

# 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

Paulo Sergio Faro Santos<sup>1</sup>  Eliana Meire Melhado<sup>2</sup>  Alexandre Ottoni Kaup<sup>3,4,5</sup>  Aline Turbino Neves Martins da Costa<sup>6</sup>  Célia Aparecida de Paula Roesler<sup>7</sup>  Élcio Juliato Piovesan<sup>8</sup>  Elder Machado Sarmento<sup>9</sup>  Giselle Oliveira Martins Theotonio<sup>10</sup>  Henrique Carneiro de Campos<sup>11</sup>  Ida Fortini<sup>12</sup>  Jano Alves de Souza<sup>13</sup>  Jayme Antunes Maciel Júnior<sup>14</sup>  João Batista Alves Segundo<sup>15</sup>  João José Freitas de Carvalho<sup>16,17</sup>  José Geraldo Speziali<sup>18</sup>  Leandro Cortoni Calia<sup>19</sup>  Liselotte Menke Barea<sup>20</sup>  Luiz Paulo Queiroz<sup>21</sup>  Marcio Nattan Portes Souza<sup>22</sup>  Marcos Ravi Cerqueira Ferreira Figueiredo<sup>23</sup>  Maria Eduarda Nobre de Magalhães Costa<sup>9,24</sup>  Mário Fernando Prieto Peres<sup>25</sup>  Mauro Eduardo Jurno<sup>26,27</sup>  Patrícia Machado Peixoto<sup>28</sup>  Pedro André Kowacs<sup>29,30</sup>  Pedro Augusto Sampaio Rocha-Filho<sup>31,32</sup>  Pedro Ferreira Moreira Filho<sup>33</sup>  Raimundo Pereira Silva-Neto<sup>34,35</sup>  Yara Dadalti Fragoso<sup>36</sup> 

<sup>1</sup> Instituto de Neurologia de Curitiba, Departamento de Neurologia, Setor de Cefaleia e Dor Orofacial, Curitiba PR, Brazil.

Address for correspondence Eliana Meire Melhado (e-mail: elianamelhado@gmail.com).

<sup>2</sup> Centro Universitário Padre Albino, Faculdade de Medicina, Departamento de Neurologia, Catanduva SP, Brazil.

<sup>20</sup> Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, Disciplina de Neurologia, Porto Alegre RS, Brazil.

<sup>3</sup> Houston Headache Clinic, Houston TX, USA.

<sup>21</sup> Universidade Federal de Santa Catarina, Hospital Universitário, Serviço de Neurologia, Florianópolis SC, Brazil.

<sup>4</sup> Universidade Federal de São Paulo, São Paulo SP, Brazil.

<sup>22</sup> Universidade de São Paulo, Hospital das Clínicas, São Paulo SP, Brazil.

<sup>5</sup> Universidade de Santo Amaro, São Paulo SP, Brazil.

<sup>23</sup> Hospital Universitário Antônio Pedro, Serviço de Neurologia, Niterói RJ, Brazil.

<sup>6</sup> Hospital Santa Marcelina, São Paulo SP, Brazil.

<sup>24</sup> Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil.

<sup>7</sup> Centro Médico de Neurologia, São Paulo SP, Brazil.

<sup>25</sup> Hospital Israelita Albert Einstein, Departamento de Neurologia, São Paulo, SP, Brazil.

<sup>8</sup> Universidade Federal do Paraná, Departamento de Clínica Médica, Disciplina de Neurologia, Curitiba PR, Brazil.

<sup>26</sup> Fundação José Bonifácio Lafayette de Andrade, Faculdade de Medicina de Barbacena, Barbacena MG, Brazil.

<sup>9</sup> Universidade Federal Fluminense, Rio de Janeiro RJ, Brazil.

<sup>27</sup> Fundação Hospitalar do Estado de Minas Gerais, Hospital Regional de Barbacena Dr. José Américo, Barbacena MG, Brazil.

<sup>10</sup> Universidade Federal do Rio de Janeiro, Centro de Pesquisas René Rachou, Editora UFRJ, Rio de Janeiro RJ, Brazil.

<sup>28</sup> Secretaria de Estado da Saúde do Distrito Federal, Brasília DF, Brazil.

<sup>11</sup> Clínica Neurológica, Belo Horizonte MG, Brazil.

<sup>29</sup> Instituto de Neurologia de Curitiba, Serviço de Neurologia, Curitiba PR, Brazil.

<sup>12</sup> Universidade de São Paulo, Faculdade de Medicina, Departamento de Neurologia, São Paulo SP, Brazil.

<sup>30</sup> Universidade Federal do Paraná, Complexo Hospital de Clínicas, Serviço de Neurologia, Curitiba PR, Brazil.

<sup>13</sup> Universidade Federal Fluminense, Departamento de Medicina Clínica, Disciplina de Neurologia, Niterói RJ, Brazil.

<sup>31</sup> Universidade Federal de Pernambuco, Centro de Ciências Médicas, Área de Neuropsiquiatria, Recife PE, Brazil.

<sup>14</sup> Universidade Estadual de Campinas, Faculdade de Ciências Médicas, Departamento de Neurologia, Campinas SP, Brazil.

<sup>32</sup> Universidade de Pernambuco, Hospital Universitário Oswaldo Cruz, Ambulatório de Cefaleias, Recife PR, Brazil.

<sup>15</sup> Centro Integrado de Saúde Lineu Araújo, Ambulatório de Neurologia, Teresina PI, Brazil.

