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GUIDELINES

Latin American consensus on guidelines for chronic migraine treatment

Consenso latino-americano para as diretrizes de tratamento da migrânea crônica

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ABSTRACT

Chronic migraine is a condition with significant prevalence all around the world and high socioeconomic impact, and its handling has been challenging neurologists. Developments for understanding its mechanisms and associated conditions, as well as that of new therapies, have been quick and important, a fact which has motivated the Latin American and Brazilian Headache Societies to prepare the present consensus. The treatment of chronic migraine should always be preceded by a careful diagnosis review; the detection of possible worsening factors and associated conditions; the stratification of seriousness/impossibility to treat; and monitoring establishment, with a pain diary. The present consensus deals with pharmacological and nonpharmacological forms of treatment to be used in chronic migraine.

Key words: migraine, treatment, headache.

RESUMO

A migrânea crônica é uma condição com prevalência significativa ao redor do mundo e alto impacto socioeconômico, sendo que seu manuseio tem desafiado os neurologistas. Os avanços na compreensão de seus mecanismos e das condições a ela associadas, bem como nas novas terapêuticas, têm sido rápidos e importantes, fato que motivou as Sociedades Latino-americana e Brasileira de Cefaleia a elaborarem o presente consenso. O tratamento da migrânea crônica deve ser sempre precedido por uma revisão cuidadosa do diagnóstico, pela detecção de possíveis fatores de piora e das condições associadas, pela estratificação de gravidade/impossibilidade de se tratar e pelo monitoramento com um diário da dor. Este consenso apresenta abordagens farmacológicas e não-farmacológicas para tratar a migrânea crônica.

Palavras-Chave: migrânea, tratamento, cefaleia.

The International Headache Classification (ICHD-2) is the result of a huge effort for preparing a taxonomic system on different conditions in which headaches are present, with over 200 morbid conditions catalogued on its second edition, in 2004[1].

Headaches can be divided, in a simplified manner, into two groups:

- primary, conditions in which mechanisms are eminently neurochemical;
- secondary or 'attributed to', when there is a clear mechanism very likely to cause it, such as a headache due to bacterial meningitis.

Migraine is the typical example of primary headache. It is about a recurring neurological illness, at times progressive and highly prevalent. Typically, its attack is characterized by moderate-to-severe, predominantly lateralized and pulsatile headache, aggravated by physical exertion. This is frequently associated with nausea, vomit, photophobia, and phonophobia. Affected individuals should have normal physical and neurological examinations.

The word chronic is used in the ICHD-2 in three different scenarios: to refer to headaches that persist for a period longer than three months subsequent to the event that has originated it or after the originating process has already been solved (for example, chronic post-traumatic headache); to refer to headaches that persist for a period longer than that convened for characterizing a given headache as episodic (for example, chronic cluster headaches); when the headache occurs 15 or more days per month for over three months, which is the meaning of the word 'chronic' in chronic migraine.

Chronic migraine is a condition with significant prevalence all around the world and a high socioeconomic impact, and its handling has been challenging neurologists. Developments in the understanding of its mechanisms and associated conditions, as well as that of new therapies, have been quick and important, a fact which has motivated the Latin American and Brazilian Headache Societies to prepare the present consensus.

EPIDEMIOLOGY

According to the World Health Organization (WHO), in 2011, headaches represent one of the most frequent reasons for medical appointments, migraines being amongst the 20 most disabling diseases[2]. This modality shows an annual prevalence from 3.0 to 24.6% of the world population, and a recent paper states that it can reach up to 27.5%[3]. It affects 2.9 to 7.8% of males and 10.1 to 17.4% of females in Latin America.

