Abstract. – Migraine is an episodic painful disorder occasionally developing into a chronic form. Such disorder represents one of the most common neurological diseases in clinical practice. Chronicization is often accompanied by the appearance of acute drugs overuse. Chronic migraine (CM) constitutes migraine’s natural evolution in its chronic form and involves headache frequency of 15 days/month, with features similar to those of migraine attacks. Medication Overuse Headache (MOH) has been defined as a headache present on ≥ 15 days/month, with regular overuse for > 3 months of one or more drugs used for acute and/or symptomatic headache management. Subtypes of MOH attributed to different medications were delineated. Misuse of ergots, triptans, opioids or combination analgesics on ≥ 10 days/month was required to make the diagnosis of MOH, while ≥ 15 days/month were needed for simple analgesic-overuse headache. CM’s low prevalence produces an extremely high disability grade. Therefore, special attention should be paid to both control and reduction of risk factors which might favour the migraine chronicization process and/or the outbreak of MOH. In MOH sufferers, the only treatment of choice is represented by drug withdrawal. Successful detoxification is necessary to ensure improvement in the headache status when treating patients who overuse acute medications. Different procedures have been suggested for withdrawal namely at home, at the hospital, with or without the use of steroids, with re-prophylaxis performed immediately or at the end of the wash-out period. At the moment we have not a total agreement whether prophylactic treatment should be started before, during, or after discontinuation of the overuse drug. Both drugs have been approved for CM treatment in view of their well-defined resistance to previous prophylaxis drugs. Recently, the PREEMPT clinical program has confirmed onabotulinumtoxinA as an effective, safe, and well-tolerated prophylactic treatment for adults with CM.

Key Words: Chronic migraine, Medication overuse headache, Risk factors, Drug abuse withdrawal, Prophylaxis, Onabotulinumtoxin A, BOTOX®, Topiramate.

Introduction

Migraine is an episodic painful disorder which can gradually chronify and it is among the most common neurological disease in clinical practice. Such process is often accompanied by the appearance of acute drugs overuse. Chronic migraine (CM) constitutes migraine’s natural evolution in its chronic form and involves headache frequency of 15 days/month, with features similar to those of migraine attacks. Chronic migraine’s prevalence rate in general population is 2-4%. Overall, population studies estimate that patients who have low-frequency episodic migraine or high-frequency episodic migraine will transition to CM at the rate of about 2.5% per year. At present, CM represents the most important challenge for tertiary headache centers, to which over 50% of patients refer for monitoring the chronicization process and its possible complication with medication overuse headache (MOH). MOH affects 1-1.4% of general population, with prevalence rates similar across different countries and an higher preponderance in women than in men. In general, compared with patients with episodic migraine, patients with migraine and MOH are more likely to be of female sex, have lower levels of educational attainment, be married, be unemployed, have migraine remission during pregnancy, be menopausal, have constipation, not use oral contraceptives, have higher use of health-care resources, and be on polypharmacy.
The first edition of the International Classification of Headache Disorders (ICHD-I) was published in 1988 by the International Headache Society (IHS) in an effort to standardize criteria for headache disorders worldwide. Since its inception, the ICHD-I has been generally accepted by headache specialists internationally as the gold standard for classification of headache disorders.

In 2004, the ICHD-II was published. Although chronic daily headache (CDH) was not included as a formal diagnosis, several different forms were described. They included chronic CM, MOH, chronic tension-type headache (CTTH) (the only CDH incorporated in the ICHD-I), new daily persistent headache (NDPH) and hemicrania continua (HC).

CDH syndromes include a group of headache disorders that occur on ≥15 days/month, for ≥4 h/day for >3 months. Whereas CM, CTTH, HC and NDPH are primary headache disorders, MOH is classified in the ICHD-II as a secondary headache. ICHD-II precludes the diagnosis of any of these headache types other than MOH if the patient is overusing acute medication. In these situations, the proposed diagnosis is just MOH.

**Chronic Migraine**

ICHD-II included criteria for CM, which was classified as a complication of migraine. The original criteria for CM required headaches to meet criteria for migraine without aura on ≥15 days/month, for ≥3 months, without medication overuse. Since the criteria were felt to be overly restrictive and not applicable to most patients with CDH in 2006, the Headache Classification Committee published more inclusive criteria for CM, in which the disorder is defined by headaches on ≥15 days/month, for ≥3 months, of which ≥8 of the days fulfill criteria for migraine without aura or were successfully treated with acute care medications such as ergots or triptans.

Although MOH and CM are associated, the causal path is controversial (MOH as a cause or consequence). There are several different theories regarding the aetiology of MOH, including: (I) central sensitisation from repetitive activation of nociceptive pathways; (II) a direct effect of the medication on the capacity of the brain to inhibit pain; (III) cellular adaptation in the brain; (IV) a decrease in blood serotonin due to repetitive medication administration with alteration of serotonin receptors; and (V) changes in the periaqueductal grey matter.
medication use for research purposes and scientific evaluation and can be used in clinical trials but not for routine clinical diagnosis.

An advantage of the research criteria is that they include patients from a prospective point of view (ie, at the time of consultation) and not retrospectively (ie, after withdrawal). Criteria for MOH were again revised by the Headache Classification Committee in 2006, eliminating the requirement that the headache resolves within 2 months after the discontinuation of the overused medication.

MOH can be distinguished as simple (MOH Type I) or complex (MOH Type II). Simple cases involve relatively short-term drug overuse, relatively modest amounts of overused medications, minimal psychiatric contribution, and no history of relapse after drug withdrawal. In contrast, complex cases often present with multiple psychiatric comorbidities and a history of relapse.

