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Consensus of the Brazilian Headache Society on the treatment of chronic migraine

Consenso da Sociedade Brasileira de Cefaleia sobre o tratamento da migrânea crônica

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ABSTRACT

Chronic migraine poses a significant personal, social and economic burden and is characterized by headache present on 15 or more days per month for at least three months, with at least eight days of migrainous headache per month. It is frequently associated with analgesic or acute migraine medication overuse and this should not be overlooked. The present consensus was elaborated upon by a group of members of the Brazilian Headache Society in order to describe current evidence and to provide recommendations related to chronic migraine pharmacological and nonpharmacological treatment. Withdrawal strategies in medication overuse headache are also described, as well as treatment risks during pregnancy and breastfeeding. Oral topiramate and onabotulinum toxin A injections are the only treatments granted Class A recommendation, while valproate, gabapentin, and tizanidine received Class B recommendation, along with acupuncture, biofeedback, and mindfulness. The anti-CGRP or anti-CGRP monoclonal antibodies, still unavailable in Brazil, are promising new drugs already approved elsewhere for migraine prophylactic treatment, the efficacy of which in chronic migraine is still to be definitively proven.

Keywords: Migraine disorders; headache; headache disorders.

RESUMO

A migrânea (enxaqueca) crônica determina uma carga pessoal, social e econômica significativa e é caracterizada por dor de cabeça presente em quinze ou mais dias por mês por ao menos três meses, com no mínimo oito dias de cefaleia migranosa a cada mês. É frequentemente associada ao uso excessivo de medicação analgésica ou antimigranosa aguda e isso não deve ser negligenciado. Este consenso foi elaborado por um grupo de membros da Sociedade Brasileira de Cefaleia, para descrever as evidências atualmente disponíveis e fornecer recomendações relacionadas ao tratamento farmacológico e não farmacológico da migrânea crônica. Estratégias de retirada na cefaleia por uso excessivo de medicamentos também são descritas, assim como os riscos dos tratamentos durante a gravidez e a amamentação. O topiramato oral e as injeções de toxina onabotulínica A são os únicos tratamentos que receberam a recomendação classe A, enquanto que o valproato, a gabapentina e a tizanidina receberam recomendação classe B, juntamente com acupuntura, biofeedback e mindfulness. Os anticorpos monoclonais anti-CGRP ou anti-CGRP, ainda não disponíveis no Brasil, são novos fármacos promissores, já aprovados em outros países para o tratamento profilático da migrânea, cuja eficácia na migrânea crônica ainda está por ser definitivamente comprovada.

Palavras-chave: Transtornos de enxaqueca; cefaleia; transtornos da cefaleia.

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Chronic migraine is a widespread disorder that poses a significant personal, social and economic burden. Although less prevalent than episodic migraine, chronic migraine patients present with more comorbidities and are more refractory to treatment^{1,2,3}. After the publication of the third edition of the International Classification of Headaches Disorders (ICHD-3)⁴ and considering new evidence published since the Latin American Consensus on Guidelines for the Treatment of Chronic Migraine was reached in 2012^{5,6}, the Brazilian Headache Society (*Sociedade Brasileira de Cefaleia*) recognized the need to elaborate on a new consensus on this subject.

METHODS

A group of 17 members of the Brazilian Headache Society met on September 29–30, 2018, after a process of literature searches made by five subgroup coordinators. The first day was dedicated to discussion of the relevant literature and to the drafting, by five independent subgroups, of the text sections. On the second day, the full text was read, discussed and modified in a plenary session. The text was then reviewed by one of the members (FK) and submitted for translation into English, which was approved by all members before being submitted for publication. Classes of evidence and levels of recommendation were described according to the American Academy of Neurology Classification for the Rating of a Therapeutic Study and Classification of Recommendations whenever possible^{7,8,9}. According to the latter, studies vary from class I (high quality well-designed randomized double- or triple-blind controlled trials) to class IV (uncontrolled studies, consensus and expert opinions). Levels of recommendation are described in Table 1. The Brazilian Headache Society received a grant from Allergan Specialty Care designated specifically to the logistics and editorial expenses.

Table 1. Levels of recommendation (adapted from AAN⁹).

Levels of recommendation	Requirements	Recommendation
Level A	At least two consistent Class I studies	Established as effective, ineffective or harmful for the given condition in the specified population
Level B	At least one Class I study or two consistent Class II studies	Probably effective, ineffective or harmful for the given condition in the specified population
Level C	At least one Class II study or two consistent Class III studies	Possibly effective, ineffective or harmful for the given condition in the specified population
Level U	Inadequate or conflicting data	Given current knowledge, treatment is unproven

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CONCEPTUALIZATION

The ICHD-3 classifies headaches into three groups. The first group comprises the primary headaches, conditions whose mechanisms are eminently neurochemical – in other words, the tendency to develop headache attacks is the disorder itself. The secondary headaches, which compose the second group, are caused by some underlying disorder, e.g. intracranial structural lesions, whereas the third group includes the painful cranial neuropathies, other facial pains, and unspecified or nonspecific headache⁴.

DIAGNOSTIC CRITERIA, EPIDEMIOLOGY AND IMPACT

According to ICHD-3, chronic migraine belongs to the primary headache group and is defined by the diagnostic criteria listed in Table 2.

It is estimated that up to 5% of patients with migraine meet the criteria for the chronic form of the disease¹. In systematic reviews of population studies, the prevalence of chronic migraine ranges from 0.9% to 5.1%^{1,10}, while in the Brazilian infant population it is around 1.7%¹¹. Since the publication of the last report by the World Health Organization's Global Burden of Disease, migraine has come to be considered the second major cause of disability among all diseases, behind only mental disorders, led by depression¹². Over the period of a year, 25% of the patients with chronic migraine return to the episodic form of the disease and another 40% oscillate between the episodic and chronic forms¹³.

Nearly 50% of individuals with headache self-medicate⁵. Overuse of symptomatic drugs is believed to cause headache in individuals previously affected by a primary headache. This headache is classified in the ICHD-3 among secondary headaches, as item 8.2 *Medication-overuse headache*. From 55%

Table 2. ICHD-3 chronic migraine diagnostic criteria⁴.

A. Headache (migraine-like or tension-type-like) on ≥ 15 days/month for more than three months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 <i>Migraine without aura</i> * and/or criteria B and C for 1.2 <i>Migraine with aura</i> *
C. On ≥ 8 days/month for > 3 months, fulfilling any of the following: <ul style="list-style-type: none"> 1. Criteria C and D for 1.1 <i>Migraine without aura</i>* 2. Criteria B and C for 1.2 <i>Migraine with aura</i>* 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

*For migraine without aura and migraine with aura diagnostic criteria, see reference 4. ICHD: International Classification of Headaches Disorders

to 70% of the patients seen at specialized centers in Latin America receive this diagnosis¹⁴. The term *chronic migraine* was first mentioned in ICHD-2, in 2004¹⁵, and its diagnostic criteria were reviewed in 2006¹⁶. In previously-proposed classifications, these diagnoses were grouped, and the terms *transformed migraine* and *chronic daily headache* were used¹⁷. Currently, a patient who meets the criteria for chronic migraine (Table 2) and for medication-overuse headache (triptans, ergot drugs, common analgesics alone or in combination and/or nonsteroidal anti-inflammatory drugs) should initially receive both diagnoses. It should be emphasized that patients who present with headache on 15 or more days per month may have primary headaches other than chronic migraine, such as chronic tension-type headache, new daily persistent headache and hemicrania continua^{15,18}.