The concept of chronic daily headache was published in 1994 as a heterogeneous group of primary headaches with minimum duration of four hours per day and occurrence in 15 or more days per month, during the last three months. Chronic tension-type headache, transformed migraine, new daily persistent headache, and hemicrania continua have been included in chronic daily headache, transformed migraine being highlighted as the main cause. The ICHD-2 was published in 2004, introducing the word "chronic headache", which diagnostic criteria, also causing discussions, were modified in 2006. These lack of criteria unification makes epidemiological studies difficult.

According to the WHO, the annual prevalence of chronic daily headache is from 1.7 to 4.0% of the adult population, and chronic migraine represents approximately half of the cases. In systematic reviews of world population studies, the prevalence of chronic migraine oscillates between 0.9 and 5.1%[4,5].

Epidemiological studies on chronic migraine in Latin America reveal the following prevalence: 5.12% in Brazil, 6.9% in Cuba, and 7.76 in Colombia (evidences B and C). There are no incidence studies in Latin America.

According to analyses carried out in the United States, the prevalence of chronic migraine in adolescents varies from 0.76 and 1.48%. There are no data for this population group in Latin America.

About 50% of people with headaches are self-medicated, and a frequent problem is the excessive use of symptomatic medication, whose diagnostic criteria are defined by the International Headache Society (IHS)[1]. Published papers inform that on a prevalence of approximately 1.4% of headaches are attributed to the excessive use of medication in the population in general, and in specialized centers this percentage increases up to 30 to 50%[6,7]. In patients with chronic migraine, 31 to 69% of them show excessive use of medication[4]. Specialized centers in Latin America reported 55 to 70%[8].

The natural history of chronic migraine reveals that 26.1% return to the episodic migraine condition, 33.9% persist with chronic migraine, and 40% made a continuous transition between the episodic and chronic forms[9]. The rate of conversion from chronic to episodic migraine will increase with age, varying 1.7 (20-year-old) to 7.1% (60-year old) in females; and 4.2 (20-year-old) to 8.3% (60-year-old) in males.

As compared to episodic migraine, the chronic form causes more disability, has a greater impact on the quality of life, and leads to an increased use of health services and number of comorbidities[10].

The annual direct cost of chronic migraine is estimated in US$ 4,144.00 and US$ 1,883.00 per patient in the health systems of the United States and Canada respectively. Correspondent expenses for patients with episodic migraine are US$ 1,533.00 and US$ 687.00. There are no data available for Latin America[11].

It is worth mentioning that there are important barriers for investigating and handling headaches in all levels, with lack of governmental policies, little repercussion of information on decision-making levels, sub-notification of the socioeconomic impact of these diseases on the health system, and training of graduation and post-graduation students[2].

EVOLUTION OF THE CHRONIC MIGRAINE CONCEPT FROM CHRONIC DAILY HEADACHE

Chronic daily headache is a descriptive word encompassing different types of headaches, which are characterized by symptoms occurring at least 15 days per month over more than three months, lasting at least four hours per day, in the absence of organic diseases[12,13].

Chronic migraine is a disabling disease. Several names were given in an attempt to classify it: chronic mixed headache[14], transformed migraine[13,15], and chronic migraine[1,16]. Currently, the IHS defines it as shown on Table 1.

Headache attributed to the excessive use of drugs up to the current classification

A headache attributed to the excessive use of painkillers or anti-migraine medication is of the secondary chronic-type. It is a result of the interaction between the therapeutic agent and the patient's susceptibility.

This problem was referred to as "rebound headache" until 2004. The IHS classification included item "headache attributed to the excessive use of medication", in which the diagnostic criteria include the excessive regular use of one or more medication that may be taken for acute or symptomatic treatment of headache for over three months. Criteria for excessive use of medication, as well as the obligatoriness of headache relief within two months subsequent to the suspension of the excessively used medication were set up on that occasion for diagnosing chronic migraine[1].

As of 2006, it was proposed that the diagnosis should be made at the moment of the consultation, thus eliminating the previous criteria[16]. Patients increase their headaches by the excessive use of painkillers (Table 2).