Chronicization of Migraine: Risk Factors

Migraine attacks sometimes increase in frequency over time. Headache experts conceptualize this process with a model that envisions transitions into and out of four distinct states: no migraine, low-frequency episodic migraine (<10 headaches per month), high-frequency episodic migraine (10-14 headaches per month), and chronic migraine (CM, ≥15 headaches per month). Transitions may be in the direction of increasing or decreasing headache frequency and are influenced by specific risk factors.

In presence of CM’s low prevalence, an extremely high disability grade has been ascertained, which is caused by such chronic form. Therefore, special attention should be paid to both control and reduction of risk factors which might favour the migraine chronicization process and/or the outbreak of MOH (Table I).

Among the risk factors for chronicization are non-changeable agents such as demography, age, and socio-economic status, as well as changeable factors, such as obesity, caffeine use/misuse (dietary and drug-containing caffeine), sleep disorders (such as snoring and sleep apnea), endocrinologic alterations and specific psychological patterns.

The underlying mechanisms explaining the relationship between the high frequency of the attacks and obesity are yet poorly understood. Anyhow, obesity is associated to a proinflammation...
infarction, diabetes (both type 1 and 2), stroke, vascular malformations, and venous thromboembolism.

Risk factors include a family history of migraine, different psychosocial factors such as stress, depression, and anxiety, adrenergic receptor polymorphisms, and smoking.

**Table 1.** Comorbidities of migraine and risk factors for developing chronicization and its complications.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Vascular</td>
<td>Frequent migraine attack pattern &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Combination with TTH &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Medication overuse &lt;sup&gt;b&lt;/sup&gt; (barbiturates &gt; ergots &gt; triptans &gt; opioids &gt; AINS &gt; analgesics)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Modified Framingham risk scores &lt;sup&gt;b&lt;/sup&gt; (smoking, obesity (BMI), self-reported BP, cholesterol levels, diabetes and not lipid profile)</td>
</tr>
<tr>
<td>Neurological</td>
<td>Snoring/sleep apnea &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Suicide risk &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Low levels of education</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
</tr>
<tr>
<td></td>
<td>Stressful events</td>
</tr>
<tr>
<td>BMI body mass index</td>
<td></td>
</tr>
<tr>
<td>BP blood pressure</td>
<td></td>
</tr>
<tr>
<td>GERD gastroesophageal reflux disease</td>
<td></td>
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<tr>
<td>IMA acute myocardial infarction</td>
<td></td>
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<tr>
<td>MS multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>PFO patent foramen ovale</td>
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</tr>
<tr>
<td>WMLs white matter lesions</td>
<td></td>
</tr>
<tr>
<td>TTH tension-type headache</td>
<td></td>
</tr>
<tr>
<td>TMD temporomandibular disorders</td>
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</tbody>
</table>

Modified from Ref. [115, pp 11, 14]. <sup>a</sup>Population-based studies; <sup>b</sup>Clinical reports; <sup>c</sup>Modifiable items.

In summary, the presence of comorbidities in patients with migraine is common and can influence the course and severity of the disease. Understanding the relationship between a patient’s comorbidities and migraine can help in the management of the condition, as well as in identifying potential targets for future research.

References:


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**Table 2.** Inflammation markers and their potential relationship with comorbidities in patients with migraine.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Connection</th>
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<tbody>
<tr>
<td>Leucocytes</td>
<td>Elevated in migraine patients</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Increased in chronic migraine</td>
</tr>
<tr>
<td>IL-6</td>
<td>Linked to pain sensitivity</td>
</tr>
<tr>
<td>TNFα</td>
<td>Increased in obesity and migraine</td>
</tr>
</tbody>
</table>

**Table 3.** Neurochemical and neuroendocrine alterations in patients with migraine.

<table>
<thead>
<tr>
<th>System</th>
<th>Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Decreased in migraine</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Altered in migraine</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Increased in migraine</td>
</tr>
</tbody>
</table>

**Table 4.** Genetic factors in migraine.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>Linked to migraine</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>Increased risk</td>
</tr>
<tr>
<td>HLA-DRA</td>
<td>Linked to migraine</td>
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</table>

Worldwide vitamin D insufficiency is common in various populations. A number of observations suggest a correlation between low serum vitamin D levels and a higher incidence of chronic pain. Some case reports have shown a beneficial effect...
of vitamin D supplementation in patients with headache. It’s well known that serum vitamin D levels show a strong relationship with latitude. In a recent study a tendency for headache prevalence to increase with increasing latitude was found. Moreover, available data indicate a higher frequency of headache attacks in autumn-winter than in summer. The presence of vitamin D receptor, 1α-hydroxylase and vitamin D-binding protein in the hypothalamus suggest a role of vitamin D deficiency in the pathogenesis of head pain.

Finally, prevalence of gastroesophageal reflux disease (GERD) has recently shown to be increased in patients affected by migraine. A proposed mechanism is related to the common etiology of both disorders. Autonomic nervous system dysfunction plays in fact, an important role in the pathogenesis of both reflux disorders and migraine attacks, which may explain the overlap of GERD and migraine.

