Consensus of the Brazilian Headache Society (SBCe) for the Prophylactic Treatment of Episodic Migraine: part I

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

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

[1] Instituto de Neurologia de Curitiba, Departamento de Neurologia, Setor de Cefaleia e Dor Orofacial, Curitiba PR, Brazil.
[2] Centro Universitário Padre Albino, Faculdade de Medicina, Departamento de Neurologia, Catanduva SP, Brazil.
[3] Houston Headache Clinic, Houston TX, United States.
[4] Universidade Federal de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil.
[5] Universidade de Santo Amaro, São Paulo SP, Brazil.
[6] Hospital Santa Marcelina, São Paulo SP, Brazil.
[7] Q2 Centro Médico de Neurologia, Depto de Neurologia, São Paulo SP, Brazil.
[8] Universidade Federal do Paraná, Departamento de Clínica Médica, Disciplina de Neurologia, Curitiba PR, Brazil.
[9] Universidade Federal Fluminense, Rio de Janeiro RJ, Brazil.
[10] Universidade Federal do Rio de Janeiro, Centro de Pesquisas, Rio de Janeiro RJ, Brazil.
[11] Clínica Neurológica, Belo Horizonte MG, Brazil
[12] Universidade de São Paulo, Faculdade de Medicina, Departamento de Neurologia, São Paulo SP, Brazil.
[13] Universidade Federal Fluminense, Departamento de Medicina Clínica, Disciplina de Neurologia, Niterói RJ, Brazil.
[14] Universidade Estadual de Campinas, Faculdade de Ciências Médicas, Departamento de Neurologia, Campinas SP, Brazil.
[15] Centro Integrado de Saúde Lineu Araújo, Ambulatório de Neurologia, Teresina PI, Brazil.
[16] Unichristus, Curso de Medicina, Disciplina de Neurologia, Fortaleza CE, Brazil.
[17] Hospital Geral de Fortaleza, Serviço de Neurologia, Núcleo de Cefaleias, Fortaleza CE, Brazil.
[18] Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurologia, Ribeirão Preto SP, Brazil.
[19] Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo SP, Brazil.

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

[20] Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, Disciplina de Neurologia, Porto Alegre RS, Brazil.
[21] Universidade Federal de Santa Catarina, Hospital Universitário, Serviço de Neurologia, Florianópolis SC, Brazil.
[22] Universidade de São Paulo, Hospital das Clínicas, Depto de Neurologia, São Paulo SP, Brazil.
[23] Hospital Universitário Antônio Pedro, Serviço de Neurologia, Niterói RJ, Brazil.
[24] Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil.
[25] Hospital Israelita Albert Einstein, Departamento de Neurologia, São Paulo SP, Brazil.
[26] Fundação José Bonifácio Lafayette de Andrada, Faculdade de Medicina de Barbacena, Barbacena MG, Brazil.
[27] Fundação Hospitalar do Estado de Minas Gerais, Hospital Regional de Barbacena Dr. José Américo, Barbacena MG, Brazil.
[28] Secretaria de Estado da Saúde do Distrito Federal, Brasília DF, Brazil.
[29] Instituto de Neurologia de Curitiba, Serviço de Neurologia, Curitiba PR, Brazil.
[30] Universidade Federal do Paraná, Complexo Hospital de Clínicas, Serviço de Neurologia, Curitiba PR, Brazil.
[31] Universidade Federal de Pernambuco, Centro de Ciências Médicas, Área de Neuropsquiatria, Recife PE, Brazil.
[32] Universidade de Pernambuco, Hospital Universitário Oswaldo Cruz, Ambulatório de Cefaleias, Recife PR, Brazil.
[33] Universidade Federal Fluminense, Hospital Universitário Antônio Pedro, Departamento de Medicina Clínica, Niterói RJ, Brazil.
[34] Universidade Federal do Pará, Belém PA, Brazil.
[35] Universidade do Estado do Pará, Belém PA, Brazil.
[36] Universidade Metropolitana de Santos, Santos SP, Brazil.

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

Abstract

The Brazilian Headache Society (Sociedade Brasileira de Cefaleia, SBCe, in Portuguese) nominated a Committee of Authors with the aim of establishing a consensus with recommendations regarding prophylactic treatment for episodic migraine based on articles published in the worldwide literature, as well as personal experience. Migraine affects 1 billion people around the world and more than 30 million Brazilians. In addition, it is an underdiagnosed and undertreated disorder. It is well known within the medical community of neurologists, and especially among headache specialists, that there is a need to disseminate knowledge about prophylactic treatment for migraine. For this purpose, together with the need for drug updates and to expand knowledge of the disease itself (frequency, intensity, duration, impact and perhaps the progression of migraine), this Consensus was developed, following a full online methodology, by 12 groups who reviewed and wrote about the pharmacological categories of the drugs used and, at the end of the process, met to read and establish conclusions for this document. The drug classes studied were: anticonvulsants, tricyclic antidepressants, monoclonal anti-calcitonin gene-related peptide (anti-CGRP) antibodies, beta-blockers, antihypertensives, calcium channel inhibitors, other antidepressants (selective serotonin reuptake inhibitors, SSRIs, and dual-action antidepressants), other drugs, and polytherapy. Hormonal treatment and anti-inflammatories and triptans in minimum prophylaxis schemes (miniprophylaxis) will be covered in a specific chapter. The drug classes studied for part I of the Consensus were: anticonvulsants, tricyclic antidepressants, monoclonal anti-CGRP antibodies, and beta-blockers.

Keywords

- Migraine Disorders
- Consensus
- Preventive Medicine

Resumo

A Sociedade Brasileira de Cefaleia (SBCe) nomeou um Comitê de Autores com o objetivo de estabelecer um consenso com recomendações sobre o tratamento profilático da enxaqueca episódica com base em artigos da literatura mundial e da experiência pessoal. A enxaqueca é um distúrbio subdiagnosticado e subtratado que acomete um bilhão de pessoas no mundo e mais de 30 milhões de brasileiros. É conhecido na comunidade médica de neurologistas e, sobretudo, dos especialistas em cefaleia, a necessidade de se divulgar o conhecimento sobre o tratamento profilático da enxaqueca. Com esta finalidade, aliada às necessidades de atualizações de drogas e de se aumentar o conhecimento sobre a doença em si (frequência, intensidade, duração, impacto e talvez a progressão da enxaqueca), foi elaborado este Consenso, com metodologia totalmente *on-line*, por 12 grupos que revisaram e escreveram sobre as categorias farmacológicas das drogas e, ao final, reuniram-se para a leitura e conclusão do documento. As classes de drogas estudadas para este Consenso foram: anticonvulsivantes, antidepressivos tricíclicos, anticorpos monoclonais do antipeptídeo relacionado ao gene da calcitonina (peptídeo relacionado ao gene da calcitonina — anti-CGRP), betabloqueadores, anti-hipertensivos, inibidores dos canais de cálcio, outros antidepressivos (inibidores seletivos de recaptação de serotonina, ISRSs, e antidepressivos de ação dual), outras drogas, e politerapia. O tratamento hormonal, bem como anti-inflamatórios e triptanas em esquema de profilaxia mínima (miniprofilaxia), será abordado em um capítulo próprio. As classes de drogas estudadas na parte I do Consenso foram: anticonvulsivantes, antidepressivos tricíclicos, anticorpos monoclonais anti-CGRP, e betabloqueadores.