It has been noted in the clinical practice that chronic migraine may occur with or without the excessive use of medication.

Mechanisms

Migraine chronification is a gradual process. Attacks evolve from being sporadic to frequent and, eventually, daily or almost daily. This mechanism is bidirectional, and spontaneous, or induced remission may take place. This phenomenon shows clinical, functional, and structural alterations[17,18].

Table 1. Criteria for chronic migraine diagnosis[16].

A: Headache occurring 15 or more days per month, for over three months
B: Previous diagnosis of episodic migraine with no aura
C: Over eight days per month: headache with migraine criteria or relief of headache with triptans or ergotics
D: Without excessive use of painkillers

Table 2. Criteria of headaches attributed to the excessive use of medication for several substances according to the International Headache Classification (ICHD-II)[6].

A: The headache occurs 15 or more days per month
B: Regular consumption of one or more medications for acute symptomatic treatment, defined in the following subtypes:
Noncombined common painkillers: ingestion at least 15 days per month for at least three months
ergotamine, triptans, opiates, or combined painkillers: ingestion at least ten days per month for at least three months
C: The headache developed or was significantly aggravated in the period of excessive use

The physiopathological mechanism of chronic migraine has not been set up yet. It is probably a multiple-factor disorder, with the participation of more than one level of the nervous system. The central hypersensitivity of the trigeminal vascular complex[19-21] increases excitability or reduces pain inhibitory mechanisms. The high frequency of migraine attacks and genetic susceptibility favor this physiopathological mechanism, among other factors, such as comorbidities.

COMORBIDITIES

Comorbidity is the occurrence of two or more conditions in a patient, in a frequency higher than that expected by chance.

There is evidence of comorbidity between migraine and cerebrovascular diseases, psychiatric disorders, and neurological diseases.

Cerebrovascular diseases

Subclinical ischemic lesions on the posterior circulation are more frequent in patients with migraine, especially those with aura[22]. Furthermore, ischemic encephalic vascular accidents (EVAs) and migraine are associated[23]. Ischemic EVA is more prevalent in chronic migraine than in the general population; comparatively, episodic migraine shows greater comorbidity with ischemic EVA than chronic migraine[24], which is also significantly less associated with family history of EVA than episodic migraine[25].

Cardiovascular diseases

Migraine, especially the one with aura, is associated with greater incidence of myocardial infarction and vascular claudication[26]. There is no data in the literature showing the association between cardiovascular diseases and chronic migraine. First papers suggest the association between migraine and patent foramen ovale[27], but this has not been confirmed in subsequent studies[28]. There are no specific papers on the association of patent foramen ovale and chronic migraine.

Psychiatric disorders

Mood disturbances, anxiety, and migraine are comorbid conditions[29]. There are few studies on comorbidity between chronic migraine and depression. Chronic migraine has revealed comorbidity with greater depression, dysthymia, bipolar disorder, generalized anxiety disorder, compulsive-obsessive disorder, somatizations, and phobias in both the population as a whole and in those who seek specialized clinics[30]. A study suggests lack of association between chronic migraine and compulsive-obsessive disorder[24].

Other neurological disorders

There is evidence of comorbidity between episodic migraine and other neurological conditions[24], such as epilepsy[31], Ménière syndrome, benign paroxysmal positional vertigo, kinetosis[32], and multiple sclerosis[33]. As to chronic migraine and epilepsy, a study has revealed no comorbidity[31]. There are no papers on chronic migraine and other neurological conditions.

Other diseases

Chronic migraine is comorbid with systemic arterial hypertension, hyperlipidaemia, sinusitis, asthma, pulmonary emphysema, peptic ulcer, insomnia, and fibromyalgia[24,34,35]. The irritable bowel syndrome is comorbid with migraine[36], however no data are available regarding its association with the chronic one.

The relation between headaches and temporomandibular headaches is controversial, although comorbidity is described with migraine[37,38].

