▪ Headache Medicine 2023, 14(3): 153-160 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2023.29

Review

The state of the art in treating patients with a dual diagnosis of chronic migraine and medication-overuse headache

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Edited by:
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Keywords:
Medication overuse headache
Chronic migraine
Treatment
Prophylaxis.

Abstract

Migraine is a common, highly prevalent genetic neurological disorder. Its most burdensome form is the chronic migraine, which is clinically defined by the presence of headache on ≥15 days/month for longer than three months, with eight or more typical migraine days. Medication-overuse headache (MOH) is a secondary headache disorder associated with the overuse of symptomatic headache medications on ≥10 days/month for longer than 3 months. Chronic migraine and medication-overuse headache often coexist and most chronic migraineurs have medication overuse headache. Despite that, general practitioners and health professionals do not know about MOH. This review aims at presenting insights, recent knowledge, and guidance regarding the approach and treatments for patients with a dual diagnosis of chronic migraine and medication-overuse headache.

Submitted: June 21, 2023
Accepted: June 24, 2023
Published online: September 30, 2023

Introduction and clinical presentation

Migraine is disabling, highly prevalent, genetically inherited and characterized by persistent alterations in the processing of nociceptive sensory information. It manifests with intermittent attacks of headache and associated symptoms.[1-3] Chronic migraine (CM) is the most burdensome form of migraine, clinically defined by the presence of headache on ≥15 days/month for ≥3 months, and typical migraine features in ≥8 days/month (Table 1). CM is associated with significantly greater disability, higher rates of comorbidity, and increased direct as well as indirect costs.[2,4] The criteria for CM are listed in Table 1.

Table 1. ICHD-3 criteria for chronic migraine

A. Headache (migraine-like or tension-type-like) on ≥ 15 days/month for > 3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without and/or criteria B and C for 1.2 Migraine with aura
C. On ≥ 8 days/month for > 3 months, fulfilling any of the following:
1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 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

A percentage of chronic migraineurs may revert to the episodic form after treatments, while nearly a third persist with the same presentation, and 40% oscillate, thru the lifespan, between the episodic and chronic forms.[4, 5]

Medication-Overuse Headache (MOH) is also highly prevalent and secondary to the overuse of analgesics, anti-inflammatory drugs, or specific migraine medications (triptans or ergots) on ≥10 days per month, which precipitates and/or perpetuates a headache on ≥15 days per month, for ≥3 months in sufferers with a primary head pain such as migraine or tension-type headache.[1-6]

The traditional clinical view, reflected in the International Classification of Headache Disorders, is that most people with chronic primary headaches have the so-called medication overuse headache and chronic migraineurs without MOH are not easily encountered in clinical practice of Brazil.[1,6,7] Therefore, the condition is secondary, and described in group 8 of the ICHD-3.[1]

In tertiary centers, MOH represents the largest group of patients reaching 70 to 80%.[6,7] Most sufferers are women (85%), with migraine as the primary headache (99%). The societal costs of treating MOH are three times higher than those of treating episodic migraine.[3, 6-8]

The criteria for MOH include patients with a preexisting primary headache disorder (at least 15 headache days/month), usually chronic migraine (CM) or more rarely, chronic tension-type headache, post-traumatic headache, new daily persistent headache.[1] MOH is defined by the diagnostic criteria listed in Table 2.

The typical scenario is MOH developing, as patients increase the quantity and frequency of their medication usage, in an effort to gain or maintain control of their painful condition. This vicious cycle of symptoms often improves days or weeks after reducing or discontinuing the intake of acute medication followed by preventive therapy of the primary headache disorder.[6, 7, 9]

Table 2. ICHD-3 criteria for medication-overuse headache

A. Headache occurring on ≥ 15 days/month in a patient with a pre-existing headache disorder
B. Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, with medication overuse defined as:
1. Ten or more days/month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
2. Fifteen or more days/month for non-opioid analgesics, acetaminophen, and NSAIDs
C. Not better accounted for by another ICHD-3 diagnosis

Epidemiological studies indicates that more than half of people with headache on ≥15 days/month have MOH[6, 10-13], with a global prevalence between 0.7 and 2%.[10-13] In Latin America, the studies are scarce, with unknown prevalence of medication overuse headache.[13]