Palavras-chave

- Transtornos de Enxaqueca
- Consenso
- Medicina Preventiva.

INTRODUCTION

The Brazilian Headache Society (Sociedade Brasileira de Cefaleia, SBCe, in Portuguese) delegated a committee of experts to compile a consensus with recommendations on the prophylactic treatment of episodic migraine (EM) based on articles in the literature and on personal experience. The detailed research methodology and involvement of the authors, as well as the review of the content provided by each author and by the coordinators, are described below in the "methods" section.

DIAGNOSTIC CRITERIA

The diagnostic criteria for migraine are based on the third edition of the International Classification of Headache Disorders, published in 2018.[1] Migraine is a painful disorder subdivided into migraine without aura, migraine with aura, chronic migraine, and complications of migraine.

Migraine without aura is a recurrent disease that manifests with headache attacks lasting between 4 and 72 hours and pain that can be unilateral, pulsatile, of moderate to severe intensity, associated with nausea and/or vomiting, photophobia and phonophobia, and aggravated by routine physical activities. At least five attacks are required for the diagnosis.[1]

Migraine with aura presents visual phenomena, sensory or speech disorders and, more rarely, motor, brainstem or retinal disorders. These precede pain or occur alongside the headache attack and can last, separately if the individual has more than 1 of them, between 5 and 60 minutes. In migraine attacks with aura, the headache may have characteristics that meet migraine criteria without aura or be a milder form of headache.

Chronic migraine is a condition in which the headache occurs on at least 15 days or more per month for at least 3 months, with 8 days of typical symptoms of migraine. For this disease, a Brazilian Consensus was written in 2019,[2] but it will not be addressed in this manuscript. The present consensus for this disease is based on the prophylactic drug treatment of EM, in which the headache has a frequency of less than 15 days per month (between 1 and 14 days of headache per month).[1]

EPIDEMIOLOGY

The epidemiology of migraine has been widely studied, and its prevalence has been estimated to range from 3.3% to 21.9% in women and between 0.7% and 16.1% in men. Much of the variation in the studies is explained by age, case definition, and region of the world. In the United States, studies have shown that the prevalence of migraine is of approximately 18% in women and of 6% in men.[3] In Brazil, it affects 15% of the population.[4] It affects one billion people worldwide, including more than 30 million Brazilians and about 40 million Americans. Despite all these alarming numbers, it remains underdiagnosed and undertreated. The proportion of migraineurs who use over-the-counter medication to treat headaches was of 59% in a 1999 study.[4] Preventive medication is little used even in the 21st century (only 12% of individuals maintain their preventive treatment after being prescribed prophylactic medication).[5]

IMPACT

Migraine imposes a great burden on its sufferers, their families, and society. According to the Global Burden of Disease Study 2016,[6] migraine is the second largest cause of years lived with disability among all diseases, second only to depression. However, among young adults aged between 18 and 50 years, migraine is the main overall cause of disability.[7] It is the largest cause of absenteeism and decreased productivity at work, and it visibly reduces quality of life.[5] For around 11% of adults who experience migraine, the attacks have a significant impact on their quality of life and productivity.[8] Given this context, one of the main interventions that professionals can implement is to start these patients on drug prophylaxis, to reduce their level of disability.

PRINCIPLES OF PROPHYLAXIS

General principles

- Consider prophylactic treatment for all migraine patients (diagnosed in accordance with the criteria of the International Classification of Headache Disorders, third edition, 2018[1]).
- Aim to improve quality of life, decrease the degree of disability regarding the attacks, reduce the frequency, duration, and intensity of migraine episodes, and facilitate the response to abortive treatment.
- Prophylaxis provides pharmacoeconomic benefits to society, since its use is associated with reduced use of public and private resources, including fewer visits to consultation offices, lower dependence on emergency services, and lesser need for complementary exams.
- Evaluate the impact on the personal, familial, social and occupational aspects of migraine in patients' lives.
- Identify associated morbidities and triggering and aggravating factors of migraine.
- Establish realistic expectations for treatment in relation to the onset of the effects of medication, adverse effects, and probability of success.
- Involve the patient in the treatment, sharing responsibilities, such as filling out a headache diary, performing physical exercises, observing sleep hygiene etc.
- Establish criteria for therapeutic efficacy, options, and modifications of treatment. Source: Recomendações para o tratamento da crise migranosa.[9]

Indications

All migraine patients should be evaluated according to their eligibility criteria for prophylaxis, described as follows:

- Frequency of attacks: in general, drug prophylaxis is indicated when three or more attacks occur per month for at least three months.

- Degree of major disability (personal, familial, social or occupational aspects): in this case, prophylaxis should be considered if attacks cause profound disability in patients, even if uncommon, that is, once or twice a month.
- Failure of abortive medication: abortive treatment is considered effective when the person becomes pain-free within two hours after using the medication; if after optimization the treatment is still ineffective in halting an attack, drug prophylaxis should be started.
- Special subtypes of migraine: hemiplegic, brainstem, retinal, prolonged aura, migraine infarction, and migraine with frequent and atypical auras.
- Inefficacy of non-pharmacological prophylaxis: when the patient has chosen to start prophylaxis with non-drug measures, but this has been shown to be ineffective. Source: Recomendações para o tratamento da crise migranosa.[9]

Choice of medication

The following criteria should be considered together:

- Efficacy, tolerability, and safety established through appropriate clinical trials or expert opinion.
- Associated diseases and symptoms in the period between attacks.
- Drug and pharmacological interactions.
- Cost-benefit ratio.
- Patient preferences.
- Particularities such as: pregnancy, intention to become pregnant, breastfeeding, age (children and the elderly), kidney disease, liver disease, and allergies.

Management strategies

The following criteria should be considered together:

- Evaluate excessive use of abortive medications and guide their discontinuity.
- Go for medications with a better relationship between therapeutic efficacy and side effects.
- Give preference to monotherapy, although polytherapy may, in selected cases, be more convenient (this topic will be addressed within the present text).
- Be familiar with possible side effects.
- Treatment should start with the lowest therapeutic dose, and titration should proceed gradually until significant clinical improvement, or the maximum allowed for each medication is reached.
- Evaluate each therapeutic regimen for a minimum of two to three months, unless the patient has important adverse effects before this.
- Maintain effective therapeutic regimens (improvement in the intensity and frequency of attacks, assessed by the headache diary, of more than 75%) for at least 6 months, and gradually discontinue the regimen when the improvement has become consolidated (around 2 years).
- Resume the previous therapeutic regimen or modify it in the case of relapse of attacks; then, prolong treatment for as long as necessary.
- Pay special attention to particular situations such as pregnancy, intention to become pregnant, breastfeeding, allergies, and age (children and the elderly). Source: Recomendações para o tratamento da crise migranosa.[9]

METHODS

The SBCe, through its current board, appointed an ad hoc committee with the purpose of creating the present Consensus on the prophylactic treatment of EM and developing recommendations for the management of these patients, in order to disseminate knowledge on 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 SBCe through following the criteria:

- Proactivity.
- Ethics.
- Experience in the writing of articles.
- Publication in journals and presented works.
- Recognition.