<sup>33</sup> Universidade Federal Fluminense, Hospital Universitário Antônio Pedro, Departamento de Medicina Clínica, Niterói RJ, Brazil.

<sup>16</sup> Unichristus, Curso de Medicina, Disciplina de Neurologia, Fortaleza CE, Brazil.

<sup>34</sup> Universidade Federal do Pará, Belém PA, Brazil.

<sup>17</sup> Hospital Geral de Fortaleza, Serviço de Neurologia, Núcleo de Cefaleias, Fortaleza CE, Brazil.

<sup>35</sup> Universidade do Estado do Pará, Belém PA, Brazil.

<sup>18</sup> Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurologia, Ribeirão Preto SP, Brazil.

<sup>36</sup> Universidade Metropolitana de Santos, Santos SP, Brazil.

<sup>19</sup> Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo SP, Brazil.

Arq. Neuropsiquiatr. 2022;80(9):953-969.

received

December 11, 2021

accepted

April 9, 2022

DOI <https://doi.org/10.1055/s-0042-1755320>

ISSN 0004-282X.

© 2022. Academia Brasileira de Neurologia. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution 4.0 International License, permitting copying and reproduction so long as the original work is given appropriate credit (<https://creativecommons.org/licenses/by/4.0/>).

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

**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, ciproheptadine, 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 recaptação de serotonina, inibidores de recaptação 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.<sup>1,2</sup>

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).<sup>3</sup>

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

### 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.<sup>5</sup>

### Enalapril

#### Studies

A single randomized double-blind study<sup>6</sup> 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.<sup>7</sup>

### 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.<sup>8</sup> This was a double-blind, randomized, placebo-controlled study with patients who had two to six migraine attacks per month. In the 1<sup>st</sup> 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  $13.6 \pm 10.7$  days with headache versus  $18.5 \pm 12.5$  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.<sup>9</sup> 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.<sup>10</sup> After 12 weeks, there was no statistically significant reduction in the number of days with migraine (telmisartan group  $80 \text{ mg} = 1.65 \pm 3.46$  days and placebo group  $= 1.14 \pm 3.78$  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,<sup>11</sup> with minimal effect on the reuptake of norepinephrine and dopamine.<sup>12-15</sup>

## Citalopram/Escitalopram

### Studies

For citalopram, two Class II studies with negative evidence have been conducted.<sup>16</sup>

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 trials<sup>17-20</sup> and subsequent reviews suggested that fluoxetine was ineffective for the prophylaxis of migraine attacks.<sup>21,22</sup>

## Sertraline

### Studies

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

## Fluvoxamine

### Studies

In the study by Bánk,<sup>24</sup> 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.<sup>25</sup>

### 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.<sup>26</sup> Bulut et al.<sup>27</sup> 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.,<sup>28</sup> 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.<sup>29</sup>

### Studies

Two studies were included: a Class II study and a Class III study. Young et al.<sup>30</sup> 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  $9.2 \pm 2.7$  days to  $4.5 \pm 3.4$  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.<sup>31</sup> 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 1<sup>st</sup> week and their dose was increased to 60 mg/day in the 2<sup>nd</sup> 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.<sup>32-42</sup> The mechanism of

action of these drugs in migraine is debatable.<sup>43,44</sup> 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<sup>45,46</sup> and verapamil.<sup>47</sup>

## Flunarizine

### General aspects

Flunarizine is the most widely used drug in this group. In addition to being a nonselective calcium channel antagonist,<sup>43</sup> it blocks the voltage-dependent sodium channels<sup>48,49</sup> and can reduce the number of occurrences and the duration of cortical spreading depression (CSD). It may decrease mitochondrial injury induced by CSD<sup>50</sup> and has antagonistic action for the dopaminergic receptor D2, which can also contribute to the prophylactic migraine effect.<sup>51</sup>

### 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.<sup>32,52-57</sup>

Three meta-analysis studies corroborate the positive results from primary outcomes,<sup>58-60</sup> with the caveat in one of them<sup>60</sup> 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<sup>60,61</sup> and topiramate.<sup>62,63</sup>

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

## 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 study<sup>60</sup> 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.<sup>67</sup> 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.<sup>68</sup> A meta-analysis on these two studies showed that nifedipine was not superior to placebo.<sup>60</sup> 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.<sup>69</sup>

### 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.<sup>60</sup>

### 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 patients<sup>70</sup> and 14 patients.<sup>39</sup> The doses used were 240 mg per day<sup>39</sup> and 320 mg per day.<sup>70</sup> 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.<sup>60</sup>

### 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 nicardipine, 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.<sup>71</sup>

#### 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).<sup>72</sup> A study by Rao et al.,<sup>73</sup> 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-HT2<sub>A</sub> and 5-HT2<sub>C</sub> receptors. It has mild antihistamine and anticholinergic action.

