

## Treatment in chronic migraine: choice of rehabilitation strategies

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### Abstract

Migraine is a disabling neurologic condition with a spontaneous clinical evolution into a chronic form. Migraine progression from an episodic into a chronic form is realized through a period of time involving several months or years, during which an increase attack frequency occurs. According to the International Classification of Headache Disorders (ICHD-3) chronic migraine is a type of primary headache occurring on 15 or more days per month for more than 3 months, in which more than 8 days per month headache meet criteria for migraine with or without aura or respond to specific migraine treatment. The prevalence of chronic migraine is estimated between 1-3% of general population. Persons with chronic migraine are more likely to suffer from severe disability; chronic migraine has an important socio-economic impact.

Diagnostic approach in chronic migraine includes exclusion of a secondary headache disorder and confirmation of a primary episodic headache. When a patient is found to overuse pain medication, diagnosis of both chronic migraine and MOH should be considered.

Treating episodic migraine early and managing attack frequency using preventive medication and behavioural interventions will be benefic in reducing the risk of chronicisation. Lifestyle changes are important for avoiding triggers for migraine attacks; treatment of comorbidities is equally important because these conditions exacerbate patient's tendency to have headaches. The initial relief step for drug abusers always relies in drug withdrawal. For migraine attacks treatment begins with non-pharmacologic interventions (staying in a quiet, dark room, pressure on painful areas, applying cold compresses ), simple OTC analgetics (NSAIDs, paracetamol, aspirin, acetaminophen). If these are not effective, triptans are the drugs of choice. Preventive treatment is always recommended in patients with chronic migraine because the high frequency of headache attacks. Treatment should be started with topiramate, because the drug has the highest level of evidence in treating CM; Onabotulinumtoxin A reduced the number headache days, headache severity, headache-related disability and improved functioning and quality of life. Additionally, complementary and alternative medicine treatments are available in CM prophylaxis, such as biobehavioral techniques (relaxation training, thermal biofeedback, electromyography feedback and cognitive-behavioral therapy). Invasive and non-invasive neurostimulation techniques have been studied in the treatment and prevention of various types of headaches, including chronic migraine. New treatment options for acute attacks and for prevention include calcitonin gene-related peptide (CGRP) antagonists and antibodies.

**Key words:** chronic migraine, attack medication, preventive treatment, rehabilitation

Migraine is a disabling neurologic condition with a spontaneous clinical evolution into a chronic form. It is characterized by episodic attacks of usually unilateral headache, pulsating character, with light and sound intolerance, associated with nausea and vomiting. The tendency to suffer from migraine has a genetic component, but attacks can be triggered by a series of internal and external factors.

Two types of migraine have been described: episodic migraine (EM) (with subtypes migraine with aura and migraine without aura) – in which by definition typical headache occur on fewer than 15 days per month, and chronic migraine (CM) with headaches on 15 or more days per month for at least 3 months (4).

Chronic migraine is the most frequent complication of migraine. In some episodic migraines, increase of crises frequency modifies the headache pattern in the chronic form, defined as chronic migraine (CM), with headache frequency of 15 days/month (1). Chronic migraine may also have distinct clinical features, like bilateral headache appearing more frequently and associated symptoms with mild intensity. The pain in CM is usually mild or moderate, photophobia, phonophobia, nausea and vomiting occur much less frequently compared to episodic migraine; in some situations, headache attack may mimic tension-type headaches. The characteristics of headaches in CM may change from day to day (10).

#### **Chronicisation of episodic migraine.**

Migraine progression from an episodic into a chronic form is realized through a period of time involving several months or years, during which an increase attack frequency occurs (2). Migraine features can change with advancing age, with transition from less-frequent episodic migraine to more frequent chronic migraine. Persons with episodic migraine can observe remission of their attacks, no change over time, or increasing in

attack frequency until chronicisation over time (7). Chronic migraine constitutes migraine's natural evolution in its chronic form (3).

The development of chronic migraine has been associated with presence of risk factors: female sex, older age, Caucasian ethnicity, familial antecedents, low level of education, low income populations, predisposition for anxiety, depression, sleep apnea or snoring, overweight, history of frequent headache, stressful life events or major life changes, asthma, allergic rhinitis, caffeine consumption and analgetics abuse (more than 10 days/month) (5). These risk factors have been demonstrated in populational studies. It is important for the physician to identify patients at risk for developing CM, and to develop early a therapeutic plan.