Some particulars of MOH in Latin America were, however, demonstrated by the COMOESTAS Project, which revealed overuse of triptans, ergots, simple analgesics and combination analgesics, respectively by 6%, 72%, 33% and 29% of the patients. Twenty seven percent of Latin American sufferers visited general practitioners, whereas 38 % consulted headache specialists and 30% visited emergency rooms.[13]

The medical knowledge about medication overuse headache is limited, leading to the overuse of prescription medications.[7, 10-14] Migraineurs are at increased risk of developing MOH, and they should be identified by general practitioners, neurologists, pain therapists, pain psychotherapists, medical students, pharmacists, and nurses. Therefore, identifying, preventing, diagnosing, and treating MOH has a high pragmatic relevance for patient care, with the prevention being particularly important, especially in patients prone to frequent headaches.[7, 10-14] If not identified, these subjects can manifest more complex clinical features, progressive use of symptomatic drugs, and greater frequency of visits to emergency services.[7, 14]

Therefore, there is an urgent need to reach consensus among real experts and not only political appointed members of specific groups, and establish region-specific

strategies for the management of MOH in Latin America.[13]

Both disorders CM and MOH often coexist[5, 7, 13], and most patients with chronic migraine have medication overuse headache.[1, 5, 7]

Types of overused acute medications

All acute headache medications have the capability to cause MOH.[9, 13] The speed MOH develops also depends on the substance taken, frequency and duration of overuse.[9, 13] Different classes of acute headache medications seem to lead to MOH with different intensities.[9, 13] The analysis of the distinct clinical characteristics of each subtype of MOH, according to the type of medication used excessively, helps to define more clearly the clinical picture of this poorly delineated headache.[9, 13]

A-MOH (simple analgesics): The chronification is slower than in those who overuse triptans, opioids and combined analgesics.[13] The study of 660 patients with MOH referred to headache centers in Europe and Latin America evidenced A-MOH as the largest group (32.1%, n = 213).[13]

M-MOH (multiple drug classes): This was the second largest group (27%, n=179).[13] It exhibited more severe clinical features, including a shorter interval between the onset of episodic and chronic daily headache, higher frequency of emergency room visits, and ingestion of greater amounts of acute medications.[9, 13]

T-MOH (triptans): Nearly 16% (n = 104) of patients.[13] These patients have fewer severe headache days and monthly days of acute medication use.[9, 13]

E-MOH (ergots) and **C-MOH** (combination analgesics): Respectively, 12.7% (n = 84) and 12.1%, (n= 80) of the patients.[13]

O-MOH (Opioid): The risk of developing CEM is high with opioid use.[7, 13] In the same way, benzodiazepines and barbiturates are even worse regarding induction of MOH and two or more days per week of drug use, may lead to transformation.[13]

Risk factors for MOH

The most important risk factors for MOH are preexisting primary headache, female gender, history of >10 headache days per month, low social status, other chronic pain disorders, family history of MOH or substance overuse, use of tranquilizers, stress, sedentarism, obesity, smoking, personality disorders and other psychiatric comorbidities.[6, 8, 9, 13, 15]

Bio behavioral disorder and personality disorders in patients with MOH

MOH can be distinguished as simple (Type I) or complex (Type II). Simple cases involve relatively short-term drug overuse, 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 especially personality disorders, with borderline and histrionic personality disorders being the most common, and a history of multiple relapses.[13-15] Comorbid psychiatric disorders are more prevalent in MOH than in control headache conditions and may precede the onset of MOH (15). There is elevated risk of family history for substance use disorders in MOH patients, and increased risk of MOH in patients with diagnosed personality disorders.[15]

Prevention

MOH is preventable.[11, 14-17] Since patients may overuse prescribed medications, the initiative should focus on educating physicians and patients about the importance of imposing limits for prescription and intake of symptomatic medication.[11-15]

MOH is a treatable condition with a high-resolution rate.[14-16] A controlled study measured the efficacy at 1 year, of three different treatment approaches: withdrawal and early prevention, prevention and withdrawal after 6 months, and withdrawal with delayed prevention. All treatment strategies proved effectiveness in treating MOH. Therefore, treatment should include both withdrawal and preventive therapies. An early initiation of both elements leads to the fastest effect and to a long-lasting treatment effect.[14, 16]