#### Studies

The efficacy and safety of pizotifen were compared against placebo in adults,<sup>74,75</sup> 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 (ipravasochrome,<sup>75,76</sup> flunarizine,<sup>77-80</sup> metoprolol,<sup>81</sup> prophylactic naproxen,<sup>82</sup> nimodipine,<sup>83</sup> propranolol, and amitriptyline),<sup>84</sup> while one study showed that pizotifen was less effective than cyclandelate.<sup>85</sup>

A double-blind, randomized, crossover dosing study was conducted to compare 2 schemes:<sup>86</sup> 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.<sup>87</sup> 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 study<sup>88</sup> 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.<sup>89,90</sup>

#### 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.<sup>91</sup>

#### 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  $\alpha_2$  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.<sup>92,93</sup> Centrally, it inhibits the electrical currents of calcium ions, thus mediating analgesia in the spinal cord.<sup>94</sup>

#### Studies

Clonidine has been evaluated through double-blind and placebo-controlled studies<sup>92,93,95-103</sup> and in comparisons with propranolol<sup>104</sup> and metoprolol<sup>105</sup> 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,<sup>104</sup> 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<sub>1a</sub> and 5-HT<sub>2</sub>), dopamine (D<sub>1</sub> and D<sub>2</sub>), histamine (H<sub>1</sub>), and adrenergic receptors (alpha-1 and alpha-2).<sup>106</sup>

#### Studies

Open case-control studies have evaluated quetiapine,<sup>107,108</sup> a case-control study has evaluated aripiprazole,<sup>109</sup> and there is a case report on ziprasidone.<sup>110</sup> 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),<sup>111</sup> acting in the coagulation cascade of intrinsic factors (factors II, VII, IX, X).<sup>112</sup>

#### Studies

Nine case reports<sup>112-120</sup> and two open studies have evaluated the use of warfarin.<sup>111,121</sup> 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 serendipitously 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.<sup>122-125</sup>

#### Studies

Montelukast has been evaluated through a multicenter, double-blind placebo-controlled study,<sup>126</sup> two case-control studies,<sup>127,128</sup> and four case reports.<sup>129-132</sup> 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,<sup>133,134</sup> vasomotor effects,<sup>135</sup> and effects on platelet coagulation,<sup>136</sup> in addition to central action on the trigeminal caudal nucleus.<sup>137</sup>

#### 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.<sup>138</sup>

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  $> 50\%$ .<sup>139</sup> 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.<sup>140</sup>

### 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 POLYTHERAPY

### 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.<sup>141</sup>

### Evidence and Justifications for rational polytherapy

Rational polytherapy in migraine is a topic that has been discussed for a long time.<sup>142</sup> 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.<sup>143</sup> 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.<sup>143-145</sup> ►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 Onyx Cann; 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, JAJM, BAJS, MRCFF, MEJ, PFMFM, 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.

### References

- 1 Ripa P, Ornello R, Pistoia F, Carolei A, Sacco S. The renin-angiotensin system: a possible contributor to migraine

**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
<b>POSITIVE EVIDENCE</b>					
<b>Angiotensin-converting enzyme inhibitors</b>					
Lisinopril	10–20 mg/day 2x/day; maximum 80 mg orally	Dry cough, fatigue, dizziness, vertigo, lipotyphnia, 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
<b>Angiotensin receptor blockers</b>					
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
<b>Calcium channel blockers</b>					
Flunarizine	5–10 mg/day 1x at night	Somnolence, weight gain, depression, fatigue, vertigo, arterial hypotension, hypokinesia, tremor, rigidity	Class II ( $\geq 2$ 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
<b>Neuroleptics</b>					
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 <sup>a</sup>					
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
	40–80 mg/day 1x/day orally	Dizziness, arterial hypotension, fatigue, paresthesia, hyperkalemia		Level B: Probably ineffectuous	C - D - D / use with care Breastfeeding: High risk
<b>Selective serotonin reuptake inhibitor</b>					
Sertraline	50–100 mg/day 1x/day Maximum 200 mg orally	See escitalopram	1 class II study	Level C: Possibly ineffectuous	Category C Breastfeeding: Very low risk
Fluoxetine	20–60 mg/day 1x/day orally		≥ 2 class II studies	Level B: Probably ineffectuous	Category C Breastfeeding: Low risk
Citalopram	10–20 mg/day 1x/day orally		2 class II studies	Level B: Probably ineffectuous	Category B and C Breastfeeding: Very low risk
<b>Other drugs</b>					
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 ineffectuous	Category C Breastfeeding: High risk
Montelukast	5–20 mg/day orally	Not reported	Class I, class II and class III studies	Level B: Probably ineffectuous	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. <sup>146</sup>	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. <sup>147</sup>	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. <sup>148</sup>	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
Keskinboraz et al. <sup>148</sup>	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. <sup>149</sup>	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	NA	A
Krymchantowski et al. <sup>150</sup>	TPM vs NTP vs TPM + NTP vs TPM + PCB vs NTP + PCB	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 norepinephrine 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; CTP, citalopram; D, duration; ES, age group; F, frequency; FNZ, flunarizine; I, intensity; NA, not assessed; NS, not significant; NTP, nortriptyline; P, pediatrics; PCB, placebo; PPN, propranolol; S, significance with  $p < 0.05$ ; TPM, topiramate; VPA, valproic acid. ↓ reduction, but without statistical analysis