Risk factors

Risk factors for migraine chronification are divided into: unmodifiable (or not easily modifiable) that include age, females, Caucasian ethnicity, genetic factors, and low educational and socioeconomic levels; and modifiable, which is described as follows.

Frequency of attacks

The higher the frequency of migraine attacks, the higher the risk of chronification. Compared to patients with zero to four days of headache per month, those with five to nine days have six-fold more chances to develop chronic daily headache, including chronic migraine. Patients with 10 to 14 days of headache show 20-fold higher risk[39].

Excessive use of pain medication

The risk of patients that make excessive use of pain medication to develop chronic migraine is 19-fold higher as compared to those who do not[39]. Medication utilized in acute treatment of migraine demonstrates different potentials to induce chronification with opioids and barbiturates, regardless of use frequency, this risk increases. On the other hand, the controlled use of triptans (less than ten days per month) showed no potential for significant chronification. Non-hormonal anti-inflammatory medicine (less than ten days per month) is associated with reduction of migraine chronification risk[40].

Obesity

A body mass index equal or higher than 30 is a risk factor for the development of chronic daily headache[41]. The Odds Ratio for overweight patients to develop chronic migraine is 1.4, 1.7 for obese and 2.2 for morbidly obese patients, as compared to those with normal weight[42].

Snoring

Snoring is twice more prevalent in patients with chronic daily headaches than in those with episodic headache, possibly being an independent risk for

progression[43]. There is no specific data available for chronic migraine.

Caffeine consumption

Consumption of more than 241 mg of caffeine per day has revealed a moderate risk factor for transforming episodic into chronic headache in females under 40 years of age. Moreover, it has been shown that subjects with chronic daily headaches consume more caffeine-based painkillers than those with episodic ones, especially females under 40 years old with migraine[44]. There is no specific data available for chronic migraine.

Psychiatric comorbidities and stressing events

Chronic migraine is three-fold more frequent in patients with anxiety and depression as compared to those without psychiatric comorbidities[45]. Chronic migraine was also more frequent in people presenting important changes in their lives during the last year, such as separation, financial losses, and loss of family members[46].

POSSIBLE CIRCUMSTANCES SUGGESTING THE HOSPITALIZATION OF MIGRAINE PATIENTS

Eventually, a patient with chronic migraine might need to be hospitalized. Circumstances for patient's admission might be related to the treatment of the disease itself, its complications, adverse effects of medicines, and associated diseases. Hospitalization can also occur for a diagnosis review. The other further recommendations are based on good clinical practice standards.

Situations when hospitalization should be considered:

- lack of response to adequate treatment, under outpatient regime;
- history of frequent care in emergency unit;
- migraine state or refractory crisis regarding acute treatment at the emergency unit;
- intense nausea, vomits or diarrhea, resulting in dehydration, hydroelectrolyctic disorder, and/or impeding oral treatment, and special attention should be paid to conditions like pregnancy, puerperium, chronic renal failure, serious ischemic heart disease, and arrhythmias;
- changes in hemodynamic (blood pressure and heart rate) and respiratory (respiration rate and O2 saturation) data;
- necessity of interrupting the excessive use of symptomatic medicines (acute analgesics and anti-migraine medicines) and the treatment of manifestations related to toxicity and/or dependence/rebound phenomena that cannot be safely handled in an outpatient regime (parenteral treatment and/or intensive monitoring of symptoms);
- sub-intrant epileptic seizures or *status epilepticus*, serious allergic reactions, renal or hepatic failure, thrombocytopenia, bleeding, vascular insufficiency, serious infection;
- concomitant need of psychiatric hospitalization (risk of aggression, suicide, moral exposure, serious psychosis, detoxification of drug addicts, abstinence);
- when diagnosis review requires procedures better performed within a hospital regime; and
- presence of psychosocial factors impeding an adequate treatment outside a controlled environment.

