosage and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy/ breastfeeding
POSITIVE EVIDENCE					
Angiotensin-converting enzyme inhibitors					
Lisinopril	10–20 mg/day 2x/day; maximum 80 mg orally	Dry cough, fatigue, dizziness, vertigo, lipothymia, hyperkalemia	1 class II study	Level C: possibly efficacious	C - D - D / Use with care Breastfeeding: Low risk
Enalapril	10–20 mg/day 1x or 2x/day; maximum 40 mg orally		1 class II study	Level C: possibly efficacious	C - D - D / use with care Breastfeeding: Potential severe adverse events in the baby; stop medication or breastfeeding
Captopril	50 mg/day; up to 450 mg/day 3x/day orally		1 class III study	Level U: conflicting data.	C - D - D / use with care Breastfeeding: Very low risk
Angiotensin receptor blockers					
Candesartan	8–16 mg/day; maximum 32 mg 1–2x/day orally	Dizziness, arterial hypotension, fatigue, paresthesia, hyperkalemia	2 class I studies	Level A: Established as efficacious	C - D - D / Contraindicated Breastfeeding: Low risk; moderately safe; monitor use
Calcium channel blockers					
Flunarizine	5–10 mg/day 1x at night orally	Somnolence, weight gain, depression, fatigue, vertigo, arterial hypotension, hypokinesia, tremor, rigidity	Class II (≥ 2 studies)	Level B: Probably efficacious	Category C Breastfeeding: High risk
Nicardipine	60–120 mg/day 3x/day orally	Headache, dizziness, facial redness, dyspnea	1 class II study and 1 class IV study	Level U: conflicting data	Unknown fetal risk due to lack of studies Breastfeeding: avoid it because of lack of information.
Nifedipine	10–60 mg/day - 1–3x/day orally	Dizziness, leg edema, facial redness, headache	2 class III studies (1 positive and one negative)	Level U: conflicting data	Category C Breastfeeding: very low risk
Drug	Frequency of dosage and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy/ breastfeeding
Neuroleptics					
Quetiapine	25–150 mg/ day 1 or 2x/day Maximum 800 mg orally	Excessive sedation, confusion, weight gain	2 class III studies	Level C: Possibly efficacious	Category C Breastfeeding: Very low risk

(Continued)

Table 1 (Continued)

Drug	Frequency of dosage and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy/breastfeeding
Aripiprazole	5–20 mg/day 1x/day Maximum 30 mg orally		1 class III study	Level U: Conflicting data	Category C Breastfeeding: Low risk
Ziprasidone	40–80 mg/day 2x/day orally		1 class IV study	Level U: Conflicting data	Category C Breastfeeding: High risk
Statins					
Atorvastatin	10–80 mg/day- average 20 mg 1x/day orally	Headache, dizziness, nausea, abdominal pain, insomnia	1 class II study	Level C: Possibly efficacious	Category X Breastfeeding: High risk
Simvastatin	5-80 mg/day - average 20 mg 1x/day orally		1 class II study and 1 class III study	Level C: Possibly efficacious	Category X Breastfeeding: High risk
Vitamin K inhibitor					
Warfarin	2.5–5 mg/day Maximum 10 mg/day (INR 2–3) 1x/day orally	Digestive, urinary, oral, and nasal bleeding	2 class III studies	Level C: Possibly efficacious	Category X Breastfeeding: Very low risk
Other drugs					
Melatonin	3 mg/day 1x at night orally	Fatigue, somnolence, difficulty in concentrating, depressive symptoms, headache, diarrhea, abnormal dreams,	1 class II study	Level C: Possibly efficacious	C / C / C Use with care Breastfeeding: Very low risk
Cyproheptadine	1–6.5 mg/day 1x/day orally	Somnolence, increased appetite, weight gain, dry mouth, blurred vision, glaucoma	≥ 2 class III studies and 1 class II study	Level C: Possibly efficacious	Category B Breastfeeding: Contraindicated
Pizotifen	1.5–3.0 mg/day 1–3x/day orally	Weight gain	≥ 2 class II studies	Level B: Probably efficacious	Category B Breastfeeding: Not recommended
Drug	Frequency of dosage and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy/breastfeeding
NEGATIVE EVIDENCE					
Angiotensin receptor blockers					
Telmisartan			1 class I study		

Table 1 (Continued)