The coordinator of each group was chosen for their expertise in headache, curriculum and experience 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 the authors assessed and approved the final text of the Consensus.

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

The evidence available in the literature was assessed based on the evidence levels and classification of recommendations stated in the guidelines of the American Academy of Neurology (AAN)[10] (►**Table 1**).

THERAPEUTIC CLASSES

Beta-blockers

General aspects

Beta-blockers are the most commonly used drugs in migraine prophylaxis worldwide.[11] The probable mechanism of action is through central regulation with reduction of noradrenergic neuronal triggers, in addition to regulation of gamma-aminobutyric acid (GABA) in the periaqueductal gray matter. Some beta-blockers act in the serotoninergic system with reduced serotonin synthesis and with blockade of 5-hydroxytryptamine receptor 2B ($5HT_{2B}$) and 2C ($5HT_{2C}$).[12]

Table 1 Recommendation levels

Recommendation levels	Requirements	Recommendation
Level A	At least two class-I studies	Established as effective, ineffective or harmful for the given condition in the population specified.
Level B	At least one class-I study or two class-II studies	Probably effective, ineffective or harmful for the given condition in the population specified.
Level C	At least one class-II study or two class-III studies	Possibly effective, ineffective or harmful for the given condition in the population specified.
Level U	Inappropriate or conflicting data	In the light of current knowledge, the treatment is not proven.

Propranolol

General aspects

Propranolol is a non-selective beta-blocker with hepatic metabolization, short half-life (four to five hours), and high protein affinity (which should be considered when used concomitantly with other high-protein molecules such as valproate, amitriptyline and nortriptyline). Due to all these pharmacokinetic variables, propranolol should be titrated slowly to reduce the likelihood of adverse effects.[13]

Although its liposolubility enbales it to cross the blood-brain barrier (BBB), it does not act directly on the cerebral vessels; instead, it can centrally modulate the sensitivity of the autonomic tone of the vessels to sensory stimuli during the migraine attack.[14] Propranolol inhibits the production of nitric oxide by blocking nitric oxide synthase. It also acts on glutamate receptors, with the inhibition of kainate-induced currents and has a synergistic effect on N-methyl-D-aspartate (NMDA) blockers, which reduce neuronal activity and have membrane-stabilizing properties.[12]

Studies

Propranolol is the beta-blocker with the highest number of studies of relevance for EM prophylaxis. In a systematic review and meta-analysis,[15] among patients with an average of 4.9 days of pain/month, propranolol was superior to placebo at the end of 8 weeks and 12 weeks in reducing the frequency of attacks. In several double-blind, randomized, placebo-controlled studies,[16–18] propranolol has been shown to be safe and more effective than placebo after 8 and 12 weeks. A study[19] comparing propranolol with other medications that are considered first-line for migraine prophylaxis indicated that propranolol has favorable results. Another study[20] comparing propranolol with valproate showed that propranolol was slightly superior in reducing the number days of pain, with fewer side effects, but without statistical significance. In yet another comparative study,[21] topiramate was superior to propranolol, but both drugs were used at low doses (50 mg topiramate versus 80 mg propranolol/day respectively). However, at higher doses (160 mg/day of propranolol), the result was the same as with topiramate at a dose of 1 mg/kg to 2 mg/kg, regarding the positive response rate, reduction of days of pain, frequency of attacks, and use of abortive medications.[22]

Metoprolol

General aspects

Metoprolol is a selective beta-blocker (beta-1) with high liposolubility, thus having good penetration in the BBB.[23] The beta-1 receptor blockade modulates inhibition of sodium ions ($Na+$) and the activity of tyrosine hydroxylase, reduces the neuronal activation threshold in response to noradrenergic stimuli of the locus ceruleus, and regulates periaqueductal gray matter activity.[24] Metoprolol has low affinity for 5-HT receptors and has a half-life from 3 to 7 hours, with primarily hepatic metabolism. Due to pharmacokinetic variability, it requires slow titration to avoid more serious side effects.[11]

Studies

There are four randomized, controlled, double-blind studies[25–28] comparing metoprolol at daily doses between 100 and 200 mg with placebo. They[25–28] have shown the superiority of this medication in reducing the frequency and intensity of migraine attacks, and also the disability and days of analgesic use.

In comparison with other drugs, metoprolol is also shown to be effective in titratable doses of up to 100 mg/day, compared with clomipramine 100 mg/day and placebo. Only metoprolol showed significant reduction in the frequency and duration of attacks ($p < 0.05$).[29] A comparative study[30] between metoprolol 200 mg and propranolol 160 mg showed that both drugs were effective in reducing the frequency of attacks, days of pain, pain intensity, and use of analgesic medications, but there was no statistically significant difference between them.

A controlled study[27] evaluated the dose-response effect and showed that metoprolol was more effective than placebo, and at a daily dose of 200 mg in comparison with 100 mg.

Timolol

General aspects
Like propranolol, timolol is a non-selective beta-blocker with no intrinsic sympathetic activity. It is a lipophilic drug with central nervous system (CNS) penetration, has good affinity for serotonergic receptors 5-HT_{2B} and 5-HT_{2C}, has hepatic clearance, low protein affinity, and short half-life, of 2 to 5 hours. It can be titrated more quickly, unlike propranolol and metoprolol.[13]

Studies
In a randomized double-blinded study,[33] timolol (30 mg/day) was superior to placebo in reducing the frequency of attacks, but there was no difference in pain intensity or duration. A multicenter crossover randomized, controlled, double-blinded study[32] compared timolol to propranolol. Both drugs were superior to placebo regarding reduction of the mean frequency and severity of attacks. There was no statistically significant difference in the reduction of the frequency of attacks between the groups treated with timolol and propranolol. The conclusion was that timolol had similar efficacy to propranolol, compared with placebo, at a dose of 10 g, to 15 mg twice a day.[32]

Atenolol

General aspects
Atenolol is a selective beta-1 beta-blocker of low liposolubility, with a half-life of six to seven hours, without intrinsic sympathetic activity.[23]

Studies
A randomized double-blinded study[33] with 24 patients showed that the atenolol 100 mg group was superior to placebo in reducing the number of migraine days. However, only four patients were included in the placebo group.