Education and counselling to treat MOH

Education and training of patients with overuse of symptomatic medications are effective therapies.[7, 14, 15] Patients at increased risk for developing MOH should be identified and monitored regarding prescriptions and over-the-counter medications consumption, which is impossible in Brazil. In addition, they should be referred to headache specialists in a timely manner. In a proportion of patients with MOH, regardless of age, counselling and education are sufficient to treat MOH. This applies mostly

for those who do not suffer from psychiatric comorbidity.[7, 15, 17]

Simple counseling is essential and can be successfully provided in primary care. It is appropriate in who overuse triptans or simple analgesics, without major psychiatric comorbidity.[14, 16] However, it is not suitable for patients who overuse opioids, tranquilizers, or barbiturates as well as on who experienced previous relapses or failed to stop the overuse.[14, 16]

Information brochures about the potential relationship between frequent use of pain medications and the transition from episodic to chronic headache are also effective in preventing MOH in at-risk patients with migraine.[14, 18]

Prevention is especially important in patients who have a high frequency of attacks.[7, 14, 18] Patients should be cautioned not to exceed dose limitations.[7, 14] Danish national awareness campaigns, for example, aimed at the public, practitioners, and pharmacists. It was successful in demonstrating increasing percentages of the public who were informed about MOH.[18]

Patients who are overusing opioids or relapsed after previous withdrawal treatment should receive multimodal care in headache centers or as inpatients, with additional psychological counselling.[7, 14-18] Weaning or rapid withdrawal with termination or reduction of medications is recommended.[7] If overuse does not stop, further treatment steps, including migraine prophylaxis, must be initiated. The greatest risk of relapse is in the first year after withdrawal.[7, 8, 15]

Withdrawal from overused drugs

Drug intake can be abruptly terminated or restricted in patients overusing simple analgesics, ergots or triptan medication. In patients with long-lasting abuse of opioids, barbiturates or tranquilizers, slow tapering is recommended. Withdrawal can be performed on an outpatient basis, in a daycare or inpatient setting. All settings have a similar success rate because of the different complexities suited for each setting.[7, 14, 15]

Nonpharmacologic therapy

Nonpharmacological treatments play an important role in the treatment of MOH. It includes counseling and education, relaxation techniques, aerobic exercise, cognitive behavioral therapy, and biofeedback.[7, 10, 14]

a) Psychological and behavioral therapies: cognitive behavioral therapy, biofeedback, relaxation therapy, stress-management, and meditation techniques such as mindfulness.[7, 14-16]

b) Physical activity: aerobic exercise three times a week showed a greater reduction in the frequency of headache days when combined with prophylactic drugs for chronic migraine.[13, 19]

c) Physical therapy: a greater reduction of headache days was observed in patients with chronic migraine and associated neck pain, when a combined approach using prophylactic drugs and physical therapy sessions was carried out (diaphragmatic breathing exercises, cervical traction and mobilization, massage therapy, myofascial release, manual compression of muscle trigger points and passive stretching of cervical muscles).[17, 20]

d) Neuromodulation: transcutaneous supraorbital stimulation, transcutaneous electrical *vagus* nerve stimulation, invasive electrical stimulation of the occipital nerves and transcranial magnetic stimulation - results are controversial.[20]

Multimodal approaches are most effective.[4, 10, 14, 20] For patients with comorbidities or relapse after initially successful medication withdrawal, multimodal approaches involving physicians, psychologists, and physical therapists should be used in an individual or group setting over several sessions.[4, 10, 14, 20]

Pharmacological treatment

Controlled studies of high quality on MOH do not exist (10). The healthcare system is not used in the appropriate manner, because a considerable proportion of MOH patients seek help at the emergency rooms, which are not optimal for managing chronic conditions.[7, 8, 10]

Withdraw overused medications and starting prophylaxis are crucial steps.[7, 16, 20] Currently, rapid withdrawal is recommended and measuring effectiveness are respectively, either >50% or >30% reduction in MMD (monthly migraine days) for episodic migraine, for chronic migraine or MOH after 12 weeks of treatment.[14, 16, 20-22]

Preventive treatment with drugs of proven efficacy

Adequate medication should be effective to prevent the development of MOH.