**Criteria for defining chronic migraine** (CM) are established in the third classification of the International Headache Society (IHS) in 2013. According to the International Classification of Headache Disorders, third edition (ICHD-3) (4) chronic migraine is a type of primary headache occurring on 15 or more days per month for more than 3 months, in which more than 8 days per month headache meet criteria for migraine with or without aura or respond to specific migraine treatment.

Specific diagnostic criteria are listed below:

A. Headache (tension-type-like and/or migraine-like) on > 15 days per month for >3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria for migraine without aura and/or criteria for migraine with aura

C. On > 8 days per month for >3 months, fulfilling any of the following:

1. criteria C and D for migraine without aura
2. criteria B and C for migraine with aura

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.

Some authors have established simplified criteria for diagnosing CM depending on headache duration and periodicity: CM is considered when headache lasts more than 4 hours per day (a criteria specific for episodic migraine), days with typical migraine pain are more than 8 per month, and days with any type of headache are more than 15 per month.

**Epidemiology of CM.** Migraine affects overall between 12% and 20% of people during lifetime, over 20% of women and 10% of men experienced migraine-type headaches (5). The prevalence of chronic migraine is not as common as episodic migraine, being estimated between 1- 3% of general population (1,3% in women and 0,5% in men), and its incidence is 2,5% per year (meaning that 2,5% of individuals suffering from episodic migraine will convert into chronic form each year) (5), (7). CM appears especially during midlife, approximately 10 years later than EM onset

**Socio-professional impact of CM.** Migraine has a significant impact on physical, social and professional functioning. More than half of migraine sufferers report high intensity of headache requiring bed rest . According to World Health Organisation Global Burden of Disease Study 2010, migraine was found to be the fourth most disabling medical condition among women and the seventh most disabling medical disorder worldwide (8). To assess the burden of disease, its social and professional impact on patient's lives and functioning in daily activities, specific questionnaires have been developed, such as the Migraine Disability Assessment (MIDAS) or the Headache Impact Test – 6 (HIT-6), useful for both episodic and chronic forms of migraine.

According to those questionnaires applied in clinical and populational studies, persons with chronic migraine are more likely to suffer from severe disability, such as inability to work, to attend social activities or to perform routine house duties; they also miss working days or family activities. As a result, chronic migraine has an important socio-economic impact.

**Comorbidities in CM.** They are several diseases which were found to be more common among chronic migraineurs, such as: obesity, ischemic stroke, cardiovascular disease, sleep disorders, asthma, or chronic pain disorders (low back pain). High prevalence of psychiatric comorbidities is also reported: mood disorders, depression, anxiety, PTSD (post-traumatic stress disorder).

**Diagnostic approach in chronic migraine** includes exclusion of a secondary headache disorder and confirmation of a primary episodic headache .

The first step in diagnosing chronic migraine is recognizing the disorder (6): migraine is the commonest cause of recurrent and severe headache. Its typical features conferred a high diagnostic probability. A detailed history should be obtained from the patient (the diagnosis of migraine relies in the history): localization, pattern of pain, nature and character of pain, presence of associated symptoms. Previous medical history, family and social history, effect of previous treatments should be assessed. The neurologic examination includes fundoscopy, examination of head and neck structures and a brief cardiovascular screening, and should be able to eliminate secondary headache disorders.

Imaging (cerebral MRI) should be reserved for situations when abnormal neurologic signs are found at examination (papilloedema, seizures, alteration in consciousness, fever, oncologic patients).

The second step in diagnosing chronic migraine is recognizing its pattern: episodic headache versus chronic headache (at least 15 days per month). Usually, patients with preexisting primary headache report increasing frequency of attacks, until they reach the level of > 15 days of headache per month. This pattern is called “transformed migraine”. Rarely, patients report a new onset headache, which simply does not go away and persists; this is called “new daily persistent headache”(6).

Differential diagnosis in CM includes other forms of primary headaches from a group called “chronic headaches of long duration”, which includes (5)(7): chronic tension-type headache, hemicrania continua and new daily persistent headache.

It is important to try to make a diagnosis, to explain it to the patient, to reassure the patient that there is no severe underlying cause for its headache (6). Correct diagnosis enables initiation of specific treatments together with risk-factor modification. These measures can improve disability, functional and social status, changing patient’s quality of life.