In a multicenter, randomized, controlled, double-blinded study,[34] atenolol 100 mg demonstrated a reduction in an outcome called integrated pain value, which considered the frequency and intensity of attacks. This study[34] did not clearly explain the primary and secondary outcomes, or the reduction values, nor did it explain what it considered the integrated pain value to be.

A crossover, randomized, double-blinded, placebo-controlled study[35] with 28 patients compared atenolol 100 mg with propranolol 160 mg and placebo. Atenolol was shown to be more effective than placebo in reducing the number of days of pain. Propranolol was superior to placebo, without statistical significance. In the comparison between atenolol and propranolol, no statistically significant difference was observed. The reduction in the number of days of pain in each group was not stated separately in the study.[35]

Nadolol

General aspects
Nadolol is a non-selective beta-blocker, with low liposolubility and long half-life (of 20 to 24 hours). It is metabolized in the liver, has moderate protein affinity (28%), and is eliminated by the kidneys.[23]

Studies
In a randomized controlled study,[36] nadolol 80 mg and 160 mg once a day was compared with propranolol 160 mg (divided into 2 intakes). It was found to be superior in efficacy and safety compared with propranolol.[36] Currently, this medication is not available in Brazil.

Nebivolol

General aspects
Nebivolol is a third-generation cardio-selective agent that is highly selective for the beta-1 receptor, with additional vasodilation effect mediated by a high release of nitric oxide.[37] It has no intrinsic sympathetic mimetic activity and has little or no stabilizing membrane activity. Its metabolism is hepatic, and its half-life is of 10 hours.[38]

Study
A double-blinded randomized study[39] was conducted among 30 migraine patients receiving 5 mg of nebivolol per day or increasing doses of metoprolol (47.5 mg in the first week, 95 mg in the second week, and 142.5 mg in the third to sixth weeks). The reduction in the mean frequency of migraine attacks per month, after a 12-week period, was from 3.4 to 1.3 (metoprolol) and from 3.3 to 1.6 (nebivolol), without statistical differences between the two groups. Nebivolol showed efficacy similar to that of metoprolol and was a well-tolerated drug at a dose of 5 mg, without the need for titration to achieve the therapeutic dose.[39]

Pindolol

General aspects
Pindolol is a non-selective beta-blocker with a high degree of intrinsic sympathetic mimetic activity, low liposolubility, and a half-life of three to four hours.[23]

Studies
No statistically significant differences were observed in two studies comparing pindolol (in doses of 2.5 mg/day and 5 mg/day,[40] and of 7.5 mg/day and 15 mg/day[41]) and placebo.

Conclusion
Among beta-blockers, propranolol and metoprolol are the drugs with the best evidence regarding the reduction of migraine attacks in EM compared with placebo (Level A recommendation).

Anticonvulsants

Topiramate

General aspects

Topiramate acts on multiple molecular targets to increase inhibitory function, such as voltage-dependent sodium channels, calcium channels, carbonic anhydrase, and glutamate kainate receptors. It is well absorbed by the gastrointestinal tract, and its maximum plasma concentration (Tmax) is reached in 2 to 3 hours. It binds little to plasma proteins, and it is eliminated unchanged by the kidney and partially by oxidation and hydrolysis. Its half-life of 20 to 30 hours becomes shortened by concomitant use of liver metabolism-inducing drugs.[42]

Studies

Silberstein et al.[43] conducted a multicenter, double-blinded, randomized study on placebo-controlled topiramate, and improvements occurred within the first month of treatment. Patients in the topiramate group had a statistically significant improvement in the group that used 100 mg/day, with a 54% reduction of migraine days/month ($p = 0.001$), compared with patients treated with placebo (reduction of 22.6%). And Brandes et al.[44] conducted a multicenter, double-blinded, randomized study on topiramate controlled by placebo and propranolol, in which the response rate was significantly higher with topiramate at 50 mg/day (39%; $p = 0.01$), 100 mg/day (49%; $p = 0.001$) and 200 mg/day (47%; $p = 0.001$) than with placebo (23%). The use of rescue medication was reduced in the groups that used topiramate 100 mg/day ($p = 0.01$) and 200 mg/day ($p = 0.005$). Diener et al. (2004)[22] compared topiramate, placebo and propranolol, and showed that topiramate and propranolol had similar efficacy and were superior to placebo. With a 95% confidence interval, both drugs diminished the frequency of days with migraine attacks and of use of acute medication. Diamond et al. (2005),[45] based on these three studies, showed that topiramate, at a dose of 100 mg/day, led to a significant increase in the quality of life of migraineurs for up to 6 months since the beginning of treatment. These authors[45] evaluated quality of life using specific tests for migraineurs: the Mini-Sleep Questionnaire (MSQ) and the Health-Related Quality of Life Assessment Questionnaire (HRQoL).

Sodium valproate/divalproate

General aspects

The anticonvulsant pharmacological properties of sodium valproate were first described in 1975,[46] and its first evaluation regarding the treatment of migraine was published in 1988.[47] Its mechanism of action is related to increased GABA, blockage of voltage-dependent sodium channels, and T-type calcium channels.[48] It reaches its plasma peak in up to 4 hours, and its half-life ranges from 8 to 12 hours in the conventional form, and is of up to 20 hours in the sustained-release form. It is a weak inhibitor of the cytochrome P450 system, epoxidrase, and glucuronyltransferase, and is almost entirely metabolized by the liver.[49]

Studies

There are consistent studies proving the efficacy of valproate/divalproate. Among more than 2 thousand publications, there are 2 main prospective studies on the preventive treatment of EM with valproate, and 4 on divalproate (a compound of valproic acid and sodium valproate in the proportions of 1:1) at doses of 500 mg/day to 1,000 mg/day.[49] The two main studies on valproate (1000mg/dia), which were prospective, randomized and double-blinded, included 63 patients. Hering and Kuritzky[50] (1992) conducted an 8-week study on 29 patients, comparing valproate at 800 mg/day with placebo. Their study showed that the use of this medication resulted in a significant reduction in the frequency of pain compared with placebo, with a mean total number of attacks of 8.826 ± 6.066 with its use compared with an average of 15.586 ± 8.330 with placebo. Jensen et al.[20] (1994) analyzed 34 patients for 4 weeks, and observed a reduction about 50% or more in the frequency of pain in the divalproate group, and of 18% in the placebo group. The number of responders increased to 65% in the last 4 weeks of the open phase of the study.[20] Mathew et al.[51] (1995) analyzed 107 patients in a multicenter, prospective, randomized, double-blinded study lasting 16 weeks. There was a 48% reduction in the frequency of pain in patients in the divalproate group, and of 14% in the placebo group, in relation to the initial frequency. In addition, there was a significant reduction in the intensity and duration of attacks in the treated patients.