In chronic patients the risk of abuse of pain killer medications increases up to 30% in general population, and to 80% in patients under treatment in specialized centers. In a study conducted on 8219 patients with Episodic Migraine (EM), as a part of the AMPP, the progression to chronic or transformed migraine (TM) had a rate of 2.5% per year, with an increased risk associated with any use of barbiturates and opiates, after adjusting for covariates, while triptans were not. NSAIDs were protective or inducers depending on the headache frequency (protective against transition to TM at low to moderate monthly headache days, associated with increased risk of transition to TM at high levels of monthly headache days). Regarding opioids’s association with migraine progression, the critical dose of exposure is around 8 days per month, and the effect is more pronounced in men. Barbiturates also induce migraine progression, and the effect is dose dependent (critical dose around 5 days of exposure per month) and more pronounced in women. Triptans induce migraine progression only in those with high migraine frequency at baseline (<14 days per month), but not overall. NSAIDs protect against migraine progression unless individuals have 10 or more headache days per month (when they become inducers, rather than protective). Finally, caffeine containing over-the-counter products increase risk of progression.

The Severity of Dependence Scale (SDS) score has appear to be a significant predictor of medication overuse among chronic headache patients with sensitivity, specificity, positive and negative predictive values of 0.79, 0.84, 0.84 and 0.79, respectively, in men and 0.76, 0.77, 0.73 and 0.79 in women. Since the value of SDS for detecting medication overuse and dependency like behaviour among people with chronic headache, it may be used to identify chronic headache patients who may benefit from detoxification.

A potential problem for the development of this form of headache arises from the recommendations that drugs have to be taken as early as possible in migraine. This approach, although correct for specific medications like triptans, increases the risk that patients will take more of the drug than is necessary, thus increasing the risk of inducing medication overuse.

It has been noted that psychiatric comorbidity is often an important factor in the transformation of episodic headache and a negative prognostic indicator for headache treatment.

Furthermore, the presence of personality disorders are considered a complication for headache management and headache represents a symptom present in about 60% of patients affected by personality disorders admitted to an Emergency Department.

Moreover, stressful events may contribute to the progression of migraine to a chronic form, modifying the inhibitory descendant mechanisms. Stress may intervene in the regulation of the immune network system. Elevated levels of TNFα, IL-1β, IL-6 and nitric oxide have been found in subjects undergoing to stressful events.

Pathological abuse of nicotine or caffeine has not been found in patients with MOH.

The relationship between migraine and smoking is controversial, even if a recent study underlined the important role of smoking as a trigger factor for migraine attacks.
The mechanisms are yet not completely understood. Some hypotheses have been suggested: an enhancing effect of smoking on the activity of brain monoamines, a decrease in nitric oxide production, nicotine dependence or the well-known comorbidity of migraine with psychiatric disorders, such as depression, where smoking prevalence has been shown to be increased. Conflicting results have also been found in population-based studies evaluating the association between caffeine and chronic headache. Some studies, in fact, have reported a positive relationship between high caffeine consumption and prevalence of migraine. Furthermore, high caffeine consumption has been found to be a modest risk factor for onset of chronic daily headache. However, there is a high prevalence of smokers and individuals with a body-mass index of more than 30 among patients with MOH. The presence of these features might be indicative of frontal lobe dysfunction in patients with MOH.

Previous studies reported that family history data uncovered an elevated risk of mood disorders and substance use disorders (alcohol, drugs) in the families of MOH patients. The risk of MOH is increased threefold if there is a family history of MOH or other substance abuse such as drug or alcohol abuse. The risk of developing drug overuse or substance abuse is increased fourfold if another family member has had MOH.

Genetic studies have found an association between the Val66Met polymorphism in brain-derived neurotrophic factor, which is related to behavioural disorders and substance abuse, and increased analgesic drug consumption in patients with MOH. Another study found that allele 10 of the dopamine transporter gene (SLC6A3; also known as DAT1) was significantly under-represented in patients with MOH compared with patients with episodic migraine.

**Withdrawal from Drug Abuse**

In MOH sufferers, the only treatment of choice is represented by drug withdrawal. Successful detoxification is necessary to ensure improvement in the headache status when treating patients who overuse acute medications.

The goal of this treatment is not only to detoxify the patients and stop the chronic headache but also to improve responsiveness to acute or prophylactic drugs. Most headache specialists consider drug withdrawal to be more effective if done abruptly because this is thought to be associated with fast resolution of the drug-induced pain-coping behaviour.

This is likely to apply particularly in overuse of triptans, ergots, paracetamol, aspirin and NSAIDs, for which outpatient withdrawal programmes can be appropriate. However, due to the possibility of severe withdrawal symptoms, gradual withdrawal might be recommended for opioids, barbiturates and, in particular, benzodiazepines to reduce withdrawal symptoms.

A survey of 22 studies dealing with therapy of drug-induced headache shows that most centres use drug withdrawal as the primary therapy. The discontinuation of the acute medication can result in worsening of the headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, nervousness and rebound headache. Seizures or hallucinations, although rare, are observed in patients who overuse barbiturates containing anti-migraine drugs. These symptoms generally last between 2 and 10 days (average 3.5 days), but can persist for up to 4 weeks.

Withdrawal symptoms are usually relieved by further intake of the overused medication, but this could lead to perpetuation of the overuse. The withdrawal headache seems to be shorter in patients who have taken triptans (mean 4.1 days) than in patients who have overused ergotamine (mean 6.7 days) or NSAIDs (mean 9.5 days). Withdrawal from triptans is generally achieved in a short period of time (approximately 80% of patients are headache-free 4 days after starting the therapy) and without serious withdrawal symptoms.

