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Medication-overuse headache. Despite the advances in understanding it, treatment evidence still lacks

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1. Introduction

Medication-overuse headache (MOH) is a highly prevalent disorder. It occurs in less than 3% of the population, but may represent the majority of patients from tertiary centers [1,2]. MOH is a subset of chronic daily headache occurring during or from overuse of headache symptomatic medications. It is clearly more prevalent in patients with migraine or chronic migraine (CM) as their primary headache [3,4]. Despite the high burden imposed to the sufferers and the recent advances in understanding its pathophysiology, scarce evidence is available regarding treatment strategies, which are mostly based on bias or recommendations from expert opinion [4–6]. However, absence of psychiatric comorbidities and overuse of drugs other than opioids, benzodiazepines, and barbiturates are favorable outcome factors as are the withdrawal of overused medications and a multidisciplinary treatment approach [6–8].

Interestingly, recent structural and functional studies have demonstrated brain areas that could identify and even predict those who will or will not respond to the treatment [5,9,10]. In addition, the studies have yielded evidence for identifying those patients who have a profile for substance overuse and may separate the sufferers who are likely to respond with withdrawal of offending medications [5,11]. Regarding treatment strategies, current evidence suggests that outpatient detoxification, with or without the use of a bridge medication, may be enough for a successful withdrawal and for a resulting pattern of decreased consumption in overused medications. A successful withdrawal may also lead to the reduction of headache parameters as well [7,12–14]. However, it may be hard to believe that a sustained response specially when based on advice alone is attainable without initiating prevention and maintaining a close look over the patients. In addition, even among those who succeed in detoxification, nearly one third may relapse within the first year of follow-up [13,14]. There is recent evidence that the neuromodulator topiramate and onabotulinumtoxinA may be useful for a subset of MOH patients even in the absence of withdrawal [15–17]. It may be possible that these patients could benefit from the choice of one or both pharmacological agents decreasing the overuse of symptomatic medications and reverting the chronic headache presentation to episodic through the time and as a consequence of its use, rather than following a withdraw. However, it is not universally accepted among clinicians who really deal with difficult patients that topiramate and/or onabotulinumtoxinA exert a beneficial effect in the presence of medication overuse especially among opioid/barbiturate over-users and in the so-called refractory patients [4,6,15–17]. Additionally, nonpharmacological treatments such as occipital nerve blocks, occipital nerve stimulation, acupuncture, and psychological therapies as mindfulness could also help MOH sufferers to reduce the burden and revert the headache pattern to an episodic presentation [18–22].

More recently, the monoclonal antibody (mAbs) erenumab was studied for the prevention of CM with or without medication overuse (MO) demonstrating interesting results [23]. Regardless of the chosen treatments and upcoming perspectives for headache amelioration, it is still uncertain whether patients who have a baseline frequency of daily headache adhere better to the treatment and experience a higher reduction of headache frequency in comparison to those who have a baseline near-daily headache, but few available studies suggest that daily headache patients perform better regarding outcomes [8]. In addition, we might argue on what is really a definition of refractory patient. Although the term is controversial and apparent synonymy such as intractable and treatment-resistant raises doubts, a refractory patient is a headache patient who, for whatever reason, do not improve despite concerted efforts with several appropriate treatment trials, which, of course, have included withdrawal of overused medications and ruling out psychiatric comorbidities [1,24].

Recent studies showed that patients with MOH have less gray matter volume in the left middle occipital gyrus, in the anterior cingulate cortex, and in the orbitofrontal cortex in addition of having a greater volume in the periaqueductal gray, left temporal pole, thalamus, and ventral striatum [9,10]. It may also represent a meaningful relationship between the volume of these brain areas and the frequency which the offending symptomatic medications are being used [9–11]. Regarding the brain function, patients with CM and MOH have less pain-induced activation in the postcentral gyrus, in the supramarginal gyrus, and in the inferior parietal
lobule, which are part of the lateral pain system responsible for discriminating the intensity and location of pain [9–11]. Taken together, it is now suggested that MOH is associated with a dysfunctional brain in nuclei of pain modulation, in nuclei of sensory-discrimination pain processing, in nuclei of cognitive pain processing, and in regions associated with addiction [5].