Topiramate: The efficacy of topiramate has been evaluated in several clinical trials in chronic migraineurs and MOH.[21] A significant reduction in the mean number of migraine days, compared to placebo was clear.[7, 21, 22]

OnabotulinumtoxinA: It has been evaluated in two large randomized, placebo-controlled trials for efficacy in the prophylactic treatment of chronic migraine. In these trials, approximately 65% of patients met criteria for MOH.[7, 23] Patients with MOH did not respond similarly to treatment with onabotulinum toxin A than those with chronic migraine without MOH.[7, 23]

OnabotulinumtoxinA has been investigated against placebo in the prophylactic treatment of chronic migraine and MOH in combination with early discontinuation of acute medications. No significant differences between onabotulinumtoxinA and placebo were detected in headache days reduction (12 vs. 15.9, P = 0.81).[24]

Calcitonin Gene-Related Peptide (CGRP)-targeted monoclonal antibodies (mAb): Monoclonal antibodies (mAbs) may represent better options in comparison to what is currently available due to its favorable profile of tolerability, posology and perhaps efficacy.[25, 26] The mAbs were effective in chronic migraineurs and medication overuse sufferers, with significant reductions in the overuse of acute medications as well as decreasing days of acute medication intake.[3, 7, 10, 26] Currently, only two are available in Brazil, galcanezumab and fremanezumab. The particulars and details of their efficacy in CM with or without MOH, are described in other paper of this supplement and will not be repeated here.

It is noteworthy that nearly 50% of patients treated with anti-CGRP mAbs had meaningful reductions in acute headache medication use and headache/migraine, suggesting resolution of both diagnoses.[3, 7, 10, 26]

Given the complexities of treating MOH, an integrated treatment strategy incorporating both mAbs and other treatment modalities may benefit patients with MOH.[7, 10, 14, 21, 22] Available trials results support the emerging evidence that anti-CGRP monoclonal antibodies may be effective in medication overuse headache patients irrespective of detoxification.[10, 14]

The state or art

Since both headache types coexist and approaching one, leads to the prevention and amelioration of both, the pragmatic view is to effectively treat the primary headache, either migraine or tension-type headache, avoid its transformation into daily or near-daily secondary headache, and ultimately reduce its burden. The crucial point here is to seek the best treatment for acute attacks of the primary headache and not provoking the secondary form of head pain. The optimal treatment for chronic migraine includes comorbidity management, risk factor modifications and discipline in using symptomatic medications. In addition, chronic migraineurs require prophylactic treatments. Despite that, poor response with least satisfaction is commonly observed.[27-29]

With limited clinical prophylactic treatment options, there remains an unmet need for more effective, tolerable preventative therapeutic targets in chronic migraine.[21] Currently, the only available therapies with proven efficacy in chronic migraine prophylaxis are onabotulinumtoxinA (BoNT-A), topiramate and anti-CGRP monoclonal antibodies.[7, 10, 14, 16] However, we all know the tolerability issues with topiramate, the limited efficacy and financial limitations of the mAbs prescription and the mercantilism involved in onabotulinumtoxinA administration.[7] Therefore, treaters in Brazil will have to search not only for the best and most efficacious options, but rather, for the addressing the crucial adhesion limitations regarding the patients.[7, 10, 14, 22]

-We frequently suggested that rational combinations should be the best, but always considering costs, independence from professionals, health plans and the overload of bureaucratic requirements.[30-35] It has been our approach during decades, initiating with two or three agents, such as a tricyclic antidepressant plus a neuromodulator and perhaps a mAb, especially for those with a history of failures in detoxification, or not responding to monotherapy. In patients with chronic migraine not overusing symptomatic medications, which is rare in our reality, a trial with a simple beta-blocker and a tricyclic antidepressant, both available and inexpensive in our country, would rate better than either of both in isolation.[30-35] Finally, considering the ubiquitous enthusiastic defenders, the use of a less expensive treatment scheme with botox, like the "follow the sutures" approach, and a mAb in patients who do not tolerate oral traditional agents and never quite responded to previous treatment attempts. These treatment options aim at addressing different migraine circuits, mediators and potential biomarkers could represent a new treatment paradigm.[36-39]

Irrespective of the choices, the patient-centered care and the quest for specific biomarkers are the goal.[16, 17,

[36] Individualizing needs and headache characteristics will always fulfill the best option and the state or art. A dual diagnosis of chronic migraine and MOH is not a huge challenge when the main objective is the patient and not the profit.

Contribution authors: All authors had the same contribution.
Funding: No
Conflict of interests: The authors report no conflict of interest.

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