Pathophysiological mechanisms probably involved in migraine include cortical hyperexcitability (or deficient inhibition), dysmodulation in areas of the brainstem and hypothalamus, and central and peripheral trigeminal sensitization, with release of vasoactive/neuroactive peptides, such as calcitonin gene-related peptide (CGRP). Episodic trigemino-vascular system activation, faulty filtering of sensorial stimuli and heredity are characteristics that point to the neural basis of this disorder^{19,20}.

ADDITIONAL INVESTIGATION

Additional investigation, such as neuroimaging, cerebrospinal fluid analysis and blood tests, should be employed judiciously and parsimoniously in chronic headache patients, considering the inherent risks and costs. Patients who meet the ICHD-3 criteria for chronic migraine and have a normal neurological examination do not require, in most cases, additional tests²¹. On the other hand, these tests may become necessary to rule out alternative diagnoses in the presence of various secondary headache red flags, listed in Table 3.

In the presence of tinnitus, visual changes, headache aggravated by Valsalva-like maneuver and/or morning

headache with improvement throughout the day, lumbar puncture with cerebrospinal fluid manometry (plus cerebral venous angioresonance, when appropriate) is recommended even in the absence of papilledema, to rule out idiopathic intracranial hypertension (pseudotumor cerebri) without papilledema (class of evidence IV, level of recommendation U). On the other hand, lumbar puncture is not necessary when the clinical picture is typical and these symptoms are absent²¹. Although epidemiological data do not correlate chronic migraine with obstructive sleep apnea headache²², this differential diagnosis may be difficult, especially in patients with headache attributed to medication overuse. In the presence of strictly morning headaches, polysomnography may be indicated²¹.

MANAGEMENT OF HEADACHE ATTRIBUTED TO MEDICATION OVERUSE ASSOCIATED WITH CHRONIC MIGRAINE

The concept of medication-overuse headache has evolved since the first edition of the ICHD, e.g. the inclusion of triptan-overuse headache, elimination of the need for a specific headache pattern and the establishment of different thresholds for each type of analgesic/antimigrainous agents. Medication-overuse headache, present in ICHD-3 as item 8.2, is defined as a secondary headache that occurs in ≥ 15 days per month, in a patient with a pre-existing primary headache, that develops as a consequence of the regular overuse of symptomatic medication for the treatment of headache (ergotamine, triptans, opioid analgesics or combined analgesics: ≥ 10 days/month; common analgesics or NSAIDs: ≥ 15 days/month)⁴. Smoking, sedentary lifestyle, metabolic syndrome, obesity, musculoskeletal diseases, psychiatric comorbidities and excessive use of caffeine increase the risk of developing medication-overuse headache^{23,24,25,26}.

Treatment of patients with medication-overuse headache is often difficult, specific guidelines are lacking and the available evidence does not establish the superiority of a strategy. The treatment modalities proposed in the literature are summarized in Table 4. The main poor prognosis risk factors are the amounts of overused drugs, the association of drugs from multiple classes, use of opioids, recurrence of a previous episode and psychiatric comorbidities^{27,28,29}.

PROPHYLACTIC PHARMACOLOGICAL MANAGEMENT OF CHRONIC MIGRAINE: SYSTEMIC TREATMENTS

General aspects of the pharmacological management of chronic migraine

Drugs included in this section were tested in randomized controlled trials (RCTs) with well-defined inclusion criteria, double-blind or open, involving chronic migraine

Table 3. Warning signs for secondary headache ("red flags").

1. Headache of sudden onset (thunderclap*)
2. New headache or progressive worsening of a pre-existing headache
3. Change in the pattern of a previously stable headache
4. Headache that is aggravated or alleviated by postural changes
5. Headache that awakens the patient
6. Headache precipitated by physical activity and/or Valsalva maneuver
7. Onset ≥ 50 years of age
8. Symptoms and/or focal neurologic signs, altered level of consciousness, seizures
9. History of cranial and/or cervical trauma
10. Neck stiffness and/or history of fever
11. Neoplasia, HIV, immunosuppression, active infection

*reaching maximum intensity in < 1 minute.

Table 4. Management of medication-overuse headache.

Management strategies	Evidence	Recommendation	References
Counseling (explain the role of medication-overuse in pain chronification and the risk of serious adverse effects; emphasize the importance of withdrawing these drugs for successful treatment; inform the possibility of headache worsening at the beginning of withdrawal with later gradual improvement)	2 class II trials	B	30, 31
Discourage the anticipatory use of symptomatic medications (cephalalgophobia)	1 class III trial	U	27
Guidance to complete the pain diary	3 class III trials	C	27, 28, 32
Full abrupt withdrawal of analgesic, ergotamine, triptans or anti-inflammatory drugs and gradual suspension of opioid analgesics	4 class III trials	C	28, 32-34
Starting prophylactic treatment simultaneously with suspension of analgesics	19 class III trials	C	27, 28, 33-51
Management in the withdrawal of overuse drugs			
Outpatient			
Suspension not associated with transitional treatment	3 class III trials	C	52-54
Suspension associated with transitional treatment, with individual or combined strategies			
Corticosteroids	1 class I trial, 4 class II trials, with conflicting results	U	29, 55-58
Neuroleptics	2 class III trials	C	27, 34
Antiemetics (metoclopramide, ondansetron, dimenhydrinate)	2 class III trials	C	27, 34
Switching acute drugs between different classes, limiting amount, frequency and duration of use (except for opioid prescription)	2 class III trials	C	27, 34
Greater occipital nerve blocks	1 class III trial	U	59
Inpatient			
This approach is indicated for patients who overuse opioids and/or barbiturates or patients with serious psychiatric and clinical comorbidities (metabolic disorders, dehydration, refractory vomiting, decompensated systemic arterial hypertension, unstable cardiovascular diseases, severe allergic reactions and others and/or failure in previous attempts to withdraw overuse drugs.	1 class II trial	C	31

patients. Uncontrolled or poor-quality trials, with small samples and/or published in periodicals considered to be unreliable ("predatory journals") were discarded. Papers published prior to the International Headache Society's adoption of diagnostic criteria for chronic migraine^{15,16} were included, provided that they had enrolled participants presenting with "chronic daily headache" and that the methods section made clear that the majority of the study population suffered from chronic migraine if the current criteria were applied⁴.

Table 5 lists oral drugs used in the treatment of chronic migraine in adults, along with levels of evidence and recommendation, doses used in daily practice and risk categories regarding use during pregnancy or breastfeeding^{60,61}.