**Interaction between chronic migraine and medication overuse headache (MOH).** Chronicization is often accompanied by the appearance of acute drugs overuse; persons with CM commonly overuse acute pain medications. Medication Overuse Headache (MOH) has been defined as a headache present on > or = 15 days/month, with regular overuse for > 3 months of one or more drugs used for acute and/or symptomatic headache management. Misuse of ergots, triptans, opioids or combination analgesics on > or = 10 days/month was required to make the diagnosis of MOH, while > or = 15 days/month were needed for simple analgesic-overuse headache (3).

Around 50% of patients apparently with CM revert to an episodic migraine

subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as chronic migraine. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of medication-overuse headache may be inappropriate (assuming that chronicity induced by drug overuse is always reversible). After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly.

When a patient is found to overuse pain medication, diagnosis of both chronic migraine and MOH should be considered (5).

**Management of chronic migraine patients.** The goals of migraine treatment are: reducing or relieving pain, restoration of normal function and reducing attack frequency. Remission in CM was defined as fewer than 10 days of headache per month (9). This goal is difficult to achieve, in a study of 400 patients with , Manack and al. found that only 26% of them obtain remission at 2 years after treatment.(10).

Treatment of chronic migraine begins even before making the diagnosis, patients with episodic migraine should be carefully treated in order to prevent chronicisation of the episodic form. Treating episodic migraine early and managing attack frequency using preventive medication and behavioural interventions will be benefic in reducing the risk of chronicisation. Special attention should be paid to both control and reduction of risk factors which might favour the migraine chronicization process. Non-pharmacological interventions like cognitive behavioral therapy, relaxation techniques, biofeedback or acupuncture are useful strategies for prevention of migraine attacks and of chronicization (7)

Potential strategies for preventing progression include: appropriate management of acute migraine attacks (both with acute medication and prevention), implementation

of lifestyle changes, weight loss, and management of comorbidities: treatment of sleep apnea, of anxiety and depression.

Management of confirmed chronic migraine is very complex, and includes three broad approaches: 1). Modification of risk factors and lifestyle changes, 2). Acute treatments for headache attacks, 3). Preventive medications.

**1). Lifestyle changes** are important for avoiding triggers for migraine attacks, and includes: regularity of meals and sleep, good hydration, involvement in regular physical exercise programs, avoid caffeine abuse and stress management.

Treatment of comorbidities is equally important because these conditions exacerbate patient's tendency to have headaches (6). Treatment of depression, anxiety, of chronic pain syndromes like back pain or fibromyalgia should be established. Sleep disorders, hypertension should be treated; weight loss is another important goal in obese patients.

All patients with migraine are already using medications (analgetics). Rehabilitation in these patients, some of them which are overusing pain medication, consists of drug withdrawal procedures, re-prophylaxis through administration of innovative drugs, such as OnabotulinumtoxinA and/or topiramate, to avoid relapsing attacks, and behavioral strategies to minimize the role of risk factors. The initial relief step for drug abusers always relies in drug withdrawal.

**2). Acute treatments for headache attacks** are a difficult task both for patient and physician. Patient report a background headache with acute exacerbations, and medication overuse is a serious concern because it is difficult to choose at which intensity the attacks should be treated. In acute treatment, same principles as in episodic migraine applies: treatment should be started early, drug choice should depend on attack intensity, effective doses are

recommended, associated symptoms should be also treated, appropriate route for medication (if vomiting) should be chosen.

Non-pharmacologic interventions are important: staying in a quiet, dark room, pressure on painful areas, applying cold compresses (7). If simple OTC analgetics (NSAIDs, paracetamol, aspirin, acetaminophen) are not effective, triptans are the drugs of choice. Triptan class include: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan available in oral, nasal, injectable and transdermic formulations. Triptans should not be given more frequently than 2, maximum 3 days per week, to avoid overuse headaches. Combinations between a triptan and an NSAID are also available.

It is recommended that use of NSAIDs should be limited at less than 15 days per month, use of triptans at less than 10 days per month, and use of ergot derivatives and barbiturates should be avoided, in order to prevent MOH.

New methods for treating acute headache are developing: transcranial magnetic stimulation (Lipton at al. 2010) and vagal nerve stimulation (Goadsby et al.2014). These methods may be as effective as standard medication, and also, prolonged use may reduce headache frequency. For migraine with aura, two devices were in use (Cerenia and Spring TMS device), which delivered single-pulse TMS, with good results if stimulation is applied during the aura.