The detoxification period is based on the use of various classes of drugs, among which corticosteroids certainly are the most frequently employed. Oral prednisone constitutes the most common treatment during detoxification; when compared with placebo, it reduces the duration of withdrawal headache.

In the follow-up period, the initial goal is to outline an effective prophylaxis therapy. Relapse percentages during the first year after withdrawal range between 22 and 44%. Different procedures have been suggested for withdrawal namely at home, at the hospital, with or without the use of steroids, with re-prophylaxis performed immediately or at the end of the wash-out period. However, no final agreement...
has been reached except for withdrawal from abuse in order to reinstate the natural course of CM or high frequency-migraine. Early introduction of preventive treatment without a previous detoxification programme reduced total headache suffering more effectively compared with abrupt withdrawal.

Between the different drug withdrawal strategies, in-patient withdrawal seems the most helpful. An inpatient therapy should be performed in patients who take barbiturates, in those who are not able to stop taking medications as outpatients or in those with high levels of depression. Conversely, an outpatient treatment can be helpful in patients who are highly motivated and who do not take barbiturates. Outpatient treatment is a viable alternative for self-disciplined patients who take a single drug or analgesic not containing barbiturates, and who do not have a high level of depression or anxiety.

A direct comparison between inpatient withdrawal and outpatient withdrawal treatment showed that both methods led to a significant decrease in headache days per month after 12 months and a reduction in migraine disability scores without superiority of one method. Since the outpatient withdrawal approach is less expensive than the inpatient approach, and is as successful in a motivated group of patients, it is the preferred choice in many cases.

Another helpful alternative can be performing drug withdrawal infusion therapy within a day-hospital setting, limiting patients permanence in hospital at a maximum of 6 h during the infusion therapy. This approach is most effective in patients who are highly motivated and self-disciplined and have showed positive results after 4 months and 1-2 years of follow-up.

Treatments for the acute phase of drug withdrawal vary considerably between studies. They generally include fluid replacement, analgesics when strictly necessary for severe rebound headache, tranquilisers, sometimes neuroleptics and steroids. Steroids effectively reduce withdrawal symptoms, including rebound headache.

In a large open-label trial involving 400 patients with chronic daily headache and medication overuse, oral prednisone (60 mg as a starting dose, then tapering down by 20 mg every second day), as part of an outpatient regimen, effectively reduced rebound headache and withdrawal symptoms.

Conversely, a recent Norwegian placebo-controlled, randomised, double-blind study, including patients with both TTH and migraine, showed that prednisolone (60 mg as a starting dose, then tapering down by 20 mg every second day), given as part of an inpatient regimen during the first 6 days after medication withdrawal, was ineffective in treating withdrawal headache.

In a very recent study prednisone 100 mg, given once a day for the first 5 days after medication withdrawal as part of an inpatient strategy, was effective in reducing medication withdrawal headache in 20 MOH patients with migraine as a primary headache.

Rossi et al. randomly assigned 120 MOH patients to one of three groups: group A received only strong advice to withdraw overused medication(s); group B underwent a standard outpatient detoxification programme based on advice to a abrupt withdrawal of overused medication(s), plus oral prednisone for the first 8 days and personalised preventive treatment starting on day 1; group C underwent a standard inpatient detoxification programme based on the abrupt withdrawal of overused medication(s) plus oral prednisone for the first 8 days, personalised preventive treatment starting on day 1, parenteral fluid replacement and administration of antiemetics, and strict observation and support for 8 days.

Boe et al. evaluated 100 MOH inpatients receiving prednisolone or placebo and pre-withdrawal advice. Krychantowski and Moreira randomly assigned 150 MOH outpatients with moderate overuse of acute drugs other than opioids to a tapering course of prednisolone, regular naratriptan or no regular medication for 6 days, in addition to advice and rescue medication.

No differences in terms of percentage of patients achieving successful withdrawal, headache frequency, headache intensity, and calculated mean headache, were found by these three studies after a follow-up period going from 8 days to 2 months.

A withdrawal and detoxification therapeutic regimen that obtained good results at 6 months of follow-up in a sample of patients suffering from probable CM and probable MOH during admission in eight italian hospitals consisted in abrupt discontinuation of the overused drug and by a therapeutic protocol including i.v. hydration, dexamethasone, metoclopramide and benzodiazepines for 7-10 days. Prophylactic medication was started immediately after admission.

Data suggest that the patients affected by CDH and medication overuse benefit from withdrawal therapy performed during hospitalization.
amethasone 4 mg i.v./day for 1 week, diazepam 6 mg/day for 10 days) plus prophylaxis with amitriptyline (from 10 to 20 mg/day) plus topiramate (from 50 to 100 mg/day) for at least 6 months. This combination seems a good pharmacological solution to reduce the risk of relapse. In patients with migraine plus MOH and low medical needs, effective drug withdrawal may be obtained through the imparting of advice alone.

Non-pharmacological approaches for treatment of MOH are important tools to help patients to learn to restructure their cognitive approach to pain and to learn to tolerate discomfort and emotional distress. Short-term psychodynamic psychotherapy in association with pharmacological therapy improves headache in MOH, and the combination of both has had better outcomes than has pharmacological therapy alone for reducing long-term relapses and improving quality of life in a non-randomised study and in a randomised 3-year follow-up study.

In the study of Rossi et al. on 120 patients with uncomplicated MOH treated with three different modalities (only strong advice to withdraw overused medication, standard outpatient detoxification or standard inpatient programme), the numbers of patients who achieved successful withdrawal and had reduced headache frequency were not different between groups during the follow-up period of 60 days after withdrawal.