Topiramate is the only oral drug with class I evidence and level A recommendation for preventive treatment in chronic migraine. Its efficacy was initially demonstrated in a small single-center double-blind RCT published in 2003⁶², involving patients with the diagnosis of "chronic daily headache" and past migraine without aura (classified as chronic migraine), overuse of acute medication and at least four previous preventive treatment failures. Topiramate (50 mg/day) caused a significant reduction in headache frequency and

was well tolerated. This was followed by another positive single-center double-blind RCT⁶³ and two larger multi-center double-blind placebo-controlled trials^{64,65}. These two to three-month duration trials showed significant reduction in monthly migraine days with topiramate (slow titration, mean final dose around 100 mg/day). The most important adverse events were paresthesias, fatigue, difficulties with memory, concentration and/or attention, taste perversion. When analyzing the results of both studies together, the authors concluded that topiramate was safe and effective in chronic migraine patients with or without concomitant medication overuse⁶⁶.

As of January 2019, three subcutaneous-administered monoclonal antibodies against CGRP⁶⁷ or its receptor⁶⁸, were not yet available in Brazil but have already been approved by the Food and Drug Administration (FDA) for the preventive treatment of migraine (without specification of the type or frequency of attacks): erenumab, fremanezumab and galcanezumab (eptinezumab, an intravenous-administered CGRP antagonist, is awaiting approval). Positive results from phase III (fremanezumab, galcanezumab) and phase IIb (erenumab) RCTs, specifically addressing chronic migraine patients, were recently published⁶⁷⁻⁶⁹.

Practical aspects of the pharmacological management of chronic migraine

The choice of prophylactic drugs should favor those with greater evidence of efficacy, considering the individual patient preferences, associated clinical conditions and absolute and relative contraindications.

Drugs acting on the central nervous system and/or with marked systemic effects should be started with low initial doses followed by gradual increments. The final therapeutic dose should be the lowest effective dose, considering the maximum dose used in each clinical trial or, eventually, at the discretion and under the responsibility of the prescriber, the maximum tolerated dose. A drug should not be considered ineffective before two to three months after the recommended dose or maximum tolerated dose has been achieved. Laboratory tests must be ordered in a predetermined manner or on demand, looking for potential hydro-electrolytic disturbances, hematological, metabolic and/or intoxication imbalances, according to the prescribed drug or drug combinations.

The strategy of associating different prophylactic drugs is not supported by high level evidence. A class II trial did not show superiority of the association of topiramate with long-acting propranolol versus topiramate alone⁸¹. However, the so-called rational polytherapy—the association of effective drugs with different mechanisms—can be used in monotherapy refractory patients⁸². Regarding comparative efficacy, one single-center double-blind RCT showed equivalence between onabotulinum toxin A (100 units at fixed points plus 100 units at “follow the pain” points) and topiramate (maximum dose of 200 mg), with better tolerability and adherence in the onabotulinum toxin A group⁸³, while one single-center open-label study showed comparable efficacy between amitriptyline (25–50 mg/day) and onabotulinum toxin A (250 U/15 sites), also with better tolerability and compliance in the group treated with onabotulinum toxin A⁸⁴. On the other hand, and acupuncture performed better than topiramate in two small single-center open-label RCTs^{77,85}. Although there is no evidence of response consistency in long term, it is usually recommended that individuals who have undergone reversal of chronic migraine for episodic migraine should be maintained on prophylactic treatment for at least one to two years⁸⁶ (class of evidence IV, level of recommendation U).

Pharmacological management of chronic migraine during pregnancy and breastfeeding

Pharmacological treatment of pregnant and breastfeeding women should be avoided, whenever possible, in favor of nonpharmacological methods. Considering the lack of RCTs specifically dedicated to the treatment of chronic migraine in pregnant women, the following recommendations (Table 5) are based on evidence from trials involving nonpregnant women in the light of current knowledge about potential consequences to the fetus. Atenolol and flunarizine

may be considered as first-choice migraine prophylactic drugs in pregnancy, if atenolol is discontinued in the third trimester to prevent bradycardia and intrauterine growth retardation. Amitriptyline (despite its classification as category C) and gabapentin, which must be discontinued early due to possible interference with fetal bone development, may also be used^{87,88}. On the other hand, topiramate and valproate should be avoided during pregnancy. Some authors consider that all prophylactic migraine drugs are poorly excreted in breast milk, but others contraindicate the use of atenolol and flunarizine in high doses. There is a consensus that topiramate may be poorly metabolized by premature infants, therefore, in these cases, discontinuation or close monitoring of the infant is necessary^{89,90}.

Pharmacological management of chronic migraine in the elderly

In the pharmacological management of chronic migraine in the elderly, the presence of other clinical conditions, potential adverse effects of medications and possible drug interactions should be considered. Some drugs, such as beta-blockers, amitriptyline and flunarizine require special attention in this age group^{91,92,93}.

Pharmacological management of chronic migraine in children

The only RCT involving drug treatment of chronic migraine in children and adolescents points towards the efficacy of the combination of amitriptyline and cognitive-behavioral therapy in the treatment of this condition⁹⁴. Despite the lack of trials, drugs with proven efficacy in episodic migraine, such as flunarizine, have been used in clinical practice.

PROPHYLACTIC PHARMACOLOGICAL TREATMENT: ONABOTULINUM TOXIN A AND PERIPHERAL NERVE BLOCKS

Onabotulinum toxin A (class I evidence, level A recommendation)

Onabotulinum toxin A is a purified neurotoxin derived from the *Clostridium botulinum* bacteria. It has been approved since 2011 by Anvisa (Agência Nacional de Vigilância Sanitária: the Brazilian government agency equivalent to the FDA) for use in the prophylactic treatment of chronic migraine in adults. This approval was based on a pooled analysis of two large double-blind clinical trials (PREEMPT 1 and 2), which demonstrated significant reduction in headache days and improvement in the patients' quality of life during the trial period, effects also observed in those patients with medication overuse (class of evidence I, level of recommendation A)^{95–97}. In a 56-week treatment period, 1,384 patients were assigned into two groups: active and control treatment (onabotulinum toxin A and placebo, respectively). In the

Table 5. Oral drugs evaluated in the treatment of chronic migraine in adults: evidence of efficacy, class of recommendation, recommended doses and risk categories regarding use during pregnancy and lactation.

Drug	Evidence	Recommendation	Dose (mg/day)	Risk during pregnancy*	Risk during lactation**†	References
Neuromodulators						
Topiramate	I	A	50-200	D	L3	62, 64-66, 70
Valproate	II	B	500-2000	X	L2	71
Gabapentin	II	B	900-1800	C	L2	72
Pregabalin	III	C	125-450	C	L2	73
Zonisamide	III	C	50-200	D	L5	74
Beta-blockers						
Atenolol	III	C	50-200	C	L3	75
Tricyclics						
Amitriptyline	II	C	50-100	C	L2	76
Calcium channel blockers						
Flunarizine	III	C	10	C	L5	77
Miscellaneous						
Tizanidine	II	B	fev/24	C	L3	78

*FDA classic classification of drug risk during pregnancy, adapted from reference⁷⁹: A – the possibility of fetal harm appears remote (adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)); B – the possibility of fetal harm is remote. Nevertheless, because the studies in humans cannot rule out the possibility of harm, it should be used during pregnancy only if clearly needed; C – animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks or there are no animal reproduction studies and no adequate and well-controlled studies in humans. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. D – there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. X – studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience (or both). It is contraindicated in women who are or may become pregnant.