## 2. Treatment options

Evidence to guide the path for the best options is still limited. In a recent systematic review, the discontinuation of the overused medications with the immediate addition of preventive treatments seems to be best strategy [25]. However, there is no robust evidence regarding the best drugs to be used or whether the combination of two or more pharmacological agents is preferable than a single medication. Additionally, strategies vary according to the environment where the patients are treated. Usually, tertiary centers tend to use combination therapy or rational polypharmacy, while in primary care monotherapy is sometimes preferable [26].

Recent studies carried out in consecutive patients with MOH demonstrated that comprehensive multidisciplinary approaches, withdrawal of overused medications, proper use of rescue treatments, and initiation of preventive therapy render decreasing of headache frequency and good adherence, despite the lack of appropriately sized, randomized controlled trials corroborating the choice of specific treatments [7,12,13]. Moreover, even in primary care, brief interventions may be successful in reducing the burden and reverting to episodic headache pattern [27].

In one specific study, 149 patients (20 men, 129 women; 18–65 years, mean 37.5) allowed interesting observations [13]. A total of 80 of 149 patients (53.7%) reported previous treatment attempts with other than acute medications. Among those 80, 52 (65%) had daily headache and 28 (40.6%) had near-daily headache ($\rho < 0.0052$) at baseline. In addition, 66 reported no improvement with previous use of preventive medications, and 14 reported failing to adhere to medical recommendations or prescriptions.

Outpatient withdrawal from overused medications was carried out with all patients, who received different preventive treatment choices (Table 1) plus the combination triptans plus NSAID for the acute attacks (maximum of 2 days/week). A total of 101 patients out of 149 (67.8%) received prednisone during the first 5–7 days as a bridge to detoxification. At this time, it was not possible to determine whether those having received specific combinations or more preventive medications performed better or presented better outcomes than those who took one or two preventive agents. However, it may illustrate how different options for preventive treatment are chosen among specialists, who rarely use monotherapy despite the lack of evidence demonstrating the superiority of combination of drugs.

After two months, 30 (20.1%) were lost to follow-up and the mean headache frequency, among those who adhered, decreased to 10.7 headache days/month. Even after eight months, 105 patients were under treatment with a mean headache frequency of 8.3 headache days/month. The intention to treat (ITT) analysis found decreasing headache frequency after two months and eight months to 13.1 and 11.4 headache days/month, respectively. After eight months, relapses or the use of symptomatic medications in 10 or higher days per month was observed in 25 patients (23.8%; ITT 36.2%).

Although treatment strategies were not studied in a controlled way, the data suggest this was an effective approach in sufferers with an incapacitating condition to which there is no consensus on the best treatment. Other authors published protocols showing efficacy in treating MOH with information regarding the nature of the pain, withdrawing abruptly, following the patients closely and initiating prevention, as well as providing for the judicious use of acute therapy [25].

Currently, there is however evidence for the use of topiramate or onabotulinumtoxinA even in MOH patients without withdrawing offending medications or for those who are unable to suspend the overuse pattern [15–17]. Two studies evaluating the Phase III development of onabotulinumtoxinA were conducted in a 24 week, parallel-group, double-blind placebo-controlled followed by a 32 week, open-label design study in which onabotulinumtoxinA or placebo were administered (155–195 U) to 1384 patients, with 65.3% ($n = 904$) having the diagnosis of MOH. At Week 24, significantly more patients of the onabotulinumtoxinA group had less headache days, less moderate/severe headache days, less cumulative headache hours on headache days, and even less specific migraine episodes. However, the intake of acute pain medications was similar between groups. The authors concluded that onabotulinumtoxinA is effective for CM patients with medication-overuse regardless of overused medication suspension despite that similar reductions in the use of acute medications were observed, both for patients receiving onabotulinumtoxinA as for those with placebo. Studies on onabotulinumtoxinA for MOH patients who withdrew early in the treatment or studies evaluating number of visits to emergency departments were also carried out. They