pathogenesis and prophylaxis. *Expert Rev Neurother* 2014;14(09):1043–1055

- Halker RB, Starling AJ, Vargas BB, Schwedt TJ. ACE and ARB Agents in the Prophylactic Therapy of Migraine—How Effective Are They? *Curr Treat Options Neurol* 2016;18(04):15
- Tronvik E, Stovner LJ, Bovim G, et al. Angiotensin-converting enzyme gene insertion/deletion polymorphism in migraine patients. *BMC Neurol* 2008;8:4. Doi: 10.1186/1471-2377-8-4
- Dorosch T, Ganzer CA, Lin M, Seifan A. Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Preventative Treatment of Episodic Migraine in Adults. *Curr Pain Headache Rep* 2019;23(11):85
- Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001;322(7277):19–22
- Sonbolestan SA, Heshmat K, Javanmard SH, Saadatnia M. Efficacy of Enalapril in Migraine Prophylaxis: A Randomized, Double-blind, Placebo-controlled Trial. *Int J Prev Med* 2013;4(01):72–77
- Paterna S, di Pasquale P, Martino S, et al. [Captopril versus placebo in the prevention of hemicrania without aura. A randomized double-blind study]. *Clin Ter* 1992;141(12):475–481
- Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289(01):65–69
- Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia* 2014;34(07):523–532. Doi: 10.1177/0333102413515348
- Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. *Cephalalgia* 2009;29(09):921–927. Doi: 10.1111/j.1468-2982.2008.01825.x
- Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007;46(04):281–290
- Lucas RA. The human pharmacology of fluoxetine. *Int J Obes Relat Metab Disord* 1992;16(Suppl 4):S49–S54
- DeVane CL. Pharmacokinetics of the selective serotonin reuptake inhibitors. *J Clin Psychiatry* 1992;53(Suppl):13–20
- Pastoor D, Gobburu J. Clinical pharmacology review of escitalopram for the treatment of depression. *Expert Opin Drug Metab Toxicol* 2014;10(01):121–128. Doi: 10.1517/17425255.2014.863873
- Lexapro FDA. (escitalopram oxalate) Tablets/Oral Solution NDA 21–323/NDA 21–365. Accessed in April 4<sup>th</sup> 2020 at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/02132s032,021365s023lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/02132s032,021365s023lbl.pdf)
- Rampello L, Alvano A, Chiechio S, et al. Evaluation of the prophylactic efficacy of amitriptyline and citalopram, alone or in combination, in patients with comorbidity of depression, migraine, and tension-type headache. *Neuropsychobiology* 2004;50(04):322–328
- Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache* 1992;32(02):101–104. Doi: 10.1111/j.1526-4610.1992.hed3202101.x
- Saper JR, Silberstein SD, Lake AE III, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994;34(09):497–502
- Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. *Cephalalgia* 1998;18(05):283–286

20 d'Amato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. *Headache* 1999;39(10):716-719

21 Tomkins GE, Jackson JL, O'Malley PG, Balden E, Santoro JE. Treatment of chronic headache with antidepressants: a meta-analysis. *Am J Med* 2001;111(01):54-63. Doi: 10.1016/s0002-9343(01)00762-8

22 Burch R. Antidepressants for Preventive Treatment of Migraine. *Curr Treat Options Neurol* 2019 Mar 21;21(04):18

23 Landy S, McGinnis J, Curlin D, Laizure SC. Selective serotonin reuptake inhibitors for migraine prophylaxis. *Headache* 1999;39 (01):28-32. Doi: 10.1046/j.1526-4610.1999.3901028.x

24 Bánk J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. *Headache* 1994;34(08):476-478. Doi: 10.1111/j.1526-4610.1994.hed3408476.x

25 Wellington K, Perry CM. Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* 2001;15(08):643-669

26 Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005;45(02):144-152

27 Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungan B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004;107(01):44-48

28 Wang F, Wang J, Cao Y, Xu Z. Serotonin-norepinephrine reuptake inhibitors for the prevention of migraine and vestibular migraine: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2020;45(05):323-330. Doi: 10.1136/rappm-2019-101207

29 Pergolizzi JV Jr, Raffa RB, Taylor R Jr, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract* 2013;13(03):239-252. Doi: 10.1111/j.1533-2500.2012.00578.x

30 Young WB, Bradley KC, Anjum MW, Gebeline-Myers C. Duloxetine prophylaxis for episodic migraine in persons without depression: a prospective study. *Headache* 2013;53(09):1430-1437. Doi: 10.1111/head.12205

31 Kisler LB, Weissman-Fogel I, Coghill RC, Sprecher E, Yarnitsky D, Granovsky Y. Individualization of migraine prevention: a randomized controlled trial of psychophysical-based prediction of duloxetine efficacy. *Clin J Pain* 2019;35(09):753-765. Doi: 10.1097/AJP.0000000000000739

32 Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. *Headache* 1981;21(06):235-239

33 Diamond S, Schenbaum H. Flunarizine, a calcium channel blocker, in the prophylactic treatment of migraine. *Headache* 1983;23 (01):39-42

34 Gelmers HJ. Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. *Headache* 1983;23(03):106-109

35 Amery WK. Flunarizine, a calcium channel blocker: a new prophylactic drug in migraine. *Headache* 1983;23(02):70-74

36 Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. *Headache* 1983;23(06):266-277

37 Meyer JS, Dowell R, Mathew N, Hardenberg J. Clinical and hemodynamic effects during treatment of vascular headaches with verapamil. *Headache* 1984;24(06):313-321. Doi: 10.1111/j.1526-4610.1984.hed2406313.x

38 Micieli G, Sances G, Pacchetti C, Trucco M, Magri M, Piazza D. Flunarizine: a wide spectrum prophylactic for migraine headache. *Int J Clin Pharmacol Res* 1984;4(03):239-245