**Risk of use during breastfeeding is described using the WHO scheme⁸⁰: L1 – Compatible with breastfeeding; L2 – Compatible with breastfeeding. Infant should be monitored for side-effects; L3 – Should be avoided if possible. Infant should be monitored for side-effects; L4 – Should be avoided if possible. May inhibit lactation; L5 – Must be avoided.

first, double-blind, 24-weeks phase of the trial, the patients received 31 to 39 injections of onabotulinum toxin A (active treatment) or saline (control) at predetermined points of the head and shoulders, every 12 weeks. In the second phase (open), all participants received onabotulinum toxin A injections, according to the same protocol, every 12 weeks, for 32 weeks. As each injection of 0.1 ml contained 5 units of the toxin and the injections were performed on 31 fixed sites and up to eight random (“follow-the-pain”) sites, each participant received 155 U to 195 U per session (Table 6).

Table 6. PREEMPT⁹⁵⁻⁹⁷ protocol: Dose of onabotulinum toxin A (Botox®) per application site.

Muscle area	Units of onabotulinum toxin A per application site ****				
	Mandatory sites		Optional sites (“follow the pain”)		Total
	Left	Right	Left	Right	
Frontal	10U	10U	Do not use		20U
Corrugators	5U	5U	Do not use		10U
Procerus	5U		Do not use		5U
Temporal	20U	20U	5U	5U	40U to 50U
Occipital	15U	15U	5U	5U	30U to 40U
Cervical paraspinal	10U	10U	Do not use		20U
Trapezius	15U	15U	10U	10U	30U to 50U
All areas	155U to 195U				

*recommended dilution is 200 units per 4 mL of saline solution; **each application site is injected with 0.1 mL (5 units); ***application is subcutaneous, except in the corrugator and procerus muscles, where it must be intramuscular.

Open-label prospective long term and observational studies conducted in different centers, according to the same injection paradigm, have corroborated the efficacy, tolerability and safety of onabotulinum toxin A^{98,99,100,101,102,103,104,105}. The Chronic Migraine Onabotulinum Toxin A Prolonged Efficacy Open Label trial, for example, evidenced that onabotulinum toxin A had its efficacy sustained for as long as 108 weeks, without further safety or tolerability problems¹⁰¹. Increase in productivity and a reduction of about 60% in expenses with medical visits and hospitalizations were suggested by pharmacoeconomics studies^{106,107}.

There is no consensus in the literature regarding the number of onabotulinum toxin A cycles required for the management of chronic migraine. Some trials suggest an increasing efficacy with regular cycle repetition for more than one year, including in patients that overuse symptomatic drugs (three class II trials, level B recommendation)^{104,108,109}. To date, no clinical features predicting responses to onabotulinum toxin A (recommendation level B) have been identified^{100,101}.

An onabotulinum toxin A trial including children¹¹⁰ showed a significant reduction in pain days, but without improvement in quality of life or reduction of pain intensity during the attacks. It should be noted that onabotulinum toxin A has its use in chronic migraine approved in Brazil for patients ≥ 18 years old.

The adverse effects caused by this treatment are rare, transient and mild. The most frequently reported were neck and shoulder muscle weakness, post-application

headache, palpebral pseudoptosis and other facial mimics asymmetries, in addition to pain at injection sites^{95-98,101,102} (class of evidence I).

Peripheral nerve blocks

Not many trials have been conducted to investigate the efficacy of cephalic segment peripheral nerve blocks in the management of chronic migraine. The heterogeneity of study cohorts, designs and techniques do not allow consistent conclusions^{111,112,113,114}. However, it is worth mentioning a double-blind RCT in which 44 participants were submitted to weekly bilateral greater occipital nerve blockades for one month, with 0.5% bupivacaine or saline solution (1.5 mL). The active group showed a significant reduction in headache days, which lasted for three weeks after the end of treatment¹¹¹ (evidence class I, recommendation level B.)

NONPHARMACOLOGICAL TREATMENT AND COMPLEMENTARY THERAPIES

The number of trials contemplating nonpharmacological treatments in patients with chronic migraine is limited, but some of these showed promising results, especially when these methods were used in association with conventional treatment with prophylactic drugs.

Psychological and behavioral therapies

Positive results were seen in some trials addressing *cognitive behavioral therapy*, biofeedback and meditation techniques such as mindfulness. In one RCT, cognitive behavioral therapy, combined with amitriptyline, was more effective than amitriptyline alone in reducing days of headache in children and adolescents with chronic migraine¹¹⁵. Two RCTs showed *biofeedback* efficacy in adult patients with chronic migraine and medication-overuse headache when combined with pharmacological treatment^{116,117}, with higher reduction of analgesic use and number of headache days in the long run. These results are supported by an RCT that demonstrated a reduction of oxidative stress indexes in women with chronic migraine who were submitted to biofeedback¹¹⁸. The *mindfulness meditation* technique has been tested in prophylactic management of chronic migraine and medication-overuse headache in a one-year follow-up RCT comparing prophylactic medication versus six weeks of mindfulness training. There was a comparable reduction in headache frequency and in the use of analgesic medication in both groups¹¹⁹. Two other trials with similar design demonstrated reduction of inflammation biomarkers¹²⁰ and catecholamine production¹²¹ in both groups.

Physical activity

One RCT comparing isolated amitriptyline versus amitriptyline associated with aerobic exercise three times a week

in the management of chronic migraine showed a greater reduction in the frequency of headache days in the combined approach group¹²².

Physiotherapeutic measures

One RCT evaluated patients with chronic migraine using prophylactic drugs (amitriptyline or topiramate). They were allocated into two groups, one of which was submitted to physiotherapy sessions (diaphragmatic breathing exercises, cervical traction and mobilization, massage therapy, myofascial release, manual compression of muscle trigger points and passive stretching of cervical muscles). A greater reduction of days of headache was observed in patients with chronic migraine and associated neck pain with the combined approach in comparison with drug treatment alone¹²³.

Acupuncture

A multicenter RCT involving 205 chronic migraine patients showed acupuncture's superiority (one session per week for 12 weeks) compared with sham acupuncture, regarding the reduction in number of headache days¹²⁴. Two subsequent class II trials comparing acupuncture with onabotulinum toxin A and topiramate demonstrated a similar or superior efficacy of acupuncture^{85,125}.