TRADITIONAL THERAPEUTIC APPROACH: PHARMACOLOGIC AND NON-PHARMACOLOGIC

The treatment of chronic migraine should always be preceded by a careful diagnosis review; the detection of possible worsening factors and associated conditions; the stratification of seriousness/impossibility to treat; and the establishment of monitoring, with a pain diary.

Complementary diagnostic investigations shall be accomplished in accordance with anamnesis and prior examination review, by considering comorbid or associated diagnoses[47].

Including a possible chronic migraine associated with a probable headache caused by excessive use of analgesics, one should give priority to a prophylactic against an acute treatment. In case pain symptoms are restrictive, one should stimulate analgesia through non-pharmacological methods. However, intense and/or impairing headaches (rebound/exacerbations) should be treated in a vigorous way.

Objective of chronic migraine treatment

It is fundamental to consider the expectance of the patient regarding the treatment. This aims at reducing the frequency and intensity of crises, and improving his/her response to acute treatment by diminishing their impact over his/her quality of life[48,49].

The approach to chronic migraine involves the following modalities of treatment: crises, transition, and preventive.

Symptomatic treatment of headache crises (exacerbation)

The headache pharmacologic treatment should consider: the excessively used medication associated with it; scenario (if out- or in-hospital); drug formulation (if oral or parenteral); drug efficacy regarding pain intensity; its potential to result in addiction; history of intolerance and idiosyncratic responses; pharmacodynamics profile; response to previous acute treatments; and patient's stratification regarding the degree of lack of clinical response with acute treatments[50,51].

There are no class I studies of symptomatic medicines for the acute treatment of individuals with chronic migraine. Existing evidences for episodic migraine must be

used. The acute treatment should be applied considering its extension to the transition phase by giving priority in this case to non-hormonal anti-inflammatory drugs, corticosteroids, and neuromodulators. Sodium valproate, magnesium sulphate, chlorpromazine, and haloperidol are medicines with analgesic and neuromodulator effects able to be used both in- as well as out-hospitals[52-54]. Chlorpromazine and haloperidol may also be used by patients in drops under the tongue, taking into account their faster absorption and lower first-pass metabolism.

The parenteral application of sodium valproate[55], magnesium sulphate[56], chlorpromazine[57,58], haloperidol[59], olanzapine[60,61], lidocaine[57], and propofol[62] is particularly useful in treatments within hospital environments, and the use of the first four of them and/or their analogues[63,64] can be extended to transition and/or preventive treatment. Parenteral dihydroergotamine, particularly useful in the treatment of migraine crises, exacerbations of chronic migraine, and rebound headaches[57], is not available in Brazil, only in some Latin-American countries.

Transition treatment

A transition treatment involves measures of a limited duration (less than 30 days before or concomitant to the beginning of preventive treatment), which include: discontinuation of the excessively used drug, if happening; symptomatic treatment of rebound headache with analgesics/anti-migraine drugs; and treatment of abstinence symptoms.

The discontinuation of the excessively used drug, also called detoxification, should be accomplished, if possible, in an abrupt way, except when it is associated with barbiturates, benzodiazepines and opioids, situations where the withdrawal must be gradual.

In order to treat headache crises, one should stimulate non-pharmacologic measures. When they are used, symptomatic medications must be different from those excessively used, under a frequency limited to two days per week.

Abstinence symptoms can be treated with antiemetics and corticosteroids, although evidences regarding their efficacy are limited or contradictory[65-68].

In the transition treatment, corticosteroids can be used for short periods, preferably up to seven days. It can also be applied in patients of difficult control submitted to preventive treatments[61] and/or those with chronic migraine associated with the excessive use of "complex" type analgesics (more than one year of chronicity, excessive use of combined medications, multiple psychiatric comorbidities, and prior "detoxification" attempt)[69].