39 Markley HG, Cheronis JC, Piepho RW. Verapamil in prophylactic therapy of migraine. *Neurology* 1984;34(07):973-976

40 Solomon GD. Verapamil in migraine prophylaxis—a five-year review. *Headache* 1989;29(07):425-427

41 Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989;29(03):167-168

42 Greenberg DA. Calcium channel antagonists and the treatment of migraine. *Clin Neuropharmacol* 1986;9(04):311-328

43 Olesen J. Calcium antagonists in migraine and vertigo. Possible mechanisms of action and review of clinical trials. *Eur Neurol* 1990;30(Suppl 2):31-34, discussion 39-41

44 Rau JC, Dodick DW. Other Preventive Anti-Migraine Treatments: ACE Inhibitors, ARBs, Calcium Channel Blockers, Serotonin Antagonists, and NMDA Receptor Antagonists. *Curr Treat Options Neurol* 2019;21(04):17

45 Peroutka SJ. The pharmacology of calcium channel antagonists: a novel class of anti-migraine agents? *Headache* 1983;23(06): 278-283

46 Peroutka SJ, Banghart SB, Allen GS. Relative potency and selectivity of calcium antagonists used in the treatment of migraine. *Headache* 1984;24(02):55-58

47 Markley HG. Verapamil and migraine prophylaxis: mechanisms and efficacy. *Am J Med* 1991;90(5A):48S-53S

48 Ye Q, Wang Q, Yan LY, et al. Flunarizine inhibits sensory neuron excitability by blocking voltage-gated  $\text{Na}^+$  and  $\text{Ca}^{2+}$  currents in trigeminal ganglion neurons. *Chin Med J (Engl)* 2011;124(17): 2649-2655

49 Ye Q, Yan LY, Xue LJ, et al. Flunarizine blocks voltage-gated  $\text{Na}^+$  and  $\text{Ca}^{2+}$  currents in cultured rat cortical neurons: A possible locus of action in the prevention of migraine. *Neurosci Lett* 2011; 487(03):394-399

50 Li F, Qiu E, Dong Z, Liu R, Wu S, Yu S. Protection of flunarizine on cerebral mitochondria injury induced by cortical spreading depression under hypoxic conditions. *J Headache Pain* 2011;12 (01):47-53

51 Ambrosio C, Stefanini E. Interaction of flunarizine with dopamine D2 and D1 receptors. *Eur J Pharmacol* 1991;197(2-3):221-223

52 Mentinopoulos G, Manafi T, Logothetis J, Bostantzopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. *Cephalgia* 1985;5(Suppl 2):135-140

53 Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalgia* 1986;6(01):7-14

54 Paterna S, Martino SG, Campisi D, Cascio Ingurgio N, Marsala BA. [Evaluation of the effects of verapamil, flunarizine, diltiazem, nimodipine and placebo in the prevention of hemicrania. A double-blind randomized cross-over study]. *Clin Ter* 1990;134 (02):119-125

55 Thomas M, Behari M, Ahuja GK. Flunarizine in migraine prophylaxis: an Indian trial. *Headache* 1991;31(09):613-615

56 al Deeb SM, Biary N, Bahou Y, al Jaber M, Khoja W. Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population). *Headache* 1992;32(09):461-462

57 Diamond S, Freitag FG. A double blind trial of flunarizine in migraine prophylaxis. *Headache Quart Curr Treatment Res* 1993; 4:169-172

58 Gray RN, Goslin RE, McCrory DC, Eberlein K, Tulsky J, Hasselblad V. AHRQ Technical Reviews. Drug treatments for the prevention of migraine headache. Rockville (MD): Agency for Health Care Policy and Research (US); 1999

59 Revez-Herault L, Cardona AF, Ospina EG, Carrillo P. [Effectiveness of flunarizine in the prophylaxis of migraine: a meta-analytical review of the literature]. *Rev Neurol* 2003;36(10): 907-912

60 Jackson JL, Cogbill E, Santana-Davila R, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. *PLoS One* 2015;10(07):e0130733. Doi: 10.1371/journal.pone.0130733

61 Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a

comparison with propranolol 160 mg daily. *Cephalgia* 2002;22(03):209–221

62 Luo N, Di W, Zhang A, et al. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. *Pain Med* 2012;13(01):80–86. Doi: 10.1111/j.1526-4637.2011.01295.x

63 Lai KL, Niddam DM, Fuh JL, et al. Flunarizine versus topiramate for chronic migraine prophylaxis: a randomized trial. *Acta Neurol Scand* 2017;135(04):476–483

64 Sørensen PS, Larsen BH, Rasmussen MJ, et al. Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991;31(10):650–657

65 Lamsudin R, Sadjimin T. Comparison of the efficacy between flunarizine and nifedipine in the prophylaxis of migraine. *Headache* 1993;33(06):335–338

66 Mitsikostas DD, Polychronidis I. Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. *Funct Neurol* 1997;12(05):267–276

67 McArthur JC, Marek K, Pestronk A, McArthur J, Peroutka SJ. Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. *Neurology* 1989;39(2 Pt 1):284–286. Doi: 10.1212/wnl.39.2.284

68 Shukla R, Garg RK, Nag D, Ahuja RC. Nifedipine in migraine and tension headache: a randomised double blind crossover study. *J Assoc Physicians India* 1995;43(11):770–772

69 Albers GW, Simon LT, Hamik A, Peroutka SJ. Nifedipine versus propranolol for the initial prophylaxis of migraine. *Headache* 1989;29(04):215–218

70 Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. *JAMA* 1983;250(18):2500–2502

71 Brunton LL, Da Fonseca AL, Langeloh A. As bases farmacológicas da terapêutica de Goodman e Gilman. McGRAW HILL - ARTMED. 2018 <https://books.google.com.br/books?id=tmrBvwEACAAJ>