Nutraceuticals

Individuals with chronic migraine using amitriptyline were enrolled in a double-blind RCT that demonstrated a greater reduction in headache days in the group that received the polyunsaturated long-chain fatty acid eicosapentaenoic acid 400mg/day and the polyunsaturated very long-chain fatty acid docosahexaenoic acid 350mg/day¹²⁶.

Neuromodulation

Transcutaneous supraorbital stimulation

Although daily transcutaneous supraorbital stimulation using the Cefaly® device is approved both by ANVISA and the FDA as a prophylactic treatment for episodic migraine, a single preliminary open prospective trial was performed in patients with chronic migraine, in which the goal of 50% reduction on headache days was achieved by only 30% of participants¹²⁷.

Transcutaneous electrical vagus nerve stimulation

In a double-blind RCT including patients with chronic migraine receiving a 1 Hz or 25 Hz stimulation in the auricular branch of the vagus nerve, only patients who underwent 1 Hz stimulation achieved a reduction greater than or equal to 50% on headache days¹²⁸. Another multicenter double-blind RCT did not show a reduction in the number of attacks compared with a sham procedure control group, except in the open phase, after eight months of treatment¹²⁹.

Table 7. Class of evidence and level of recommendation of nonpharmacological methods used for the treatment of chronic migraine.

Methods of treatment	Evidence	Recommendation	References
Acupuncture	1 class I trial and 2 class II trials	B	85, 124, 125
Psychological and behavioral therapies			
Cognitive behavioral therapy	1 class II trial	C	115
Biofeedback	3 class II trials	B	116-118
Mindfulness	2 class II trials	B	119-121
Physiotherapeutic measures (see text)	1 class II trial	C	123
Aerobic exercises	1 class II trial	C	122
Nutraceuticals (see text)	1 class II trial	C	126
Neuromodulation			
Transcutaneous electrical stimulation of supraorbital nerve (Cefaly®)	1 class III trial	U	127
Transcutaneous electrical vagus nerve stimulation	2 class I trials with opposite results	U	128, 129
Invasive electrical stimulation of the occipital nerves	2 class II trials with opposite results and one III positive trial	U	130-132
Transcranial magnetic stimulation	1 negative class I trial and 1 positive class II trial	U	133, 134

Invasive electrical stimulation of the occipital nerves

The results obtained with invasive occipital electrical stimulation of patients with chronic migraine considered refractory are controversial. A multicenter RCT with 110 participants showed that only 39% of them achieved a reduction of 50% or more in the number of headache attacks per month¹³⁰. Another RCT compared effective stimulation with sham stimulation and no stimulation. In this trial, participants who underwent effective stimulation showed a reduction of pain severity¹³¹. On the other hand, a third double-blind multicenter RCT found no difference between the active stimulation and sham stimulation groups in relation to the primary endpoint of 50% or more reduction of headache days after twelve weeks¹³².

Transcranial magnetic stimulation

Two transcranial magnetic stimulation trials have shown opposite results in the management of chronic migraine. A first double-blind RCT showed a reduction of more than 50% in the frequency and intensity of attacks in the active group compared with the placebo group¹³³. However, a more recent RCT demonstrated a significantly greater reduction in the

frequency of headache days in the sham group in relation to the active group¹³⁴.

Table 7 summarizes level of recommendation and class of evidence for the nonpharmacological modalities in the treatment of chronic migraine. It should be remembered that the evaluation of the efficacy of these methods is compromised by the limited number and heterogeneity of the trials, as well as by the variability of methods and conflicting results.

CONCLUSION

Chronic migraine carries a substantial burden and is recognized as a difficult-to-treat condition, particularly when associated with acute medication overuse. Despite this, the use of some oral or non-oral pharmacological approaches are supported by good quality evidence. Additionally, nonpharmacological techniques are currently being subjected to a more profound scrutiny and some of them seem to be probably helpful. Novel biological therapies are currently being tested for efficacy in chronic migraine and new evidence is likely to be available soon.

References

1. Natoli JL, Manack A, Dean B, Butler Q, Turkel CC, Stovner L, et al. Global prevalence of chronic migraine: a systematic review. *Cephalgia*. 2010;30(5):599-609.
2. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology*. 2008;71(8):559-66.
3. Schwedt TJ. Chronic migraine. *BMJ*. 2014;348:g1416.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalgia*. 2018;38(1):1-211.
5. Giacomozzi AR, Vindas AP, Silva AA, Jr., Bordini CA, Buonanotte CF, Roesler CA, et al. Latin American consensus on guidelines for chronic migraine treatment. *Arq Neuropsiquiatr*. 2013;71(7):478-86.
6. Giacomozzi AR, Vindas AP, da Silva Junior AA, Bordini CA, Buonanotte CF, Roesler CA, et al. Consenso Latino-Americano para as Diretrizes de Tratamento da Migrânea Crônica. *Headache Medicine*. 2012;3(4):150-61.
7. American Academy of Neurology. Clinical Practice Guideline Process Manual. 2011 ed. St. Paul, MN: The American Academy of Neurology; 2011.