In the follow-up period, the primary goal is to outline an effective prophylaxis therapy. Therapeutic success is usually strictly defined as a total absence of headache or an improvement (in terms of headache days/month) of more than 50% in a period of time from 1 to 6 months. In a review of 17 studies (1,101 patients), the mean success rate of withdrawal therapy, within a time window of 1-6 months, was found to be 72.4%.

The treatment can be considered successful when clinical improvement is confirmed after at least 1 year of follow-up after withdrawal. Findings observed from recent studies suggest that patients have greatest risk for relapse within the first 12 months but have a decreased risk of relapse when they have avoided medication overuse for 12 months after withdrawal.

Other three investigations considering a longer observation period (9-35 months) recorded success rates of 60, 70 and 73%, respectively. Studies with a longer follow-up period (4-6 years) found relapse rates of between 40 and 60%.

An Italian report on different methods of withdrawal therapy found an increased risk for relapse of MOH in association with a long duration of migraine before medication overuse, a high number of previous preventive treatments and a high frequency of migraine after withdrawal therapy.

In another work male sex, intake of combination analgesics after withdrawal therapy, and using the causative medication again after withdrawal therapy were found to be predictors of relapse.

In the subgroup of patients with MOH plus migraine studied by Katsarava et al., after binary logistic regression analysis, three variables emerged as significant predictors of relapse: years with more than eight migraine days per month, higher frequency of migraine attacks after drug withdrawal, and a greater number of previous preventive treatments.

More recently, use of codeine-containing drugs, high self-reported bodily pain as measured by the SF-36 questionnaire, and low self-reported sleep quality, were found to be predictors of a poor outcome.

Conversely, in a multivariate analysis, the frequency of primary headache disorder, ergotamine overuse, and disability score for chronic headache estimated by MIDAS were indicated to be independent predictors of treatment efficacy at 1-year follow-up.

Some researches, reported a better prognosis for patients who had migraine as the underlying primary headache disorder than for patients who had tension-type headache and for ergotamine or triptan withdrawal than for analgesic withdrawal.

The future in relapse prevention of CM complicated by MOH consists in considering how drugs currently used, such as triptans and emerging therapies present responsivity profiles related to well-defined genetic polymorphisms. The feasible diagnostic setting for a tailored treatment of CM based on the application of pharmacogenomics will allow us to predetermine the efficacy of single old and new drugs by avoiding abuse and chronicization due to non-responsivity of the abused drug.

Chronic Migraine Prophylaxis After Detoxification

At the moment we have not a total agreement whether prophylactic treatment should be started...
before, during, or after discontinuation of the overuse drug. A recent prospective, multicentre trial investigated three treatment groups: personalised preventive medication from day 1 (n=17); abrupt withdrawal plus rescue medication (n=20); and no preventive medication plus no advice to stop overused drugs (n=19). There was not a significant difference between all three groups for the primary endpoint, change in headache days. The more pronounced reduction in the headache index in the first group compared with the second group might indicate an advantage for a personalised preventive medication without abrupt withdrawal.

Even though many Authors are in favour of starting first line preventive treatments as soon as possible, these treatments have no influence on the prognosis. It is generally agreed that behavioural and psychological factors could potentially influence the induction, maintenance and outcome of MOH. Numerous factors (e.g. adverse effects, tolerability, cost, frequency of dosage, hesitancy to take daily medication, failure to complete treatment) negatively influence compliance with the preventive pharmacology for migraine prophylaxis. The choice of prophylactic drug in MOH should be based on the primary headache (migraine vs. tension-type headache), the possible side-effects of the drugs, the comorbidities, and the patient’s preference and previous therapeutic experiences.

A study conducted in a large series to assess prospectively the impact of prophylaxis on health-related quality of life (HRQOL), using the Short Form 36 (SF-36), and daily activities, using the Migraine Disability Assessment Score (MIDAS), indicates that migraine prophylaxis has the potential to reduce the global burden of migraine on individuals and society. Several epidemiologic surveys indicate that preventive therapies are significantly underutilized; only a minority of patients who could benefit from preventive therapy are currently treated (6-13% in population-based surveys). A study of patient adherence to prophylactic migraine medication showed that 35% of enrolled patients were non-adherent. Another report revealed that approximately 75% of the study population (n = 729) had stopped or switched prophylactic treatment for migraine after 1 year.

Possible therapeutic agents in CM rephrophylaxis after detoxification are OnabotulinumtoxinA and Topiramate. Both drugs have been approved for CM treatment in view of their well-defined resistance to previous prophylaxis drugs.

**OnabotulinumtoxinA (BOTOX®)**

OnabotulinumtoxinA is a substance obtained from the Gram-positive anaerobic bacterium *Clostridium botulinum*. Its action occurs through the block of peripheral acetylcholine release at the level of peripheral cholinergic nerve endings.

Travelling in the general vascular circulation, OnabotulinumtoxinA reaches the extra-cellular space. The mechanism through which OnabotulinumtoxinA exits from vasculature is unknown. At the level of neuromuscular injection, OnabotulinumtoxinA arrests spontaneous quantal release of acetylcholine via cleavage of SNAP-25 protein (synaptosomal protein with a molecular weight of 25 kDa), producing muscular relaxation. Such mechanism of action is the base for both the botulism disorder then the use of OnabotulinumtoxinA as a therapeutic agent in clinical practice. Paralysis at muscular local level and reduced muscular contraction cannot explain alone OnabotulinumtoxinA’s pain-relief. This suggests indirect reduction on central sensitization by inhibition of peripheral sensitization of nociceptive fibers, by inhibiting the release of neuromediators such as glutamate, substance P, calcitonin gene-related peptide (CGRP) or c-fos gene expression from the peripheral termini of nociceptive fibers.