Preventive treatment

Few medicines were tested for chronic migraine preventive treatment. There are class I studies with evidence level A for onabotulinumtoxinA[70,71] and topiramate[72-74], and one of evidence level B for sodium valproate[75]. The preventive treatment duration of chronic migraine is not established, but there are data showing a substantial relapse rate in patients treated for one year or less with its early suspension (less than one year)[54,74].

Topiramate

The use of topiramate in the prophylactic treatment of "episodic" migraine is based on class I studies with evidence level A[76-78]. Double-blind, placebo-controlled, randomized, and parallel-group studies evaluating patients with chronic migraine who excessively used analgesics showed that topiramate in relatively low doses (50 to 100 mg/day) reduced the frequency of days with pain[71,74] and improved the quality of life of these patients[79]. This action was more efficient after the first four weeks of drug use[79].

Sodium valproate and divalproate

Sodium valproate and divalproate are also recommended in the prophylaxis of episodic migraine, as based on class I studies with evidence level A[80-82]. One analysis with sodium valproate also showed efficacy in the treatment of chronic migraine with doses around 1,000 mg/day, showing higher efficacy when compared to chronic tension-type headache.

Other drugs

Amitriptyline, gabapentin, pregabalin, and tizanidine, although studied for chronic daily headache by revealing efficacy (evidence levels from I to III), were not specifically researched for chronic migraine. Methysergide, a prophylactic medication very useful when handling difficult patients[83], is progressively becoming unavailable in local and international markets.

Neurostimulation procedures[84], despite promising, do not have a well-established role yet. Accordingly, medicines already proven as preventive for "episodic" migraine can be used alone or in combination, even without any evidence of their efficacy for chronic migraine[53].

Type A botulinum toxin

OnabotulinumtoxinA is indicated for the prophylactic treatment of chronic migraine in patients aged 18 to 65[85,86].

Two studies (Phase I/II Research Evaluating Migraine Prophylaxis Therapy – PREEMPT I and II)[70,71], using a new toxin application protocol, showed a reduction in the number of days with headache and migraine, in the intensity and number of hours with pain, in the consumption of triptans and other analgesic medicines[85,86], regardless the interruption of excessive use of analgesics. The improvement of these parameters resulted in an increment in the quality of life of patients[85,86] (class I evidence).

Each session should be repeated after 12 weeks until satisfactory response is achieved for at least two to three cycles[87]. For patients without a satisfactory response following this period, there is no evidence of benefit from continuing treatment[88]. There is no consensus on the duration of treatment. Importantly, follow-up in the studies was carried out for up to 56 weeks[71,85]. Presence of allodynia[89] is considered as a predictive factor of good response. The use of onabotulinumtoxinA is already accepted as a first-line prophylactic treatment in patients with chronic migraine or as second-line for drug-resistant individuals[90].

Recent studies showed similar efficacy between onabotulinumtoxinA and topiramate in the prophylactic treatment of chronic migraine, and patients who received onabotulinumtoxinA had less side effects and lower treatment abandonment rate[91] (class II evidence). OnabotulinumtoxinA represents another weapon in the modest therapeutic arsenal against chronic migraine.

Non-pharmacologic treatments and complementary therapies

The use of non-pharmacologic measures and complementary therapies for chronic migraine is limited due to the lack of studies for this specific condition. One exception to this affirmation is acupuncture, which has been evaluated and obtained promising results[92].

Non-pharmacologic measures and complementary therapies most used by patients, despite solid evidences[93-96], include: valuing the beginning of treatment with change of activities, such as interruption of general activities for one week; yoga; meditation; relaxation; physical therapies of relaxation; massage; thermotherapy; hygiene of sleep; regular and healthy nutrition habits; dietary restriction specific for patients with food as an eliciting factor; limitation to caffeine consumption; light to moderate aerobic activity regularly made; stress handling; behavioral cognitive therapy; pleasant activities and thoughts; acupuncture; and biofeedback.

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