72 Ryan RE. BC-105 a new preparation for the interval treatment of migraine—a double blind evaluation compared with a placebo. *Headache* 1971;11(01):6–18. Doi: 10.1111/j.1526-4610.1971.hed110106.x

73 Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. *Neurol India* 2000;48(03):223–226

74 Carroll JD, Maclay WP. Pizotifen (BC 105) in migraine prophylaxis. *Curr Med Res Opin* 1975;3(02):68–71. Doi: 10.1185/03007997509113649

75 Osterman PO. A comparison between placebo, pizotifen and 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindol (Divascan) in migraine prophylaxis. *Acta Neurol Scand* 1977;56(01):17–28. Doi: 10.1111/j.1600-0404.1977.tb01405.x

76 Kangasniemi P. Placebo, 1-isopropylnoradrenochrome-5-monosemicarbazono and pizotifen in migraine prophylaxis. *Headache* 1979;19(04):219–222. Doi: 10.1111/j.1526-4610.1979.hed1904219.x

77 Louis P, Spierings EL. Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: a double-blind study. *Cephalgia* 1982;2(04):197–203. Doi: 10.1046/j.1468-2982.1982.0204197.x

78 Cerbo R, Casacchia M, Formisano R, Buzzi MG, Boni B, Feliciani M, Grillo G, Cusimano G, Agnoli A. Double-blind clinical study: flunarizine versus pizotifen in a single nightly dose in hemigrana patients. [Article in Italian]. *Riv Neurol* 1985 Mar-Apr;55(02):139–146

79 Cerbo R, Casacchia M, Formisano R, et al. Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis. *Cephalgia* 1986;6(01):15–18. Doi: 10.1046/j.1468-2982.1986.0601015.x

80 Rascol A, Montastruc JL, Rascol O. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. *Headache* 1986;26(02):83–85. Doi: 10.1111/j.1526-4610.1986.hed2602083.x

81 Vilming S, Standnes B, Hedman C. Metoprolol and pizotifen in the prophylactic treatment of classical and common migraine. A double-blind investigation. *Cephalgia* 1985;5(01):17–23. Doi: 10.1046/j.1468-2982.1985.0501017.x

82 Behan PO, Connelly K. Prophylaxis of migraine: a comparison between naproxen sodium and pizotifen. *Headache* 1986;26(05):237–239. Doi: 10.1111/j.1526-4610.1986.hed2605237.x

83 Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in comparison with pizotifen in the prophylaxis of migraine. *Cephalgia* 1987;7(01):7–13. Doi: 10.1046/j.1468-2982.1987.0701007.x

84 Israel A, Ahmed S, Rahman KM, et al. Efficacy of amitriptyline, pizotifen and propranolol in the prevention of migraine. *Mymensingh Med J* 2013;22(01):93–100

85 Mastrosimone F, Iaccarino C, de Caterina G. Efficacy and tolerance of cyclandelate versus pizotifen in the prophylaxis of migraine. *J Med* 1992;23(01):1–16

86 Capildeo R, Rose FC. Single-dose pizotifen, 1.5 mg nocte: a new approach in the prophylaxis of migraine. *Headache* 1982;22(06):272–275. Doi: 10.1111/j.1526-4610.1982.hed2206272.x

87 Cleland PG, Barnes D, Erlington GM, Loizou LA, Rawes GD. Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997;38(01):31–38. Doi: 10.1159/000112899

88 Wörz R, Drillisch C. [Migraine prevention by a calcium channel blocker. Results of a double-blind study of flunarizine vs. pizotifen]. *MMW Munch Med Wochenschr* 1983;125(32-33):711–714

89 Vogler B, Rapoport AM, Tepper SJ, Sheftell F, Bigal ME. Role of melatonin in the pathophysiology of migraine: implications for treatment. *CNS Drugs* 2006;20(05):343–350. Doi: 10.2165/00023210-200620050-00001

90 Singh M, Jadhav HR. Melatonin: functions and ligands. *Drug Discov Today* 2014;19(09):1410–1418

91 Gonçalves AL, Martini Ferreira A, Ribeiro RT, Zukerman E, Cipolla-Neto J, Peres MF. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry* 2016;87(10):1127–1132. Doi: 10.1136/jnnp-2016-313458

92 Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. A randomized crossover trial. *J Fam Pract* 1989;29(02):153–156, discussion 157–158

93 Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine: a pilot and double-blind study. *Dev Med Child Neurol* 1982;24(06):837–841

94 Fairbanks CA, Stone LS, Kitto KF, Nguyen HO, Posthumus IJ, Wilcox GL. alpha(2C)-Adrenergic receptors mediate spinal analgesia and adrenergic-opioid synergy. *J Pharmacol Exp Ther* 2002;300(01):282–290

95 Shafar J, Tallett ER, Knowlson PA. Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. *Lancet* 1972;1(7747):403–407

96 Ryan RE Sr, Diamond S, Ryan RE Jr. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. *Headache* 1975;15(03):202–210. Doi: 10.1111/j.1526-4610.1975.hed1503202.x

97 Sillanpää M. Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children. *Headache* 1977;17(01):28–31

98 Stensrud P, Sjaastad O. Clonidine (Catapresan)-double-blind study after long-term treatment with the drug in migraine. *Acta Neurol Scand* 1976;53(03):233–236

