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► To cite this version:

V. Corand, Xavier Moisset, F. Radat, C. Lucas. Medication overuse headache: Updating of the French recommendations regarding the treatment strategies. *Revue Neurologique*, 2021, 177 (7), pp.760-764. 10.1016/j.neurol.2021.07.003 . hal-04721487

HAL Id: hal-04721487

<https://hal.science/hal-04721487v1>

Submitted on 13 Nov 2024

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Medication overuse headache: updating of the French recommendations regarding the treatments strategies

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Declaration of interest

V. Corand has received honoraria from Grünenthal and Novartis during the last 5 years not related to the submitted work.

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Abstract

Regular and frequent use of analgesics and acute antimigraine drugs can increase the frequency of headache, and induce the transition from episodic to chronic migraine or medication-overuse headache (MOH).

The one-year prevalence of this condition is between 1% and 2% in Europe, provoking substantial burden. MOH is more prevalent in people with comorbid depression, anxiety, and other chronic pain conditions. This paper aims at presenting an updating of French recommendations regarding treatments strategies. Prior French recommendations, published in 2014, were written in French.

A literature search in the major medical databases including the terms “medication overuse headache”, “symptomatic medication overuse”, published between 2010 and 2020 was carried out.

Three main strategies can be recommended and conducted in parallel: education and explanations about the negative consequences of overusing acute antimigraine drugs, discontinuation of the overused medication, and finally, preventive drug therapy and non-pharmacological prevention. Medication overuse headache remains a debated problem and evidence for the most effective treatment strategy is needed.

Key-words: medication overuse headache, systematic review, randomized controlled trials, withdrawal, treatment, recommendation

1. Introduction

The frequent use of medication to treat primary headache attacks, including migraine can lead to an increase in headache frequency and is called medication-overuse headache (MOH). MOH is very prevalent among chronic headache disorders (1-4). The new definition for overuse was launched in the ICHD-3 (Headache classification committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018 (1): Headache occurring on 15 or more days/month in a patient with a pre-existing primary headache, (e.g. migraine), and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than three months. It usually, but not invariably, resolves after the overuse is stopped (boxes 1 and 2).

The one-year prevalence of this condition is between 1% and 2% in Europe (5). MOH is also amongst the most costly headache disorders for both the patient and society.

The annual socioeconomic costs of MOH have been estimated to approximately 37 billion euro in Europe primarily due to reduced work ability and illness-related absence from work (6) and MOH is thus one of the costliest neurological disorders. There has been an attempt to establish international, evidence-based guidelines (7) but there is also a lack of evidence concerning several aspects of MOH treatment which varies greatly. Based on most national recommendations, the first step in patient management is education and counselling. Here, we aimed to propose new French recommendations encompassing all the available therapeutic options for MOH.

2. Methods

These recommendations are based on a systematic review encompassing all treatments for MOH, including pharmacological but also non-pharmacological therapies. Prior French guidelines, published in 2014, were written in French. This systematic review was prepared under the auspices of the SFEMC (*Société Française d'Etude des Migraines et des Céphalées*).

A literature search in the major medical databases including the terms “medication overuse headache, symptomatic medication overuse”, published between 2010 and 2020 was carried out. Only articles published in English were selected. Studies published only as abstracts were excluded. At the end of the process, 36 publications were available for full reading.

Moreover, we used guidelines for the treatment of MOH published by the European, German and Spanish societies of neurology (8, 9,10) and also those published by the European headache federation regarding the use of onabotulinumtoxinA in chronic migraine (11).

The American Pain Society published a systematic review and meta-analysis concerning the effectiveness of treatments that was also taken into account (12).

The grading of recommendations assessment development and evaluation (GRADE) system was used to assess the quality of evidence and to elaborate recommendations.

3. Results: updating the French recommendations

3.1 Comorbidity

The large Eurolight survey (3) established that depression and especially anxiety are comorbidities of episodic migraine, and the same is true, but more strongly, for MOH.

A five-fold risk for developing MOH was found in the HUNT study (13) among individuals who at baseline reported regular use of tranquilizers [OR: 5.2 (3.0–9.0)] or who had a combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Hospital Anxiety and Depression Scale score ≥ 11 [OR: 4.7 (2.4–9.0)]. Smoking and physical inactivity more than doubled the risk of MOH.

3.2 Outcome prognosis factors

3.2.1 Type of medication overuse

Despite the large controversies about whether medication overuse should be regarded as a cause or a consequence of headache chronicization, to date, the worldwide consensus agrees that withdrawal of acute painkilling drugs is an important part for the management of MOH patients.

The best positive effect of withdrawal has been described in patients overusing triptans (14, 15, 16).

The effect of withdrawal is also discussed for patients using simple analgesics (14, 15, 17) and combination analgesics (15, 16, 17).

Negative outcome for opioids and barbiturates was found in one study (16).

3.2.2 Score of dependence

A high dependence score on the Severity of Dependence Scale (18) or the Leeds Dependence Questionnaire (19) at baseline was related to higher relapse to MOH or higher risk of failing withdrawal. These dependence scales provide a score measuring addiction.

3.2.3 Psychiatric comorbidities

Psychiatric comorbidity and especially depression (estimated with the HAD score) is more prevalent in patients who did not succeed in withdrawing from the overused drug (20, 21).