Regarding valproate, valproic acid, and divalproate molecules, divalproate has been shown to be most effective and best tolerated, especially in its sustained-release form.[52]

Lamotrigine

General aspects

Lamotrigine is an anticonvulsant sodium-channel blocker that can suppress the release of glutamate and aspartate. It blocks T-type calcium channels and inhibits native voltage-dependent calcium channels (types N/P/Q/R) and $5HT_3$ receptors. This may reduce glutamate release from the ventral striatal limbic projections. Chronic treatment with lamotrigine suppresses cortical spreading depression (CSD), in accordance with its selective action on the migraine aura. Its half-life is of 29 hours, it is completely and rapidly absorbed after oral administration, it has absolute bioavailability of 98%, and its plasma C_{max} ranges from 1.4 to 4.8 hours.[53]

Studies

Two double-blinded placebo-controlled studies[54,55] on lamotrigine for the prophylaxis of migraine with and without aura have failed to prove its efficacy. However, in one of these studies,[55] lamotrigine proved to be effective in reducing the monthly frequency of migraine (one of its secondary outcomes). In three studies (open model)[56–58] that tested the efficacy of lamotrigine among individuals with migraine with

aura, with doses reaching 100 mg/day, there was a positive prophylactic effect on the frequency and duration of the auras. In one of these studies,[56] after halting lamotrigine, there was recurrence of the aura episodes. In another study,[57] the episodes of migraine with aura practically disappeared after three months of treatment, but there was no impact of the treatment on episodes of migraine without aura.

In another prospective, controlled, open study, in individuals with migraine with aura and with/without headache, lamotrigine at doses of up to 300 mg/day was effective in reducing the frequency and duration of the auras. In a prospective and retrospective study[59] among subjects with complicated auras, which could be very frequent, long-lasting, affecting the brainstem aura, hemiplegic, aphasic or without headache, there was satisfactory control of 64% of these auras.

There is also a description of two cases in which lamotrigine was effective in controlling (persistent auras) with durations ranging from three months to three years.[60]

Levetiracetam

General aspects

Levetiracetam is a drug that acts on type-N calcium channels and in the allosteric inhibition of GABA and glycine-dependent currents and of synchronized and excessive interneuronal activity.[61] It binds little (10%) to proteins and less than 40% is metabolized by acetamides, without participation of the cytochrome P450 system. Most levetiracetam is excreted unchanged by the kidneys, so dose adjustment is required in cases of renal failure.[62,63]

Studies

Two randomized double-blinded studies,[64,65] one placebo-controlled and one controlled with placebo and topiramate for migraine prophylaxis, were conducted. In the first study, levetiracetam was superior in reducing the frequency, intensity, disability and consumption of analgesics. The second study, which was designed not to evaluate efficacy but to assess other parameters (post hoc), showed that in most individuals the frequency of migraine was reduced in relation to the baseline time, while the opposite was seen in the placebo group.

Three open studies[66,67] tested the efficacy of levetiracetam in the prevention of migraine. One was performed in individuals with migraine with and without aura,[66] another, among elderly migraineurs,[67] and the third, only in individuals with migraine with aura.[68] In the first two,[66,67] there were significant reductions in the frequency of episodes in relation to baseline and in the intake of symptomatic drugs, while in the third[68] there were reductions in the frequency, intensity and duration of headache episodes and better aura control.

Gabapentin/pregabalin

General aspects

The modulation of the release of neurotransmitters exerted by gabapentin and pregabalin is related to binding to the calcium channel α2δ1 subunit in neuronal membranes. Neither of these agents undergoes hepatic metabolism. They do not bind to plasma proteins and are excreted unchanged by the kidneys. The half-life of both gabapentin and pregabalin ranges from five to nine hours.

Studies

Two double-blinded, placebo-controlled studies[69,70] were conducted. In one,[69] gabapentin enacarbil did not outperform placebo. In the other,[70] with gabapentin, the authors found a reduction of 50% or more in the occurrence of migraine for 4 weeks compared with placebo — 50% or less — about 50% (46×16). These results were not maintained when analyzed using the "intention to treat" criterion, that is, when the population who received at least one dose of the medication under study (active or placebo) was analyzed, not just the individuals who concluded the whole study. In a randomized, open class-III study[71] controlled with topiramate, the use of gabapentin and topiramate led to a significant reduction in the frequency, duration and severity of the episodes, and in the intensity of pain. Although topiramate was more effective than gabapentin in all outcomes, it also presented lower tolerability.[71] In a randomized, open, class-IV, uncontrolled study,[72] the authors observed a reduction in the frequency and intensity of migraine episodes, and in the duration of pain, and they suggested that gabapentin doses of 1,200 mg/day were as effective as 2,000 mg/day.

A randomized, double-blinded class-II study[73] compared pregabalin with sodium valproate in the prevention of migraine, and revealed that both were effective after the first month, and that they were comparable in the third month of treatment, in relation to the baseline, in terms of reduction in the average monthly frequency, intensity and duration of migraine episodes. Although this study[73] was conducted with an adequate number of subjects, both drugs were used at low doses (valproate: 400 mg/day; pregabalin: 100 mg/day). In an uncontrolled open study[74] with a target dose of pregabalin of 300 mg/day, the authors found a statistically significant reduction in the frequency of migraine episodes from the first to the third month of treatment compared with the baseline. The greatest reduction in the frequency of migraine episodes was observed in patients whose dose was increased in the first month of therapy.

Carbamazepine

General aspects

Carbamazepine is a modulator of sodium channels of neuronal membranes. Its bioavailability is high, reaching 90%, and its metabolism is hepatic.[75]

Studies

Regarding migraine, there is a single crossover placebo-controlled clinical trial[76] which only reports on the individuals who completed the entire study, and does not provide information about exclusions and their reasons. The authors[76] reported an improvement in 38 out of 45 (84.4%) patients in the carbamazepine arm and only in 13 out of 48

(27.1%) in the placebo arm ($p < 0.001$). The duration of the treatment was of 12 weeks. Mulleners et al.[77] (2015) calculated the confidence interval of this study and found it to be very low (11.77; 3.92 - 35.32), which makes it difficult to assume that these results can be properly interpreted.

Oxcarbazepine

General aspects
Oxcarbazepine is structurally related to carbamazepine; thus, it modulates sodium channels of neuronal membranes, but also modulates the release of glutamate.[78]

Studies
Regarding migraine, only one randomized, double-blinded clinical trial[79] has tested oxcarbazepine (n = 85) versus placebo. There was no statistically significant advantage of oxcarbazepine over placebo, except for the secondary variable of improvement in functional capacity.