99 Kallanranta T, Hakkarainen H, Hokkanen E, Tuovinen T. Clonidine in migraine prophylaxis. *Headache* 1977;17(04):169–172

100 Mondrup K, Moller CE. Prophylactic treatment of migraine with clonidine. A controlled clinical trial. *Acta Neurol Scand* 1977;56(05):405–412

101 Adam El, Gore SM, Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. *J R Coll Gen Pract* 1978;28(195):587–590

102 Boisen E, Deth S, Hübbe P, Jansen J, Klee A, Leunbach G. Clonidine in the prophylaxis of migraine. *Acta Neurol Scand* 1978;58(05):288–295

103 Das SM, Ahuja GK, Narainaswamy AS. Clonidine in prophylaxis of migraine. *Acta Neurol Scand* 1979;60(04):214–217

104 Kåss B, Nestvold K. Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine. A comparative trial. *Acta Neurol Scand* 1980;61(06):351–356

105 Louis P, Schoenen J, Hedman C. Metoprolol v. clonidine in the prophylactic treatment of migraine. *Cephalalgia* 1985;5(03):159–165

106 Mascia A, Afra J, Schoenen J. Dopamine and migraine: a review of pharmacological, biochemical, neurophysiological, and therapeutic data. *Cephalalgia* 1998;18(04):174–182

107 Krymchantowski AV, Jevoux C. Quetiapine for the prevention of migraine refractory to the combination of atenolol + nortriptyline + flunarizine: an open pilot study. *Arq Neuro-psiquiatr* 2008;66(3B):615–618. Doi: 10.1590/S0004-282×2008000500002

108 Brandes JL, Roberson SC, Pearlman SH, Abu-Shakra S. Quetiapine for migraine prophylaxis. 44th annual scientific meeting. American Headache Society 2002; Abstract S101. <https://doi.org/10.1046/j.1526-4610.2002.t01-1-04250.x>

109 LaPorta LD. Relief from migraine headache with aripiprazole treatment. *Headache* 2007;47(06):922–926

110 Boeker T. Ziprasidone and migraine headache. *Am J Psychiatry* 2002;159(08):1435–1436

111 Nilsson B, Back V, Wei R, Plane F, Jurasz P, Bungard TJ. Potential antimigraine effects of warfarin: An exploration of biological mechanism with survey of patients. *TH Open* 2019;3(02):e180–e189. Doi: 10.1055/s-0039-1692989

112 Maggioni F, Bruno M, Mainardi F, Lisotto C, Zanchin G. Migraine responsive to warfarin: an update on anticoagulant possible role in migraine prophylaxis. *Neurol Sci* 2012;33(06):1447–1449. Doi: 10.1007/s10072-011-0926-4

113 Narasimhan P. Letter: Decreased sensitivity to oral anticoagulant therapy after attacks of migraine. *Lancet* 1974;2(7889):1143. Doi: 10.1016/s0140-6736(74)90905-2

114 Suresh CG, Neal D, Coupe MO. Warfarin treatment and migraine. *Postgrad Med J* 1994;70(819):37–38. Doi: 10.1136/pgmj.70.819.37

115 Fragoso YD. Reduction of migraine attacks during the use of warfarin. *Headache* 1997;37(10):667–668. Doi: 10.1046/j.1526-4610.1997.3710667.x

116 Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of patent foramen ovale in migraine with aura. *J Headache Pain* 2005;6(02):71–76

117 Russo A, Santi S, Gueraldi D, De Paola M, Zani F, Pini LA. An unusual case report on the possible role of Warfarin in migraine prophylaxis. *Springerplus* 2013;2(01):48. Doi: 10.1186/2193-1801-2-48

118 Maggioni F, Zanchin G, Mainardi F. Warfarin prophylaxis in migraine without aura but not in primary exercise headache. *Acta Neurol Belg* 2016;116(02):215–216. Doi: 10.1007/s13760-015-0527-8

119 Nilsson BG, Bungard TJ. A case of migraine with aura resolving on warfarin but not on apixaban. *Headache* 2017;57(10):1614–1617. Doi: 10.1111/head.13190

120 Beh SC. A case of vestibular migraine resolving on Warfarin and topiramate. *Headache* 2018;58(04):599–600. Doi: 10.1111/head.13266

121 Mohanty S, Mohanty P, Rutledge JN, et al. Effect of catheter ablation and periprocedural anticoagulation regimen on the clinical course of migraine in atrial fibrillation patients with or without pre-existent migraine: results from a prospective study. *Circ Arrhythm Electrophysiol* 2015;8(02):279–287

122 Selmaj K, de Belleroche J, Das I, Rose FC. Leukotriene B4 generation by polymorphonuclear leukocytes: possible involvement in the pathogenesis of headache. *Headache* 1986;26(09):460–464. Doi: 10.1111/j.1526-4610.1986.hed2609460.x

123 Gazzaniga PP, Ferroni P, Lenti L, et al. Identification of blood leukotrienes in classical migraine. *Headache* 1987;27(04):211–215. Doi: 10.1111/j.1526-4610.1987.hed2704211.x

124 LaMancusa R, Pulcinelli FM, Ferroni P, et al. Blood leukotrienes in headache: correlation with platelet activity. *Headache* 1991;31(06):409–414. Doi: 10.1111/j.1526-4610.1991.hed3106409.x

125 Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007;14(18):1966–1977. Doi: 10.2174/092986707781368522