### Table 1. Preventive medications prescribed to the patients with ‘daily headaches’ and ‘near-daily headaches’.

<table>
<thead>
<tr>
<th>Preventive treatment choices</th>
<th>Daily headaches ($n = 80$)</th>
<th>Near-daily headaches ($n = 69$)</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Divalproate</td>
<td>1</td>
<td>11</td>
<td>0.0010</td>
</tr>
<tr>
<td>Nortriptyline + Topiramate</td>
<td>6</td>
<td>8</td>
<td>0.3931</td>
</tr>
<tr>
<td>Topiramate + Sodium Divalproate</td>
<td>2</td>
<td>6</td>
<td>0.0943</td>
</tr>
<tr>
<td>Nortriptyline + Tizanidine†</td>
<td>8</td>
<td>2</td>
<td>0.0841</td>
</tr>
<tr>
<td>Nortriptyline + Tizanidine + Flunarizine†</td>
<td>24</td>
<td>22</td>
<td>0.8040</td>
</tr>
<tr>
<td>Sodium Divalproate + (Nortriptyline + Tizanidine)†</td>
<td>8</td>
<td>8</td>
<td>0.7540</td>
</tr>
<tr>
<td>Sodium Divalproate + Nortriptyline</td>
<td>4</td>
<td>0</td>
<td>0.0598</td>
</tr>
<tr>
<td>Sodium Divalproate + Candesartane</td>
<td>3</td>
<td>1</td>
<td>0.3863</td>
</tr>
<tr>
<td>Nortriptyline + Tizanidine + Flunarizine + Pizotifen†</td>
<td>10</td>
<td>4</td>
<td>0.1620</td>
</tr>
<tr>
<td>Topiramate + (Nortriptyline + Tizanidine)†</td>
<td>12</td>
<td>6</td>
<td>0.2390</td>
</tr>
<tr>
<td>Topiramate + (Nortriptyline + Tizanidine)†</td>
<td>2</td>
<td>0</td>
<td>0.1861</td>
</tr>
<tr>
<td>Topiramate + Candesartane</td>
<td>0</td>
<td>1</td>
<td>0.2800</td>
</tr>
</tbody>
</table>

*chi-square test; †compounded in the same capsule (posology = once a day).
demonstrated that onabotulinumtoxinA and early withdraw of overused medications is better than early discontinuation alone and reduces by 90% the emergency department visits [16,28]. More recently, the mAbs erenumab was studied for the prevention of CM with or without MO showing promising results [23]. In the study, patients were randomized to placebo (n = 286), 70 mg erenumab (n = 191), or 140 mg erenumab (n = 190). Among the patients of each group, 41% had MOH. During the final four weeks of the double-blind study phase, respectively, 40% and 41% of the erenumab 70 mg and 140 mg patients had a 50% or greater reduction in monthly migraine days compared to 23% of the placebo patients. However, no differences were found in chronic migraineurs with or without MO regarding decreasing headache frequency [23].

The effectiveness of the detoxification is also noteworthy. Most of the patients are able to detoxify [7,12,25]. The discussion on why specific preventive medications are chosen or to claim its effectiveness since the choice is frequently based in personal experience and not in available evidence, do not eliminate the fact that choosing one or more pharmacological agents for the prevention of migraine and MOH still depends on bias, personal experience, or both. In addition, no available evidence is definitive in assuring superiority of drug combinations over monotherapy, but one must consider that studies on that specific objective are purely dependable on commercial interest from pharmaceutical industry and therefore are lacking. Moreover, it is common sense among headache specialists acting in tertiary centers that monotherapy is not the rule [26,27].

Regardless of choosing solely evidence-based medicine or deciding for an option of the patient’s best interest to ameliorate, it is gratifying to find reasonable adherence rates in the few available studies. It must be considered however that most studies had the advantage of a patient population not including opioid or barbiturate overuses, and this often predicts a greater likelihood of success [7,27]. It is probable that the results would have being less favorable if these medications were the rule.

Although relapse is common, it seems that most of the daily headache patients maintain and follow the treatment orientations. One might consider baseline degree of burden suggesting that patients formerly experiencing more headache days adhere better than those who have head pain fewer days a week [8,13].

The use of a bridge therapy for detoxification is also controversial. Oral prednisone or anti-dopaminergic agents, including metoclopramide, may be used and administering parenteral drugs in the emergency setting may be necessary for some patients [1,4,7,13].

3. Conclusions

The majority of MOH patients undergoing comprehensive treatments show dramatic reduction in headache days, sometimes restoration of episodic headache pattern, and good adherence with specialized and personalized headache care, despite previous therapeutic failures. Careful evaluation, education, and follow-up even with patients previously felt to be refractory can result in optimal clinical outcomes. It is truer in those not overusing specific drug classes. Controlled studies on different treatment strategies are warranted.

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Declaration of interest

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