Vigabatrin

General aspects
Vigabatrin exerts its GABA-ergic effect through selective and non-competitive inhibition of GABA-transaminase.[80]

Studies
There is a single double-blinded crossover trial,[81] in which 23 migraineurs were evaluated. However, due to the possible beta-type bias, the duration of the study, and the possibility of potentially limiting and irreversible adverse events, such as GABAergic retinopathy, a consensus was reached, which states that vigabatrin should not be used for the preventive treatment of migraine.[81]

Clonazepam

General aspects
Clonazepam belongs to the benzodiazepine group and increases the effect of the GABA neurotransmitter on GABA-A receptors in a highly potent and prolonged manner, besides having a serotoninergic agonist effect.[82]

Studies
A double-blinded, placebo-controlled study[83] with clonazepam at doses of 1 mg/day to 2 mg/day revealed that its use led to a reduction in the number of headache days compared with placebo.[83] However, due to the risk of addiction,[84] this is not a drug recommended for the prophylactic treatment of migraine.

Zonisamide (ZNZ)

General aspects
Zonisamide is an antiepileptic drug that has weak carbonic anhydrase-inhibiting action and blocks voltage-dependent sodium channels, thus modulating GABA-ergic and glutamatergic neurotransmission. In addition, it reduces the activity of the low-voltage T-type calcium channels (they are found in the trigeminal ganglion and caudal nucleus) and they play a role in mediating the release of calcitonin gene-related peptide (CGRP).[85]

Studies
Two randomized double-blinded studies[86,87] that compared ZNZ and another prophylactic drug for EM prophylaxis were evaluated. In one,[86] ZNZ was superior to topiramate in reducing the intensity of migraine attacks; in the other,[87] ZNZ had an efficacy similar to that of valproate, differing from the latter only in terms of adverse events.

Three other studies[88–90] reported that ZNZ was effective in reducing the intensity and frequency of attacks: a prospective open study[88] on patients who responded to topiramate but discontinued it due to adverse events; another[89] on patients with refractory migraine; and a retrospective study[90] on patients who did not respond to topiramate. The doses used in these studies ranged from 100 mg to 400 mg per day.

Conclusion
Among anticonvulsants, the most studied are topiramate and valproate/divalproate. These have unambiguous efficacy, are well documented, and have A-level recommendation. For levetiracetam, and ZNZ, the level of recommendation is B. For gabapentin/pregabalin, the recommendation is C. There is no evidence to support the routine prescription of lamotrigine, carbamazepine, oxcarbazepine, vigabatrin and clonazepam. However, lamotrigine shows efficacy in the prophylaxis for migraine aura. When prescribing an anticonvulsant, close attention needs to be paid not only to its efficacy but also to its sedative, psychotropic, and systemic effects, which often compromise its tolerability.

Tricyclic antidepressants (TADs)

General aspects
The mechanism of action common to tricyclic antidepressants (TADs) at the presynaptic level is the blocking of monoamine reuptake, mainly norepinephrine (NA) and serotonin (5-HT), and, to a lesser extent, dopamine (DA). Tertiary amines (amitriptyline and clomipramine) preferentially inhibit the reuptake of 5-HT, while secondary amines (nortriptyline) inhibit that of NA. There are no significant differences in the selectivity of presynaptic reuptake blockade. Postsynaptic activity varies depending on the neurotransmitter system involved, and it is usually responsible for the side effects of these drugs. Tricyclic antidepressants block the muscarinic (cholinergic), type-1 histaminergic, α2- and β-adrenergic, and several rarer dopaminergic receptors. These actions do not necessarily correlate with the antidepressant effect, but they may correlate with the side effects. Blockade of the 5-HT_1 receptor contributes to the therapeutic effect of TADs.[91]

The degree of blockade of monoamine reuptake varies according to the specific TAD, and amitriptyline is the most potent, with the most complex pharmacological profile. Its

main metabolite is nortriptyline, which has a more pronounced effect as a transporter of NA.[92]

Amitriptyline

Studies

Amitriptyline was evaluated in a randomized, double-blinded, controlled study[93] among migraineurs, with 94 patients receiving amitriptyline, and 92, placebo, for 20 weeks. Among the subjects with EM, amitriptyline was significantly more effective than placebo in decreasing the frequency of headaches in the eighth week, but not in the following weeks due to the large placebo effect.[93] In a randomized, double-blinded, non-inferiority study[94] comparing topiramate and amitriptyline in 331 migraine patients, 172 received topiramate, and 159, amitriptyline, for 26 weeks. The efficacy was similar between the two medications.[94] In another comparative, randomized, double blinded, placebo-controlled study[95] comparing amitriptyline and melatonin among 196 migraineurs for 12 weeks, both medications were significantly more effective than placebo in terms of decreasing the number of days with headache.[95]

Clomipramine

Studies

Two studies have been conducted with clomipramine: one comparing it with placebo,[96] and the other, with metoprolol.[29] In both, clomipramine was not significantly better than placebo.

Nortriptyline

Study

In a Brazilian study comparing preventive treatments for migraine with low doses of nortriptyline (25 mg/day) and propranolol (40 mg/day), alone or in combination, nortriptyline alone was not effective in reducing the number of days with headache.[97]

Conclusions

Among TADs, amitriptyline is the best studied medicine, with evidence of significant improvement through reduction of migraine attacks, compared with placebo (Level A recommendation). Clomipramine has not been shown to be significantly more effective than placebo. Although no randomized, double-blinded, adequate studies have been conducted on nortriptyline, this drug is recognized by the participants of this consensus as equally effective as amitriptyline and with fewer side effects, such as drowsiness and weight gain.

Calcitonin gene-related peptide (CGRP) or CGRP-receptor monoclonal antibodies

General aspects

Calcitonin gene-related peptide is a 37-amino acid neuropeptide that is produced primarily in the cellular body of ventral and dorsal root neurons. Two isoforms of CGRP (α and β) have been described; they differ in three amino acids in humans, have different tissue distributions, and are potent vasodilators.[98]

The α-CGRP isoform is expressed in the peripheral nervous system predominantly in nociceptive fibers A∂ and C, which have wide distribution throughout the body, including extensive perivascular distribution. The β-CGRP isoform is the predominant form expressed in the enteric nervous system and pituitary system. The distribution of CGRP and CGRP receptors in the CNS is complex and still little understood.[98,99]

Calcitonin gene-related peptide is located in the trigeminal nerve terminations and trigeminal ganglion. Outside of the BBB, release of CGRP in trigeminal nerve terminations results in vasodilation, inflammation, and (questionable) degranulation of dural mast cells.[98]

With the development of monoclonal antibodies (MAbs), new methods of targeting CGRP have emerged. With the target specificity inherent to MAbs, as well as typically prolonged pharmacokinetic half-lives and the reduced potential for liver toxicity, CGRP-specific MAbs are an excellent drugs for the migraine prevention.[99]

Currently, four MAbs (eptinezumab, erenumab, fremanezumab and galcanezumab) are indicated in the treatments of EM. Erenumab specifically blocks the CGRP receptor, while the others bind to the CGRP[100] molecule.