Blocking release of these neurotransmitters inhibits neurogenic inflammation; that, in turn, inhibits peripheral sensitization of nociceptive (pain-conducting) nerve fibers. As a result, peripheral pain signals to the central nervous system are reduced and, indirectly, central sensitization is blocked.

This was proven in a human model of trigeminal sensitization in which OnabotulinumtoxinA effectively prevented capsaicin-induced pain, flare, and secondary hyperalgesia. A contribution of calcitonin gene-related peptide (CGRP) to migraine pathophysiology is suggested by a study on cultures of trigeminal ganglia neurons incubated with toxin; this incubation has shown the reduction of secretory stimulation of CGRP neurotransmitter respect to control cultures.

One recent investigation conducted in female rats demonstrated that injection of BoNT type A into craniofacial muscles can rapidly decrease mechanical sensitivity of temporalis muscle noc-
ceptors through inhibition of glutamate release, and attenuate the vasogenic vasodilation caused by release of CGRP from muscle nociceptors.

Initially used to treat strabismus in the 1970s, botulinum toxin now has more than a hundred possible medical applications. Its utility in neurologic conditions has largely involved treating movement disorders (particularly dystonia and conditions with muscle hyperactivity), although practically any hyperkinetic movement disorder may be relieved by botulinum toxin, including hemifacial spasm, tremor, tics, myoclonus, and spasticity. Recently, botulinum toxin has been shown to impact autonomic disorders by acting at acceptors on glands and smooth muscle, and consequently it has been used in the management of a number of other conditions including hypersecretory disorders, detrusor sphincter dyssnergy or overactivity and gastrointestinal smooth muscle/sphincter spasm.

OnabotulinumtoxinA has been reported to relieve pain in a variety of conditions, including migraine. OnabotulinumtoxinA has been extensively used in our University-based Hospital during the last decade as pioneering off-label drug to treat drug-resistant CM patients.

In 2000, an open-label study employing BOTOX (OnabotulinumtoxinA; Allergan, Inc., Irvine, CA, USA) reported its success in migraine prophylaxis. However, subsequent studies investigating the efficacy of BoNT on episodic migraine with different dosages or injection paradigms showed inconsistent but generally disappointing results. Nonetheless, trials targeting patients with chronic daily headache suggested that onabotulinumtoxinA might be effective in treatment of CM.

Results of 2 additional exploratory, well-designed, randomized, double-blind, placebo-controlled trials have provided further insight into which patients, dosages, and injection protocol may yield the best results from prophylactic OnabotulinumtoxinA therapy.

All patients received a minimum intramuscular (IM) dose of 155 U of OnabotulinumtoxinA evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program. Another controlled study demonstrated the effectiveness of 100 U OnabotulinumtoxinA in the treatment of patients with CM who specifically did not overuse pain medication.

Efficacy results from previous trials in patients with episodic migraine (generally understood as occurring <15 days per month) have been negative. Results from exploratory trials in episodic migraine, chronic tension-type headache, and CDH have been mixed, but have suggested that OnabotulinumtoxinA may be useful as preventive treatment for CDH, specifically patients suffering from CM.

In another work subjects treated with OnabotulinumtoxinA showed improvements from baseline in measures of headache frequency, and improvements from baseline and in comparison with placebo treatment in headache impact and treatment satisfaction but did not differ from placebo-treated subjects in measures of headache frequency and severity.

A recent meta-analysis of eight randomized, double-blind, placebo-controlled trials considering 1601 patients with a history of episodic migraine did not find significant clinical and statistical differences from placebo in lowering the frequency of migraine headaches.

More recently, the PREEMPT clinical program has confirmed OnabotulinumtoxinA as an effective, safe, and well-tolerated prophylactic treatment for adults with CM.

The Preempt Clinical Program

These two phase 3, multicenter studies (PREEMPT 1 & 2) included a 28-day baseline screening phase and a 24-week randomized, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase. PREEMPT recruited 1384 adult patients with CM who have 50% or more headache days fulfilling migraine or probable migraine criteria and have four or more distinct headache episodes at baseline screening. Qualified patients were equally randomized (1:1) to OnabotulinumtoxinA or placebo injection.

The PREEMPT clinical program evaluated a standardized treatment paradigm on the basis of two previous exploratory phase 2 CM studies.

All patients received a minimum intramuscular (IM) dose of 155 U of OnabotulinumtoxinA...
administered to 31 injection sites across 7 head and neck muscles using a fixed-site, fixed-dose (FSFD) injection paradigm (each injection was 5 U in 0.1 mL). Up to 40 U of additional OnabotulinumtoxinA could have been administered IM at the physician’s discretion using a FTP strategy into 8 additional injection sites across 3 head and neck muscles (temporalis, occipitalis, and/or trapezius muscles). Thus, the minimum dose was 155 U and the maximum dose was 195 U administered to 39 sites. The injections were administered every 12 weeks for two injection cycles. Afterwards, all patients received another three cycles of OnabotulinumtoxinA injections during the open-label phase.