8. Appendix C: AAN Classification of Evidence for the Rating of a Therapeutic Study. *Continuum* (Minneapolis, Minn). 2015;21(4):1165-72.
9. Appendix D: Classification of Recommendations. *Continuum* (Minneapolis, Minn). 2015;21(4):1165-72.
10. Queiroz LP, Peres MF, Kowacs F, Piovesan EJ, Ciciarelli MC, Souza JA, et al. Chronic daily headache in Brazil: a nationwide population-based study. *Cephalalgia*. 2008;28(12):1264-9.
11. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Frequent headaches in the preadolescent pediatric population: a population-based study. *Neurology*. 2010;74(11):903-8.
12. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211-59.
13. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology*. 2011;76(8):711-8.
14. Allena M, Katsarava Z, Nappi G, COMOESTAS Consortium. From drug-induced headache to medication overuse headache. A short epidemiological review, with a focus on Latin American countries. *J Headache Pain*. 2009;10(2):71-6.
15. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24 Suppl 1:9-160.
16. Headache Classification Committee, Olesen J, Bousser MG, Diener HC, Dodick D, First M, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia*. 2006;26(6):742-6.
17. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology*. 1996;47(4):871-5.
18. Silva-Neto RP, Rodrigues AB, Cavalcante DC, Ferreira PHPB, Campelo V. Evolution of the concept of daily or almost daily headaches - a review. *Headache Medicine*. 2014;5(4):37-40.
19. Nosedà R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization, and modulation of pain. *Pain*. 2013;154 Suppl 1:S44-53.
20. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553-622.
21. Mitsikostas DD, Ashina M, Craven A, Diener HC, Goadsby PJ, Ferrari MD, et al. European Headache Federation consensus on technical investigation for primary headache disorders. *J Headache Pain*. 2015;17:5.
22. Russell MB, Kristiansen HA, Kvaerner KJ. Headache in sleep apnea syndrome: epidemiology and pathophysiology. *Cephalalgia*. 2014;34(10):752-5.
23. Chiang CC, Schwedt TJ, Wang SJ, Dodick DW. Treatment of medication-overuse headache: A systematic review. *Cephalalgia*. 2016;36(4):371-86.
24. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA. Risk factors for medication-overuse headache: an 11-year follow-up study. *The Nord-Trøndelag Health Studies*. *Pain*. 2012;153(1):56-61.
25. He Z, Dong L, Zhang Y, Kong Q, Tan G, Zhou J. Metabolic syndrome in female migraine patients is associated with medication overuse headache: a clinic-based study in China. *Eur J Neurol*. 2015;22(8):1228-34.
26. Scher AI, Lipton RB, Stewart WF, Bigal M. Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study. *Cephalalgia*. 2010;30(3):321-8.
27. Tassorelli C, Jensen R, Allena M, De Icco R, Sances G, Katsarava Z, et al. A consensus protocol for the management of medication-overuse headache: Evaluation in a multicentric, multinational study. *Cephalalgia*. 2014;34(9):645-55.
28. de Goffau MJ, Klaver ARE, Willemsen MG, Bindels RJE, Verhagen AP. The Effectiveness of Treatments for Patients With Medication Overuse Headache: A Systematic Review and Meta-Analysis. *J Pain*. 2017;18(6):615-27.
29. Carlsen LN, Munksgaard SB, Jensen RH, Bendtsen L. Complete detoxification is the most effective treatment of medication-overuse headache: A randomized controlled open-label trial. *Cephalalgia*. 2018;38(2):225-36.
30. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia*. 2006;26(9):1097-105.
31. Rossi P, Faroni JV, Tassorelli C, Nappi G. Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. *J Headache Pain*. 2013;14:10.
32. Hagen K, Albrechtsen C, Vilming ST, Salvesen R, Gronning M, Helde G, et al. Management of medication overuse headache: 1-year randomized multicentre open-label trial. *Cephalalgia*. 2009;29(2):221-32.
33. Hagen K, Albrechtsen C, Vilming ST, Salvesen R, Gronning M, Helde G, et al. A 4-year follow-up of patients with medication-overuse headache previously included in a randomized multicentre study. *J Headache Pain*. 2011;12(3):315-22.
34. Munksgaard SB, Bendtsen L, Jensen RH. Treatment-resistant medication overuse headache can be cured. *Headache*. 2012;52(7):1120-9.
35. Bendtsen L, Munksgaard S, Tassorelli C, Nappi G, Katsarava Z, Lainez M, et al. Disability, anxiety and depression associated with medication-overuse headache can be considerably reduced by detoxification and prophylactic treatment. Results from a multicentre, multinational study (COMOESTAS project). *Cephalalgia*. 2014;34(6):426-33.
36. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia*. 2005;25(1):12-5.
37. Usai S, Grazi L, D'Amico D, Andrasik F, Bussone G. Reduction in the impact of chronic migraine with medication overuse after day-hospital withdrawal therapy. *Neurol Sci*. 2008;29 Suppl 1:S176-8.
38. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. *Cephalalgia*. 2004;24(6):483-90.
39. Andrasik F, Grazi L, Usai S, D'Amico D, Kass S, Bussone G. Disability in chronic migraine with medication overuse: treatment effects at 3 years. *Headache*. 2007;47(9):1277-81.
40. Boe MG, Salvesen R, Mygland A. Chronic daily headache with medication overuse: predictors of outcome 1 year after withdrawal therapy. *Eur J Neurol*. 2009;16(6):705-12.
41. Sances G, Ghiotto N, Loi M, Guaschino E, Marchioni E, Catarci T, et al. A CARE: pathway in medication-overuse headache: the experience of the Headache Centre in Pavia. *J Headache Pain*. 2005;6(4):307-9.
42. Trucco M, Meineri P, Ruiz L, Gruppo Neurologico Ospedaliero Interregionale per lo Studio delle Cefalee. Preliminary results of a withdrawal and detoxification therapeutic regimen in patients with probable chronic migraine and probable medication overuse headache. *J Headache Pain*. 2005;6(4):334-7.
43. Relja G, Granato A, Bratina A, Antonello RM, Zorzon M. Outcome of medication overuse headache after abrupt in-patient withdrawal. *Cephalalgia*. 2006;26(5):589-95.
44. Zidverc-Trajkovic J, Pekmezovic T, Jovanovic Z, Pavlovic A, Mijajlovic M, Radojicic A, et al. Medication overuse headache: clinical features predicting treatment outcome at 1-year follow-up. *Cephalalgia*. 2007;27(11):1219-25.