Erenumab

Studies

Two phase-3, controlled, randomized, multicenter clinical trials[101,102] were analyzed. In the first, the Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention (STRIVE),[101] 3 arms were compared: the erenumab 70 mg group, the erenumab 140 mg group, and the placebo group, who were followed for 24 weeks. The erenumab groups showed a statistically significant decrease in the number of migraine days in relation to the baseline frequency (primary outcome), a decrease in the number of migraine days of more than 50% from the third to the sixth months in relation to the baseline frequency, decreased use of migraine-specific medication, and decreased impact of headache (secondary outcomes) compared with the placebo group. There was no significant difference between those who used 70 mg or 140 mg of erenumab.[101]

The second one, called Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) Compared to Placebo in Migraine Prevention (ARISE),[102] compared 2 groups: patients who received erenumab 70 mg and those who received placebo, who were followed for 12 weeks. The erenumab group showed a statistically significant decrease in the number of migraine days in relation to the baseline frequency (primary outcome), a decrease in the number of migraine days greater than 50% in relation to the baseline frequency, and decreased use of migraine-specific medication (secondary outcomes) compared with the placebo group.[102]

Galcanezumab

Studies

Two randomized, controlled, multicenter, phase-3 clinical trials[103,104] on EM compared galcanezumab art doses of 240 mg in the first month, followed by 120 mg/month in the following months, galcanezumab at a dose of 240 mg/month, and placebo. The patients were followed for six months. The results of the galcanezumab groups were better than those of the placebo group, with statistical significance in relation to the primary outcome [decrease in the Monthly frequency of headache days (migraine characteristics in relation to the baseline frequency)] and secondary outcomes: decrease greater than 50%, greater than 75%, and 100% in the number of headache days, quality of life scales, and headache impact respectively. There was no difference between the results of the two galcanezumab groups (120 or 240 mg). There was no difference between the results of the two galcanezumab groups.[103,105]

Fremanezumab

Studies

Fremanezumab has been studied with regard to prevention of EM in 2 phase-3 clinical studies.[105,106]

A monthly dose regimen of 225 mg or a higher single dose of 665 mg was compared with placebo among 875 patients with a mean age of 41.8 years.[105] The number of migraine days during the 12-week period after the first dose was lower in the study groups than in the placebo group. The average number of migraine days per month decreased: from 8.9 days to 4.9 days in the monthly fremanezumab dosage group; from 9.2 days to 5.3 days in the highest single-dose fremanezumab group; and from 9.1 days to 6.5 days in the placebo group. This resulted in a difference between the monthly and placebo dosages of -1.5 days, and between the highest single dose and placebo of -1.3 days ($p < 0.001$).[105]

In the second study,[106] migraine patients who had previously had negative experiences with two to four classes of preventive medications were assessed. Using the methodology to divide the groups, 329 patients with EM were included and the results were also positive, with a significant difference between the fremanezumab groups and the placebo group.[106]

Eptinezumab

Studies

Eptinezumab differs from other MAbs in that it is administered intravenously rather than subcutaneously. Two studies have been conducted in relation to EM. A phase-2 study[107] was carried out with administration of 1,000 mg of intravenous eptinezumab (81 patients), compared with placebo (82 patients), and it showed that this drug present a good degree of safety and tolerability and was superior to placebo with regard to improving the number of migraine days per month.

The other study[108] evaluated 888 patients with EM who were randomized into 4 groups: eptinezumab 30 mg, 100 mg, or 300 mg, and placebo, with up to 4 intravenous infusions every 12 weeks. Doses of 100 mg and 300 mg significantly reduced the number of migraine days per month, with similar tolerability in comparison with the placebo group.[108] In a subsequent analysis,[109] the authors observed that the treatment was effective on the first day after the initial dose.

CONCLUSIONS

Erenumab, galcanezumab, fremanezumab and eptinezumab each have two Class-I clinical trials with positive results in relation to placebo, and they have been shown to be effective to treat EM (recommendation level A) (►**Table 2**).

Authors' contributions:
EMM, PAK: discussion, group coordination, writing, review, conceptualization, editing, data collection; PSFS: discussion, group coordination, writing, review, conceptualization; AOK, ATNMC, CAPR, EMS, GOMT, IF, LCC, LMB, MFPP, PMP, PFMF: writing, review, discussion, conceptualization; EJP, JJFC, HCC: writing, review, editing, group coordination, discussion; JAS, LPQ, MNPS: writing, review, editing, discussion; JAMJ, MENMC: writing, review, discussion; JBAS: writing, discussion; JGS: writing; MRCFF, MEJ, YDF: writing, review; PASRF: conceptualization, data collection, writing, review, editing.

Conflict of Interest
AOK: speaker for Allergan, Ipsen Pharma, Merz, Onyxcann Cantera; ATNMC: speaker for Lilly, Teva, Ache, Supera, Allergan, Novartis; CAPR: speaker for Teva, Novartis, Eli Lilly, Lundbeck, Aché, Apsen, Cellera; EJP: speaker for Novartis, Allergan, Libbs, Lilly; EMS: speaker for Libbs, Allergan, Novartis, Lilly, Lundbeck, Teva; advisory board: Allergan, Libbs, Teva, Lundbeck; EMM: speaker for Teva, Eli Lilly, Allergan; advisory board: Libbs, Eli Lilly; GOMT: speaker for Eli Lilly; HCC: speaker for Allergan, Eli Lilly; JAS: speaker for Eli Lilly, Novartis, Teva; JJFC: speaker for Eli Lilly, Novartis, TEVA, Libbs; advisory board: TEVA, Novartis, Eli Lilly; JGS: speaker for Teva, Novartis, Allergan, Lilly; LCC: speaker for Allergan, Novartis, Sanofi; advisory board: Allergan; LMB: speaker for Novartis; LPQ: speaker for Eli Lilly, Allergan; advisory board: Eli Lilly, TEVA; MNPS: speaker for Lilly, Novartis, Teva, Allergan, Libbs; advisory board: Sanofi, Lilly, Libbs; MENMC: speaker for Eli Lilly, Novartis, Teva, 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, Libbs; advisory board: Libbs; PSFS: speaker for Teva, Novartis, Allergan, EMS, Politec; advisory board: Libbs, Lilly; PAK: fees for services to Libbs, Novartis, Allergan, Livanova, Teva; PASRF: speaker for Eli Lilly, Novartis, Allergan, Libbs; advisory board: Novartis, Eli Lilly; IF, JAMJ, JBAS, MRCFF, MEJ, PFMF, RPSN, YDF: no conflict of interests to declare.