**3). Preventive treatment in chronic migraine.** Generally, preventive treatment is recommended in patients with high frequency of migraine attacks (usually more than 4-5 days per month) – which is always the case in chronic migraine, but also when attacks are rare, but very severe and disabling (intense pain), or when patients have contraindications or no response to triptans. Preventive treatment will decrease headache frequency but efficacy begin after up to 6-8

weeks of treatment, and it takes up to 6 months before full efficacy is established (5). Compliance with the therapeutic plan is mandatory for treatment success. Preventive medication should be started at a low dose and increased progressively, in order to minimize possible adverse events. If the treatment is efficient, it should be continued for few months, and then dose is tapered down.

It is common among physicians to start preventive treatment in CM with the same drugs approved for episodic migraine (eg beta-blockers or tricyclics). Recommended preventive drugs for chronic migraine are antiepileptic drugs (especially topiramate, but also sodium valproate) and botulinum toxins (Onabotulinumtoxin A).

Treatment should be started with topiramate, because the drug has the highest level of evidence in treating CM (9). Several double-blind, randomized, placebo-controlled clinical trials showed that topiramate cause a significant reduction in migraine days in patients with CM. The drug was useful even in patients with MOH (5). The mean dose of topiramate was 100 mg per day. Sodium valproate efficacy was also proved in smaller trials (mean dose 1000 mg per day) (9). Other antiepileptic drugs with some evidence in preventing CM are: gabapentin, levetiracetam, lacosamide (11).

Onabotulinumtoxin A (Botox) injections could be considered when at least two trials with oral medications have failed in preventing CM attacks. Botulinum toxin is a neurotoxin which inhibits the release of nociceptive mediators from the peripheral terminals of primary afferents and inhibits sensitization of central trigeminovascular neurons, believed to be key factors in development and progression of migraneous headaches (7), (9). In United States it is the only treatment specifically approved for the prophylaxis of CM, based on the evidence of PREEMPT clinical trials (5). Onabotulinumtoxin A

reduced the number headache days, headache severity, headache-related disability and improved functioning and quality of life (5). It is delivered via injections (150 Units) in 31 specific sites on the head and neck (fixed dose of 5 UI each muscle); injections should be repeated every 12 weeks.

Few studies have compared the effect of topiramate and of Onabotulinumtoxin A; they found similar efficacy (9).

Additionally, complementary and alternative medicine treatments are available in CM prophylaxis, such as biobehavioral techniques, including relaxation training, thermal biofeedback, electromyography feedback and cognitive-behavioral therapy (12), (9). Relaxation training and biofeedback focus on the perception of pain, biofeedback training focus on the physical response involved in pain persistence, and cognitive-behavioral techniques targets the experience of feeling pain. Knowing the factors that produced chronic headaches may allow the patient to modulate the pain. Patients are taught self-regulation techniques to enhance individual control of pain and coping strategies for chronic headache and reducing migraine-related stress (9).

Acupuncture may be beneficial if added to medical treatment and to cognitive-behavioral strategies.

The effect of infiltrations on the occipital nerve is unknown for chronic migraine; some small trials shown efficacy is a cervicogenic headache is associated (9).

Neurostimulation - invasive or non-invasive - techniques have been studied in the treatment and prevention of various types of headaches, including chronic migraine. The non-invasive techniques effective in CM prevention are transcutaneous supraorbital and supratrochlear nerve stimulation (tSNS), vagus nerve stimulation (VNS) and high-rate, repetitive transcranial magnetic stimulation (TMS). Invasive techniques are reserved for patients with refractory CM; occipital nerve

stimulation (ONS) with an implantable stimulator near the occipital nerve is effective in reducing the number of headache days (9),(13).

New treatment options for acute attacks and for prevention include calcitonin gene-related peptide (CGRP) antagonists and antibodies. Recently, humanized monoclonal antibodies directed to CGRP ligand or to its receptor appear very promising in ongoing studies, displaying comparable efficacy to the available oral therapies (12).

In the future, pharmacogenomics will allow us to predict the efficacy of migraine treatments, and will permit avoiding of drug abuse due to non-responsivity to a specific drug. There is a strong need to improve diagnosis methods and therapy choices in patients with chronic migraine. Essential steps is obtaining an optimal response to treatment are patient education and choice of realistic expectations in curing chronic migraine.

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