45. Rossi P, Faroni JV, Nappi G. Medication overuse headache: predictors and rates of relapse in migraine patients with low medical needs. A 1-year prospective study. *Cephalalgia*. 2008;28(11):1196-200.
46. Imai N, Kitamura E, Konishi T, Suzuki Y, Serizawa M, Okabe T. Clinical features of probable medication-overuse headache: a retrospective study in Japan. *Cephalalgia*. 2007;27(9):1020-3.
47. Trucco M, Meineri P, Ruiz L, Gionco M, Gruppo Neurologico Ospedaliero Interregionale per lo Studio delle Cefalee. Medication overuse headache: withdrawal and prophylactic therapeutic regimen. *Headache*. 2010;50(6):989-97.
48. Zebeholzer K, Thamer M, Wober C. Quality of life, depression, and anxiety 6 months after inpatient withdrawal in patients with medication overuse headache: an observational study. *Clin J Pain*. 2012;28(4):284-90.
49. Corbelli I, Caproni S, Eusebi P, Sarchielli P. Drug-dependence behaviour and outcome of medication-overuse headache after treatment. *J Headache Pain*. 2012;13(8):653-60.
50. Creac'h C, Frappe P, Cancade M, Laurent B, Peyron R, Demarquay G, et al. In-patient versus out-patient withdrawal programmes for medication overuse headache: a 2-year randomized trial. *Cephalalgia*. 2011;31(11):1189-98.
51. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. *Neurology*. 2006;67(1):109-13.
52. Zeeberg P, Olesen J, Jensen R. Probable medication-overuse headache: the effect of a 2-month drug-free period. *Neurology*. 2006;66(12):1894-8.
53. Rossi P, Faroni JV, Nappi G. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. *Eur J Neurol*. 2011;18(3):396-401.
54. Grande RB, Aaseth K, Benth JS, Lundqvist C, Russell MB. Reduction in medication-overuse headache after short information. The Akershus study of chronic headache. *Eur J Neurol*. 2011;18(1):129-37.
55. Taghdiri F, Togha M, Razeghi Jahromi S, Paknejad SM. Celecoxib vs prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind clinical trial. *Headache*. 2015;55(1):128-35.
56. Pageler L, Katsarava Z, Diener HC, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia*. 2008;28(2):152-6.
57. Boe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology*. 2007;69(1):26-31.
58. Rabe K, Pageler L, Gaul C, Lampl C, Kraya T, Foerderreuther S, et al. Prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2013;33(3):202-7.
59. Karadas O, Ozon AO, Ozelik F, Ozge A. Greater occipital nerve block in the treatment of triptan-overuse headache: A randomized comparative study. *Acta Neurol Scand*. 2017;135(4):426-33.
60. Goadsby PJ, Goldberg J, Silberstein SD. Migraine in pregnancy. *BMJ*. 2008;336(7659):1502-4.
61. Hutchinson S, Marmura MJ, Calhoun A, Lucas S, Silberstein S, Peterlin BL. Use of common migraine treatments in breast-feeding women: a summary of recommendations. *Headache*. 2013;53(4):614-27.
62. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia*. 2003;23(8):820-4.
63. Mei D, Ferraro D, Zelano G, Capuano A, Vollono C, Gabriele C, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol*. 2006;29(5):269-75.
64. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2007;27(7):814-23.
65. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache*. 2007;47(2):170-80.
66. Diener HC, Dodick DW, Goadsby PJ, Bigal ME, Bussone G, Silberstein SD, et al. Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. *Cephalalgia*. 2009;29(10):1021-7.
67. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *N Engl J Med*. 2017;377(22):2113-22.
68. Tepper S, Ashina M, Reuter U, Brandes JL, Dolezil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425-34.
69. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211-e21.
70. Silberstein S, Lipton R, Dodick D, Freitag F, Mathew N, Brandes J, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache*. 2009;49(8):1153-62.
71. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. *J Headache Pain*. 2008;9(1):37-41.
72. Spira PJ, Beran RG, Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology*. 2003;61(12):1753-9.
73. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM. Pregabalin in the treatment of chronic migraine: an open-label study. *Clin Neuropharmacol*. 2010;33(1):35-9.
74. Bermejo PE, Dorado R. Zonisamide for migraine prophylaxis in patients refractory to topiramate. *Clin Neuropharmacol*. 2009;32(2):103-6.
75. Edvardsson B. Atenolol in the prophylaxis of chronic migraine: a 3-month open-label study. *Springerplus*. 2013;2:479.
76. Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache*. 2011;51(1):33-51.
77. Lai KL, Niddam DM, Fuh JL, Chen SP, Wang YF, Chen WT, et al. Flunarizine versus topiramate for chronic migraine prophylaxis: a randomized trial. *Acta Neurol Scand*. 2017;135(4):476-83.
78. Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache*. 2002;42(6):470-82.
79. Food_and_Drug_Administration. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. Federal Register. 2008;73(104):30831-68.
80. Department_of_Child_and_Adolescent_Health_and_Development. Breastfeeding and Maternal Medication - Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs. Geneva: World Health Organization; 2002.
81. Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology*. 2012;78(13):976-84.
82. Peroutka SJ. Beyond monotherapy: rational polytherapy in migraine. *Headache*. 1998;38(1):18-22.

83. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxinA (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache*. 2009;49(10):1466-78.
84. Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clinical neurology and neurosurgery*. 2010;112(6):463-6.
85. Yang CP, Chang MH, Liu PE, Li TC, Hsieh CL, Hwang KL, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. *Cephalalgia*. 2011;31(15):1510-21.
86. Silva-Neto RP, Almeida KJ, Bernardino SN. Analysis of the duration of migraine prophylaxis. *Journal of the neurological sciences*. 2014;337(1-2):38-41.
87. Brandes JL. Headache related to pregnancy: management of migraine and migraine headache in pregnancy. *Curr Treat Options Neurol*. 2008;10(1):12-9.
88. Marcus DA. Pregnancy and chronic headache. *Expert Opin Pharmacother*. 2002;3(4):389-93.
89. Amundsen S, Nordeng H, Nezvalova-Henriksen K, Stovner LJ, Spigset O. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol*. 2015;11(4):209-19.
90. Davanzo R, Bua J, Paloni G, Facchina G. Breastfeeding and migraine drugs. *Eur J Pharmacol*. 2014;70(11):1313-24.
91. Berk T, Ashina S, Martin V, Newman L, Vij B. Diagnosis and Treatment of Primary Headache Disorders in Older Adults. *J Am Geriatr Soc*. 2018;66:2408-16.
92. Weaver DF, Purdy RA. The geriatric headache: a unique clinical ailment. *Can Fam Phys*. 1986;32:2687-91.
93. Oliveira MG, Amorim WW, Oliveira CRB, Coqueiro HL, Gusmão LC, Passos LC. Consenso Brasileiro de Medicamentos Potencialmente Inapropriados para Idosos. *Geriatr Gerontol Aging*. 2018;10(4):168-81.
94. Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. *JAMA*. 2013;310(24):2622-30.
95. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50(6):921-36.
96. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30(7):793-803.
97. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30(7):804-14.
98. Matharu M, Pascual J, Nilsson Remahl I, Straube A, Lum A, Davar G, et al. Utilization and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine from an observational study in Europe. *Cephalalgia*. 2017;37(14):1384-97.
99. Grazzi L, Grignani E, Sansone E, Raggi A, Leonardi M, D'Amico D. Onabotulinumtoxin A for chronic migraine with medication overuse: clinical results and changes in catastrophizing attitude. Preliminary data. *Neurol Sci*. 2018;39(Suppl 1):173-4.
100. Barbanti P, Ferroni P. Onabotulinum toxin A in the treatment of chronic migraine: patient selection and special considerations. *J Pain Res*. 2017;10:2319-29.
101. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19(1):13.
102. Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. *J Headache Pain*. 2018;19(1):91.
103. Khalil M, Zafar HW, Quarshie V, Ahmed F. Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. *J Headache Pain*. 2014;15:54.
104. Guerzoni S, Pellesi L, Baraldi C, Pini LA. Increased efficacy of regularly repeated cycles with OnabotulinumtoxinA in MOH patients beyond the first year of treatment. *J Headache Pain*. 2015;17:48.
105. Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. *Springerplus*. 2015;4:826.
106. Piovesan EJ, Cadecaro P, Pepe C. Análise de custo-efetividade da toxina onabotulínica A no tratamento preventivo da migrânea crônica sob a perspectiva do sistema privado de saúde do Brasil. *J Bras Econ Saúde* 2017;9(Suppl 1):71-80.
107. Rothrock JF, Bloudek LM, Houle TT, Andress-Rothrock D, Varon SF. Real-world economic impact of onabotulinumtoxinA in patients with chronic migraine. *Headache*. 2014;54(10):1565-73.
108. Silberstein SD, Dodick DW, Aurora SK, Diener HC, DeGryse RE, Lipton RB, et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. *J Neurol Neurosurg Psychiatry*. 2015;86(9):996-1001.
109. Sarchielli P, Romoli M, Corbelli I, Bernetti L, Verzina A, Brahimi E, et al. Stopping Onabotulinum Treatment after the First Two Cycles Might Not Be Justified: Results of a Real-life Monocentric Prospective Study in Chronic Migraine. *Front Neurol*. 2017;8:655.
110. Kabbouche M, O'Brien H, Hershey AD. OnabotulinumtoxinA in pediatric chronic daily headache. *Curr Neurol Neurosci Rep*. 2012;12(2):114-7.
111. Viganò A, Torrieri MC, Toscano M, Puledda F, Petolicchio B, Sasso D'Elia T, et al. Neurophysiological correlates of clinical improvement after greater occipital nerve (GON) block in chronic migraine: relevance for chronic migraine pathophysiology. *J Headache Pain*. 2018;19(1):73.
112. Dilli E, Halker R, Vargas B, Hentz J, Radam T, Rogers R, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, double-blinded, placebo-controlled study. *Cephalalgia*. 2015;35(11):959-68.
113. Cuadrado ML, Aledo-Serrano A, Navarro P, Lopez-Ruiz P, Fernandez-de-Las-Penas C, Gonzalez-Suarez I, et al. Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. *Cephalalgia*. 2017;37(9):864-72.
114. Palamar D, Uluduz D, Saip S, Erden G, Unalan H, Akarim U. Ultrasound-guided greater occipital nerve block: an efficient technique in chronic refractory migraine without aura? *Pain physician*. 2015;18(2):153-62.
115. Kroner JW, Hershey AD, Kashikar-Zuck SM, LeCates SL, Allen JR, Slater SK, et al. Cognitive behavioral therapy plus amitriptyline for children and adolescents with chronic migraine reduces headache days to ≤4 per month. *Headache*. 2016;56(4):711-6.
116. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass SJ, et al. Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. *Headache*. 2002;42(6):483-90.
117. Rausa M, Palomba D, Cevoli S, Lazzerini L, Sancisi E, Cortelli P, et al. Biofeedback in the prophylactic treatment of medication overuse headache: a pilot randomized controlled trial. *J Headache Pain*. 2016;17(1):87.
118. Ciancarelli I, Tozzi-Ciancarelli MG, Spacca G, Di Massimo C, Carolei A. Relationship between biofeedback and oxidative stress in patients with chronic migraine. *Cephalalgia*. 2007;27(10):1136-41.