The primary end point of PREEMPT 1 was the mean change in number of headache episodes per 4 weeks at week 24, while in PREEMPT 2 and the pooled studies, the primary end point was amended to mean change in frequency of headache days. At baseline, the OnabotulinumtoxinA group had significantly fewer headache episodes, migraine episodes, and more total cumulative hours of headache occurring on headache days compared with the placebo group in the PREMPT 1 and the pooled PREMPT. In PREEMPT 1, no significant between-group difference for OnabotulinumtoxinA versus placebo was observed for the primary end point, headache episodes (-5.2 vs -5.3; p = 0.344). However statistically significant reductions from baseline for frequency of headache days after OnabotulinumtoxinA treatment compared with placebo treatment in both PREEMPT 1 (p = .006) and PREEMPT 2 (p < .001) were observed at week 24 and at all other time points. Statistically significant improvement from baseline after OnabotulinumtoxinA compared with placebo treatment was seen for headache episodes in PREEMPT 2 (p = .003), but not in PREEMPT 1. Pooled analysis demonstrated that OnabotulinumtoxinA treatment significantly reduced mean frequency of headache days (-8.4 OnabotulinumtoxinA, -6.6 placebo; p < .001) and headache episodes (-5.2 onabotulinumtoxinA, -4.9 placebo; p = .009).

Secondary end points included mean change in frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes, frequency of migraine/probable migraine episodes, frequency of acute headache pain medication intakes, and the proportion of patients with severe Headache Impact Test-6 (HIT-6) score (60 or higher) at week 24. Disability and HRQoL (Migraine-specific Quality of Life questionnaire [MSQ version 2.1]) also were assessed. All efficacy analyses used the intent-to-treat population. All these efficacy variables, except for the frequency of acute medication intakes, showed significant between-group differences favoring OnabotulinumtoxinA at all time points.

Adverse events (AEs) occurred in 62.4% of the OnabotulinumtoxinA group and 51.7% of the placebo group. Most AEs were mild to moderate in severity, and few patients discontinued the trial (OnabotulinumtoxinA, 3.8%; placebo, 1.2%) due to AE. The only AEs reported with an incidence over 5% in the OnabotulinumtoxinA group were neck pain (8.7%) and muscular weakness (5.5%).

### Comments

One major achievement of PREEMPT is that it proves that patients with CM is an appropriate target group and offers a guide of injection paradigm. PREEMPT results support previous studies which identified CM patients as the ones most likely to benefit from OnabotulinumtoxinA treatment. Results from the OnabotulinumtoxinA pivotal studies confirm that patients with CM, including those who were overusing acute headache medication during the 28-day baseline period, benefit from this treatment.

In addition, the primary end point of the pooled study was the frequency of headache days, which is considered more sensitive than headache episodes and fulfills recently proposed clinical trial guidelines for evaluating headache prophylaxis in CM.

Despite these data, the design of the PREEMPT study was object of critics, particularly regarding the diagnosis of CM (65% of patients had medication overuse, which precludes the diagnosis of CM according to the HIS), the high percentage (35%) of patients that never before received any pharmacological prophylaxis, and the effectiveness of blinding (since OnabotulinumtoxinA weakens muscles and changes the facial expression while placebo does not).

Another important achievement of PREEMPT is having provide an injection paradigm which uses a combination of fixed and FTP injection sites ensuring optimal distribution of OnabotulinumtoxinA on the basis of symptoms of the individual patients. The fixed-site approach, with sites
remain unchanged regardless of where the patient’s pain is located, distributes OnabotulinumtoxinA to muscles that align with the peripheral nerve distribution of the cervical and trigeminal sensory system, which is believed to be the target-end organ for OnabotulinumtoxinA in treating CM.

**The PREEMPT Injection Paradigm**

The injection paradigm adopted in PREEMPT studies can be used as a guideline for a correct administration of OnabotulinumtoxinA155.

The first injections have to be done into the corrugator, procerus, frontalis, and temporalis, following that order, with patient placed supine while is sitting for injections into the occipitalis, cervical paraspinal, and trapezius muscles. Before the injection the physician palpates each muscle to verify muscle delineation, and determined whether there was any muscle tenderness and areas of pain that required additional treatment, and cleans the skin in accord to standard practice for IM injections (e.g., with alcohol). To ensure the stability of the protein, the package insert for OnabotulinumtoxinA (BOTOX®) recommends reconstitution with preservative-free normal saline (0.9% Sodium Chloride, USP)156.

Once a 100 U vial of OnabotulinumtoxinA has been reconstituted, it must be injected or immediately stored in a refrigerator at 2-8°C in the original vial (not in a syringe) and bused within 24 hours156 or as indicated in the local package insert.

It is suggested the use of a sterile 30-gauge, 0.5-inch needle while a 1-inch needle is allowed in the neck region for patients with thick neck muscles. The insertion of the with the bevel up is at approximately a 45-degree angle. After the insertion into the muscle the plunger is pulled back with the other hand to ensure no blood return, and the plunger is then pushed to administer 0.1 mL (5 U) to each injection site.

After the procedure is recommended to take patients under observation for 10-15 minutes. An important is no to rub or massage the affected areas for 24 hours.

In July 2010 botulinum toxin type A has been licenced by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK for the prophylaxis of headaches in adults who have CM. This is the first licence worldwide of botulinum toxin type A for this indication, and is also the first prophylactic (preventative) treatment to receive a specific licence for patients with chronic migraine.

In October 2010, the U.S. Food and Drug Administration (FDA) approved injection of OnabotulinumtoxinA (BOTOX®) for the treatment of chronic migraine headaches in adult patients.