Drug	Frequency of dosage and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy/breastfeeding
Selective serotonin reuptake inhibitor					
Sertraline	50–100 mg/day 1x/day Maximum 200 mg orally	See escitalopram	1 class II study	Level C: Possibly ineffective	Category C Breastfeeding: Very low risk
Fluoxetine	20–60 mg/day 1x/day orally		≥ 2 class II studies	Level B: Probably ineffective	Category C Breastfeeding: Low risk
Citalopram	10–20 mg/day 1x/day orally		2 class II studies	Level B: Probably ineffective	Category B and C Breastfeeding: Very low risk
Other drugs					
Clonidine	25 to 75 µg/day 2x/day Maximum 900 µg orally	Anxiety, tiredness, dry mouth, dizziness, dyspnea, palpitations, nausea, vomiting, stomachache, abdominal bloating, orthostatic hypotension, fainting, somnolence, rash, headache, irritability, insomnia	≥ 2 class I studies	Level A: Established as not efficacious	Category C Breastfeeding: High risk
Montelukast	5–20 mg/day orally	Not reported	Class I, class II and class III studies	Level B: Probably ineffective	Category C Breastfeeding: Low risk

Table 2 Clinical trials that used polytherapy in episodic migraine

Study	Drug	Type	n	Doses	I	D	F	AC	AG
Bordini et al. ¹⁴⁶	PPN vs FNZ vs PPN + FNZ	Double-blind and parallel randomized clinical trial	15 15 15	PPN 60 mg/day FNZ 10 mg/day	S	NA	S	NA	A
Pascual et al. ¹⁴⁷	BB vs VPA vs BB + VPA	Open clinical trial	52	BB 40–160 mg/day VPA 300–1,000 mg/day	NA	NA	↓	NA	A
Rampello et al. ¹⁶	AMT vs CTP vs AMT + CTP	Open and parallel randomized clinical trial	44 44 29	AMT 50 mg/day CTP 20 mg/day	NS	S	S	NA	A
Keskinboraet al. ¹⁴⁸	TPM vs AMT vs TPM + AMT	Double-blind and parallel randomized clinical trial	5 4 6	TPM 25–200 mg/day AMT 10–150 mg/day	NS	NS	NS	NA	A
Domingues et al. ¹⁴⁹	PPN vs NTP vs PPN + NTP	Double-blind and parallel randomized clinical trial	25 24 27	PPN 80 mg/day NTP 40 mg/day	NA	NA	S NS S	NA	A
Krymchantowski et al. ¹⁵⁰	TPM vs NTP vs TPM + NTP	Parallel randomized, placebo-controlled trial	80	TPM 100 mg/day NTP 30 mg/day	NA	NA	S	NA	A
Drug	Frequency of dosage and administration route	Adverse events		Evidence level	Recomm- endation level			Pregnancy/ breastfeeding	
Nimodipine	90 mg/day – 3x/day; Maximum 360 mg orally	Vertigo, facial redness, muscle pain, abdominal pain, weight loss, pruritus		1 class I study (negative) 2 class II studies (negative) and 2 class III studies (positive)	Level U: Conflicting data.			Undetermined risk in pregnancy Breastfeeding: Very low risk	
Verapamil	120–480 mg/day 3–4x/day or R** 1–2x/day orally	Constipation, skin erythema, headache		2 class IV studies	Level U: Conflicting data			Category C Breastfeeding: Very low risk	

Table 2 (Continued)

Study	Drug	Type	n	Doses	I	D	F	AC	AG
Serotonin and noradrenaline reuptake inhibitors									
Venlafaxine	37.5–150 mg/day 1x/day orally	Insomnia, headache, dizziness, sedation, nausea, dry mouth, constipation, hyperhidrosis, abnormal dreams, decreased libido		≥ 2 class II studies	Level B: Probably efficacious		Category C Breastfeeding: Use with care		
Duloxetine	30–120 mg/day 1x/day orally			2 class II studies	Level B: Probably efficacious		Category C Breastfeeding: Use with care		
Serotonin reuptake inhibitors									
Escitalopram	5–10 mg/day 1x/day orally	Insomnia, nausea, headache, asthenia, diarrhea, anorexia, somnolence, anxiety, nervousness, dry mouth, decreased libido, tremor, ejaculatory dysfunction, impotence, abnormal dreams, constipation, vomiting		1 class III study	Level C: Possibly efficacious		Category B Breastfeeding: Very low risk		
Paroxetine	20 mg/day 2x/day orally			1 class IV study	Level U: Conflicting data		Category D Breastfeeding: Very low risk		
Fluvoxamine	50 mg/day 1x at night orally	Somnolence, constipation, dry mouth, nausea, weakness		1 class II study	Level C: Possibly efficacious		Category C Breastfeeding: Very low risk		

Abbreviations: A, adults; AC, consumption of analgesics; AMT, amitriptyline; BB, beta-blocker; CTP, citalopram; D, duration; ES, age group; F, frequency; FNZ, flunarizine; I, intensity; NA, not assessed; NS, not significant; NTP, nortriptyline; P, pediatric; PCB, placebo; PPN, propranolol; S, significance with $p < 0.05$; TPM, topiramate; VPA, valproic acid.
↓ reduction, but without statistical analysis

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