126 Brandes JL, Visser WH, Farmer MV, et al; Protocol 125 study group. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. *Headache* 2004;44(06):581–586. Doi: 10.1111/j.1526-4610.2004.446006.x

127 Freitag FG, Diamond S, Diamond ML, Urban G. Preventive treatment of migraine headache with rofecoxib and montelukast. In: Proceedings of 10th Congress of the International Headache Society, 2001 Jun 29 to Jul 3, Nova York, USA. *Cephalalgia* 2001; 21(4):375–376. P2–118. <https://doi.org/10.1046/j.1468-2982.2001.00022.x>

128 de Souza Carvalho D, Fragoso YD, Coelho FM, Pereira MM. Asthma plus migraine in childhood and adolescence: prophylactic benefits with leukotriene receptor antagonist. *Headache* 2002;42(10):1044–1047. Doi: 10.1046/j.1526-4610.2002.02236.x

129 Sheftell D, Rapoport AM, Walker B, Gamerman I, Weeks R, Baskin S. Leukotriene (LK) antagonists in the prophylaxis of migraine: a potential role for a new class of agents. *ASH Meeting* 1999; 39:381. <https://doi.org/10.1111/head.1999.39.5.344>

130 Sheftell F, Rapoport A, Weeks R, Walker B, Gamerman I, Baskin S. Montelukast in the prophylaxis of migraine: a potential role for leukotriene modifiers. *Headache* 2000;40(02):158–163. Doi: 10.1046/j.1526-4610.2000.00022.x

131 Pearlman EM, Fisher S. Preventive treatment for childhood and adolescent headache: role of once daily montelukast sodium. In: Proceedings of 10th Congress of the International Headache Society, 2001 Jun 29 to Jul 3, Nova York, USA. *Cephalalgia* 2001; 21(4):461. P3–O18. <https://doi.org/10.1046/j.1468-2982.2001.00028.x>

132 Souza Carvalho DS, Fragoso YD, Coelho FM, Pereira MM. Asthma + migraine in childhood and adolescence: prophylactic benefits with leukotriene receptor antagonist. In: Proceedings of 10th Congress of the International Headache Society, 2001 Jun 29 to Jul 3, Nova York, USA. *Cephalalgia* 2001; 21(4):375–376. P2–117. <https://doi.org/10.1046/j.1468-2982.2001.00022.x>

133 Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005;45:89–118

134 Larose E, Ganz P. Statins and endothelial dysfunction. *Semin Vasc Med* 2004;4(04):333–346

135 Couch JR, Hassanein RS. Platelet aggregability in migraine. *Neurology* 1977;27(09):843–848. Doi: 10.1212/wnl.27.9.843

136 Yetkin E, Turhan H. Is it worthwhile to test statin in migraine? *Headache* 2007;47(03):448–450. Doi: 10.1111/j.1526-4610.2007.00738.x

137 Yin Z, Fang Y, Ren L, et al. Atorvastatin attenuates NF-κappaB activation in trigeminal nucleus caudalis in a rat model of migraine. *Neurosci Lett* 2009;465(01):61–65. Doi: 10.1016/j.neulet.2009.08.081

138 Hesami O, Sistanizad M, Asadollahzade E, Johari MS, Beladi-Moghadam N, Mazhabdar-Ghashghai H. Comparing the effects of atorvastatin with sodium valproate (Divalproex) on frequência and intensity of frequent migraine headaches: A double-blind randomized controlled study. *Clin Neuropharmacol* 2018;41(03):94–97. Doi: 10.1097/WNF.0000000000000280

139 Medeiros FL, Medeiros PL, Valen a MM, Dodick D. Simvastatin for migraine prevention. *Headache* 2007;47(06):855–856. Doi: 10.1111/j.1526-4610.2007.00824.x

140 Buettrner C, Nir RR, Bertisch SM, et al. Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial. *Ann Neurol* 2015;78(06):970–981. Doi: 10.1002/ana.24534

141 D'Amico D. Controversies in migraine: monotherapy. *Neurol Sci* 2012;33(Suppl 1):S141–S145

142 Prusi ski A. Monotherapy or polytherapy in migraine. *Neuroepidemiology* 1987;6(04):186–189

143 Casucci G, Villani V, Cologno D, D'Onofrio F. Polytherapy for migraine prophylaxis. *Neurol Sci* 2012;33(Suppl 1): S147–S150

144 Evans RW, Pascual J, L inez MJ, Leira R. Bending the rule of monotherapy for migraine prevention? *Headache* 2005;45(06): 748–750

145 Krymchantowski AV, Bigal ME. Polytherapy in the preventive and acute treatment of migraine: fundamentals for changing the approach. *Expert Rev Neurother* 2006;6(03):283–289

146 Bordini CA, Arruda MA, Ciciarelli MC, Speciali JG. Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. *Arq Neuropsiquiatr* 1997; 55(3B):536–541

147 Pascual J, Leira R, L inez JM. Combined therapy for migraine prevention? Clinical experience with a beta-blocker plus sodium valproate in 52 resistant migraine patients. *Cephalalgia* 2003;23(10):961–962

148 Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. *Clin Neurol Neurosurg* 2008;110(10):979–984

149 Domingues RB, Silva AL, Domingues SA, Aquino CC, Kuster GW. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. *Arq Neuropsiquiatr* 2009;67(04):973–977

150 Krymchantowski AV, da Cunha Jevoux C, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. *J Headache Pain* 2012;13 (01):53–59. Doi: 10.1007/s10194-011-0395-4