**Topiramate**

The use of topiramate in preventing migraine’s chronicization process or in reverting consolidated CM is well known157,158.

Topiramate is a sulfamate-substituted monosaccaride, presenting several mechanisms of molecular action such as effects inhibition of voltage dependent channels of calcium and sodium, signal enhancement of GABA_A receptors, modulation of glutamate-mediated neurotransmission and carbonic anhydrase inhibition159.

In migraine, such spectrum of actions could reduce nociceptive transmission at the central system level through trigeminovascular modulation and inhibition of the cortical spreading depression160-162.

A 26 week randomized double-blind placebo-controlled trial have shown that migraine’s preventative treatment with Topiramate at a dosage of 100 or 200 mg/day, but not 50 mg/day, is able to reduce the risk of transformation to a chronic form159.

The most common adverse events (AEs) during topiramate treatment were paresthesias (8.0%), cognitive symptoms (7.3%), fatigue (4.7%), insomnia (3.4%), nausea (2.3%), loss of appetite, anxiety, and dizziness (2.1%)2. Paresthesia, due to the inhibition of carbonic anhydrase, is the most common side-effect although it does not constitute the main reason for therapy discontinuation. Cognitive symptoms are represented by concentration/attention as well as memory difficulties158.

In a randomized double-blind placebo-controlled trial in patients with chronic migraine and MOH, both topiramate’s efficacy and tolerance have been investigated in the prevention of CM, with a dose target of 100 mg per day. Topiramate considerably reduced the mean number of monthly headache days (primary endpoint) compared with placebo. In the subgroup of patients with drugs abuse, mostly triptans, topiramate reduced significantly the mean number of monthly migraine days from baseline. However, side-eff
ects were reported by 75% of the patients in the topiramate group compared with 37% in the placebo group163.

In another randomized, double-blind placebo-controlled parallel group multicenter trial, topiramate has been tested in the prevention of CM. Titration period was of 4 weeks with a maintenance period of 12 weeks and the final mean topiramate maintenance was 86 mg/day. Topiramate proved to be effective in reducing migraine headache days and migraine headache days relative to baseline164.

Although from these investigations Topiramate results well-tolerated, eventual adverse events are possible. Láinez et al. analysed three large multicentre studies and found that therapy discontinuation occurred in 25% of patients administered with Topiramate and in 1% of patients treated with placebo. The majority of AEs appeared during the titration period, generally within 6 weeks. These data suggest that in case patients do no present AEs in such period, they will be safe from such events165. In conclusion, migraine’s preventative treatment with Topiramate is able to reduce the risk of transformation into a chronic form. Such progression risk is extremely high in a subset of patients with elevated migraine frequency and frequent acute medication intake158.

Furthermore, a recent study pooled HRQoL data from 3 large randomized, placebo-controlled trials of topiramate for prevention of migraine166. They found improvement in 3 domains of functionality: restriction of daily activities, prevention of daily activities, and emotional function.

**OnabotulinumtoxinA vs. Topiramate**

In 2009 were published the results of the first randomized, controlled comparison of OnabotulinumtoxinA with another preventive agent for CM167. This trial compared the efficacy and safety of OnabotulinumtoxinA and topiramate prophylactic treatment in patients with CM. Significant within, but no between-group, improvements were observed for all primary (treatment responder rate) and secondary endpoints (mean change from baseline in number of HA/migraine days per month, HA/migraine-free days per month, days on HA medication, and average severity of HA/migraine episodes per month). The only between-group difference was a marked improvement at month 9 in the topiramate respect the OnabotulinumtoxinA group, likely because a different timing of somministration between the two groups.

Although OnabotulinumtoxinA and topiramate resulted in similar efficacy in this study, the 2 treatments resulted in different AE profiles. The overall discontinuation rate was higher in the topiramate than in the OnabotulinumtoxinA group (43.3% vs. 36.7%), with AEs being the primary reason for withdrawal in the topiramate group and lost to follow-up in the OnabotulinumtoxinA group. Of relevance is the difference between groups in discontinuation rates because of treatment-related AEs. Fewer than 10% of patients taking OnabotulinumtoxinA withdrew from the study because of unacceptable treatment-related AEs, while more than 20% of patients taking topiramate withdrew for such reasons.

The results of this study are in accord with controlled trials in the CM population that have reported discontinuation rates of 25% to 44.2% in the topiramate group compared with 10% to 25% in the OnabotulinumtoxinA group126,143,163,164. Migraine patients often suffer greatly as a result of the adverse effects of the drugs used, showing fatigue, dizziness, reduced concentration, loss of appetite, weight gain, hair loss and changes in libido. These side effects are not known in association with OnabotulinumtoxinA168.

Given the substantial AEs and adherence issues associated with available pharmacotherapies for CM, the relatively mild AEs associated with OnabotulinumtoxinA treatment may present an attractive treatment alternative.

The safety profile indicates that OnabotulinumtoxinA is safe and well-tolerated in the CM population, with few patients discontinuing treatment due to AEs (1.4-3.8%)126,143,150-152,169. In contrast, other prophylactic headache treatments report discontinuation rates due to AEs as high as 12.7%169.

**Conclusions**

Chronic migraine represents today the most important challenge in the area of clinical headache medicine. Refractoriness of patients to therapies, high risk of coexistence with MOH and forthcoming multiple comorbidities that these patients present should focus our attention
on innovative therapies with low rate of AEs such as Onabotulinumtoxin A, in order to contrast such growing clinical evidence.

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