Table 2 Drugs, dosages, adverse effects, evidence level, recommendation level, pregnancy and breastfeeding

Drugs	Target dose and maximum daily dose	Dosage frequency and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy
POSITIVE EVIDENCE						
Anticonvulsants						
Topiramate	50–200 mg*/day	2x/day orally	Paresthesia, fatigue, nausea, weight loss, difficulty concentrating, memory loss, drowsiness, ataxia, kidney stones	Class I (≥ 2 studies)	Level A: established as efficacious	Category D breastfeeding: very low risk–can be used while breastfeeding
Valproic acid	250–1,000 mg/day	2–3x/day orally	Nausea and/or vomiting, tremors, weight gain, asthenia, and alopecia	Class I (> 2 studies)	Level A: established as efficacious	Category X breastfeeding: very low risk–can be used while breastfeeding
Sodium divalproate	250–1,000 mg/day 1x/day–sustained release, or 125 -500 mg 2x/day orally	Orally		Class I (> 2 studies)	Level A: established as efficacious	Category D breastfeeding: very low risk–can be used while breastfeeding
Levetiracetam	250–1,500 mg	2x/day orally	Drowsiness, fatigue, mood swings, agitation, irritability, aggression, depression, memory loss, confusion, paresthesia, cognitive decline, and increased risk of suicide	2 class-II studies and 3 class-III studies	Level B: possibly efficacious	Category C breastfeeding–not recommended
Gabapentin	900–3,600 mg/day	3x/day Orally	Dizziness, fatigue, nausea, and drowsiness	2 class-II studies (1 effective and 1 not), 2 class-III studies, and 1 class-IV study	C Level: possibly efficacious	Category C breastfeeding: very low risk–can be used while breastfeeding
POSITIVE EVIDENCE						
Anticonvulsants						
Pregabalin	75–600 mg/day	2x/day orally	–	1 class-II study and 1 class-IV study	Level C: possibly efficacious	Category C breastfeeding: low risk–moderately safe for use; monitor treatment
Zonisamide	100–400 mg/day	1x/day; not available in Brazil	Weight loss, mood disorders, paresthesia, and difficulty concentrating	2 class-II studies	Level B: probably efficacious	Category C breastfeeding: unsafe for use
Carbamazepine	200–2,000 mg/day ÷ in 3 intakes and sustained release: 2 intakes orally	–	Vertigo, headache, ataxia, drowsiness, fatigue, diplopia, nausea, vomiting, and allergic skin reactions	1 class-III study	Level U: conflicting data.	Category D breastfeeding: very low risk–can be used while breastfeeding
Vigabatrin	1–3 g/day ÷ in 1–2x/day; increase 500 mg/week orally		Sedation, drowsiness, fatigue, difficulty concentrating, and visual field change	1 class-III study	Level U: conflicting data.	Category C breastfeeding: very low risk–can be used while breastfeeding

Table 2 (*Continued*)

Drugs	Target dose and maximum daily dose	Dosage frequency and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy
Clonazepam	0.25–4 mg/day ÷ in 1–3x/day orally		Drowsiness, dizziness, irritability, and chemical dependence	1 class-III study and 1 class-IV study	Level U: conflicting data	Category C breastfeeding: low risk–moderately safe for use; monitor treatment
Beta-blockers						
Propranolol	40–240 mg/day 2–3x/day orally	–	Bradycardia, hypotension, lethargy, nightmares, mental confusion, depression, gastrointestinal disorders, paresthesia, and weight gain	Class I (> 2 studies)	Level A: established as efficacious	Category C breastfeeding: very low risk–can be used while breastfeeding
Metoprolol (succinate and tartrate)	50–200 mg/day 1–2x/day orally	–		Class I (> 2 studies)	Level A: established as efficacious	Category C breastfeeding: very low risk–can be used while breastfeeding
Beta-blockers						
Timolol	20–60 mg/day 2x/day	Oral	–	Class I (> 2 studies)	Level A: established as efficacious	Category C breastfeeding: unsafe for use–potential adverse reactions
Atenolol	50–100 mg/day 1–2x/day; maximum of 200 mg orally	–	Bradycardia, hypotension, lethargy, nightmares, mental confusion, depression, gastrointestinal disorders, paresthesia, and weight gain	Class III (3 studies)	Level C: possibly efficacious	Category D breastfeeding: high risk–unsafe for use
Nadolol	40–80 mg/day and up to 160 mg/day; 1x/day orally	Not available in Brazil	–	Class II (1 study)	Level C: possibly efficacious	Avoid it: newborn may present bradycardia, hypoglycemia, and associated symptoms; breastfeeding: potential risk of causing adverse effects in infants
Nebivolol	5 mg/day 1x/day orally			Class III (1 study) or Class II	Level C: possibly efficacious	Category C breastfeeding: low risk–moderately safe for use; monitor treatment
Tricyclic Antidepressants (TADs)						
Amitriptyline	10–150 mg/day 1x/day orally	–	Dry mouth, drowsiness, fatigue, weight gain, constipation, and dizziness	Many class-I and-II studies	Level A: established as efficacious	C - C - C / dreastfeeding: high risk–contraindicated
Clomipramine	25–75 mg/day 1–3x/day orally	–		2 class-II studies	Level B: probably efficacious	C - C - C / breastfeeding: contraindicated
Nortriptyline	10–50 mg/day 1–3x/day orally	–		1 class-II study	Level C: possibly efficacious	C - C - C /breastfeeding: very low risk

(*Continued*)

Table 2 (*Continued*)

Drugs	Target dose and maximum daily dose	Dosage frequency and administration route	Adverse events	Evidence level	Recommendation level	Pregnancy
POSITIVE EVIDENCE						
Anti-calcitonin gene-related (anti-CGRP) monoclonal antibodies or anti-CGRP receptor						
Erenumab	70–140 mg/month 1x/month subcutaneously		Pain in the injection site, upper respiratory tract infection, nasopharyngitis, nausea, and abdominal discomfort	3 class-I studies	Level A: established as efficacious	Category B: breastfeeding: moderately safe for use–monitor treatment
Galcanezumab	240 mg in the 1st month and 120 mg/month in the subsequent months subcutaneously	–		4 class-I studies	Level A: established as efficacious	Category B breastfeeding: moderately safe for use–monitor treatment
Fremanezumab	225 mg/month 1x/month or 675 mg/month every 12 weeks subcutaneously	–		2 class-I studies	Level A: established as efficacious	There are no data on the presence of fremanezumab in breast milk
Eptinezumab	100 mg/month	every 12 weeks intravenously		1 class-I study	Level B: probably efficacious	There are no controlled data on human pregnancy. There are no data on the effects of this drug on infants or its effects on milk production.
NEGATIVE EVIDENCE						
Betab-lockers						
Pindolol	7.5–15 mg /day orally	–	Similar to other beta-blockers	2 class-II studies	Level B: probably inefficacious	Category B breastfeeding: unlikely to affect the child when therapeutic doses are used.
Anticonvulsants						
Lamotrigine#	100–200 mg/day 2x/day orally	–	As in "Anticonvulsants"	2 class-II studies	Level B: probably inefficacious	Category C breastfeeding: low risk; moderately safe for use–monitor treatment
Oxcarbazepine	600–1,500 mg/day 2x/day orally	–	Fatigue, dizziness, and nausea	1 class-II study	Level C: possibly inefficacious	Category C breastfeeding: high risk–unsafe for use.

Notes: *For the prophylaxis of migraine with aura; # for the prophylaxis of migraine without aura.

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