119. Grazzi L, Sansone E, Raggi A, D'Amico D, De Giorgio A, Leonardi M, et al. Mindfulness and pharmacological prophylaxis after withdrawal from medication overuse in patients with Chronic Migraine: an effectiveness trial with a one-year follow-up. *J Headache Pain*. 2017;18(1):15.
120. Grazzi L, D'Amico D, Raggi A, Leonardi M, Ciusani E, Corsini E, et al. Mindfulness and pharmacological prophylaxis have comparable effect on biomarkers of inflammation and clinical indexes in chronic migraine with medication overuse: results at 12 months after withdrawal. *Neurol Sci*. 2017;38(Suppl 1):173-5.
121. Grazzi L, Raggi A, D'Amico D, Sansone E, Leonardi M, Andrasik F, et al. A prospective pilot study of the effect on catecholamines of mindfulness training vs pharmacological prophylaxis in patients with chronic migraine and medication overuse headache. *Cephalalgia*. 2018;333102418801584.
122. Santiago MD, Carvalho DS, Gabbai AA, Pinto MM, Moutran AR, Villa TR. Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study. *Arq Neuropsiquiatr*. 2014;72(11):851-5.
123. Bevilacqua-Grossi D, Goncalves MC, Carvalho GF, Florencio LL, Dach F, Speciali JG, et al. Additional effects of a physical therapy protocol on headache frequency, pressure pain threshold, and improvement perception in patients with migraine and associated neck pain: a randomized controlled trial. *Arch Phys Med Rehabil*. 2016;97(6):866-74.
124. Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, et al. Acupuncture for chronic headache in primary care: large, pragmatic, randomised trial. *BMJ*. 2004;328(7442):744.
125. Naderinabi B, Saberi A, Hashemi M, Haghighi M, Biazar G, Abolhasan Gharehdaghi F, et al. Acupuncture and botulinum toxin A injection in the treatment of chronic migraine: A randomized controlled study. *Caspian J Intern Med*. 2017;8(3):196-204.
126. Soares AA, Loucana PMC, Nasi EP, Sousa KMH, Sa OMS, Silva-Neto RP. A double-blind, randomized, and placebo-controlled clinical trial with omega-3 polyunsaturated fatty acids (OPFA -3) for the prevention of migraine in chronic migraine patients using amitriptyline. *Nutr Neurosci*. 2018;21(3):219-23.
127. Di Fiore P, Bussone G, Galli A, Didier H, Peccarisi C, D'Amico D, et al. Transcutaneous supraorbital neurostimulation for the prevention of chronic migraine: a prospective, open-label preliminary trial. *Neurol Sci*. 2017;38(Suppl 1):201-6.
128. Straube A, Ellrich J, Eren O, Blum B, Ruscheweyh R. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. *J Headache Pain*. 2015;16:543.
129. Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology*. 2016;87(5):529-38.
130. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia*. 2011;31(3):271-85.
131. Slotty PJ, Bara G, Kowatz L, Gendolla A, Wille C, Schu S, et al. Occipital nerve stimulation for chronic migraine: a randomized trial on subthreshold stimulation. *Cephalalgia*. 2015;35(1):73-8.
132. Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia*. 2012;32(16):1165-79.
133. Misra AK, Sharma PK. Pharmacotherapy of Insomnia and Current Updates. *J Assoc Physicians India*. 2017;65(4):43-7.
134. Conforto AB, Amaro E, Jr., Goncalves AL, Mercante JP, Guendler VZ, Ferreira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia*. 2014;34(6):464-72.

Erratum

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Consensus of the Brazilian Headache Society on the treatment of chronic migraine

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The table 5:

Table 5. Oral drugs evaluated in the treatment of chronic migraine in adults: evidence of efficacy, class of recommendation, recommended doses and risk categories regarding use during pregnancy and lactation.

Drug	Evidence	Recommendation	Dose (mg/day)	Risk during pregnancy*	Risk during lactation**†	References
Neuromodulators						
Topiramate	I	A	50-200	D	L3	62, 64-66, 70
Valproate	II	B	500-2000	X	L2	71
Gabapentin	II	B	900-1800	C	L2	72
Pregabalin	III	C	125-450	C	L2	73
Zonisamide	III	C	50-200	D	L5	74
Beta-blockers						
Atenolol	III	C	50-200	C	L3	75
Tricyclics						
Amitriptyline	II	C	50-100	C	L2	76
Calcium channel blockers						
Flunarizine	III	C	10	C	L5	77
Miscellaneous						
Tizanidine	II	B	fev/24	C	L3	78

Should be:

Table 5. Oral drugs evaluated in the treatment of chronic migraine in adults: evidence of efficacy, class of recommendation, recommended doses and risk categories regarding use during pregnancy and lactation.

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Zonisamide	III	C	50-200	D	L5	74
Beta-blockers						
Atenolol	III	C	50-200	C	L3	75
Tricyclics						
Amitriptyline	II	C	50-100	C	L2	76
Calcium channel blockers						
Flunarizine	III	C	10	C	L5	77
Miscellaneous						
Tizanidine	II	B	2-24	C	L3	78