3.3 Treatments

3.3.1 Inpatient versus outpatient treatment

No significant difference in treatment outcome is found between inpatient versus outpatient treatment except in complicated MOH for which inpatient treatment is more efficient (22).

Complicated MOH was defined as fulfilling at least one of the following criteria: coexisting significant and complicating medical illness; current diagnosis of mood disorder, anxiety disorder, substance addiction disorder, or eating disorder; moderate/severe psycho-social or environmental disorder; daily or almost daily use of multiple symptomatic medication or anticipatory use of medication; or history of relapse after previous detoxification treatment (23, 24, 25). No standardized therapeutic protocol for medication withdrawal for inpatients is accepted worldwide.

3.3.2 Education and prevention

Education: It has been documented that even after simple advice, many MOH patients are able to reduce their medication intake sufficiently to no longer fulfill the criteria for MOH (26).

3.3.3 Non-pharmacologic treatment

The chances of successful withdrawal are greater with the support of a headache nurse during withdrawal treatment (27) and the number of patients who relapse to MOH is significantly reduced when patients have the possibility to contact the headache team (28).

Short psychotherapy after inpatient withdrawal results in reduced medication use and less relapse to MOH (29).

3.3.4 Initial versus postponed administration of prophylactic medication

Prophylactic medication must be started from the beginning of detoxification (30).

3.3.5 Prophylactic drugs for medication overuse headache

Topiramate (50-100 mg/d), sodium valproate and onabotulinumtoxinA (two 155-195 U injections during a 24-week period) have been investigated in clinical trials that considered not only chronic migraine patients or chronic daily headache patients, but also patients with MOH. New advances may be obtained in MOH with anti-CGRP monoclonal antibodies.

3.3.5.1 Topiramate

The first choice MOH migraineurs is topiramate despite frequent adverse events (31, 32, 33, 34).

Two similarly designed randomized, placebo controlled, multicenter studies of patients with chronic migraine, conducted in the United States and in the European Union investigated the safety and efficacy of topiramate for the treatment of this condition in patients with and

without medication overuse (33). A post-hoc analysis in the subset of patients with medication overuse in the American trial showed no difference in reducing migraine and its frequency between topiramate and placebo; however, the European trial did show a significant reduction. Key differences were evident between the patient populations in the two studies. In the American trial, 115 (38%) of 306 patients versus 46 (78%) of 59 patients in the European trial reported using acute medications for migraine fulfilling the criteria for medication overuse during the 28-day prospective baseline period.

3.3.5.2 Sodium valproate

Only one study (88 patients) has been performed with sodium valproate 800 mg/d or placebo for chronic migraine with medication overuse combined with detoxification for the overused drug (35). At week 12, patients using sodium valproate had a significantly greater reduction in headache compared with the placebo group; 8.1 d/mo (CI –14.8 to –1.4) vs 4.6 (CI –11.7 to 1.9) d/mo. At week 24, there was no significant difference between the groups, so there was no carry-over effect.

3.3.5.3 OnabotulinumtoxinA

There is scientific evidence supporting the use of onabotulinumtoxinA (OBTA) for the prevention of chronic migraine. OBTA has nevertheless produced diverging results in clinical trials involving MOH patients. One study (planned secondary analysis of a 24-week PREEMPT study) reported a positive effect with reduction in headache frequency: 8.2 d/mo (CI –14.5 to –1.9) and 6.2 (CI –12.8 to 0.4) d/mo at week 24, respectively, for OBTA and placebo (36). Another study investigating the effect of only 100 U OBTA (usual dose 155-195 UI with the technique “follow the pain”) reported a negative outcome compared with saline placebo in MOH patients treated with inpatient withdrawal (37). There was no significant difference between the groups in reduction in headache frequency, 12.2 compared with 10.3 d/mo reduction. In general, OBTA is better tolerated than antiepileptic drugs (37, 38). OnabotulinumtoxinA has just received, in June 2021, approval in France for use in chronic migraine with or without medication overuse.

3.3.5.4 Anti-CGRP monoclonal antibodies

In a placebo-controlled trial (39) fremanezumab reduced the frequency and severity of headaches in patients with chronic migraine and MOH. Fremanezumab significantly reduced the frequency of headache of at least moderate severity without withdrawal in patients with medication overuse at baseline by 4.7 days in the group who received quarterly injections and 5.2 days in those who received monthly injections, compared with a 2.5 days reduction in the placebo group.

In a study evaluating the efficacy of erenumab, monthly migraine days were reduced by 6.6 days versus 4.2 days for placebo after 12 weeks in 667 patients with chronic migraine, 41% of whom had medication overuse (40).

Finally, the role of monoclonal antibodies against CGRP or the CGRP receptor concerning the treatment of MOH remains to be determined by dedicated randomized placebo-controlled trials.

3.3.5.5 Prevention

The initiation of preventive therapy is a fundamental therapeutic step to prevent episodic migraine converting into a chronic condition.

4 Conclusion

MOH is a worldwide problem with an incidence of about 1-2 %. Awareness of MOH and education of patients, and healthcare workers, especially general practitioners and pharmacists, are important for primary prevention.

Discontinuation or at least reduction of the overused medication should be recommended to all patients and can be done on an out-patient basis, or in an in-patient setting, depending on the type of drug being overused, the degree of overuse, the presence of comorbid disorders, and resource availability. It is recommended to prescribe a first-line prophylactic medication at the same time. Topiramate, possibly valproate (but never to be used in women of childbearing potential), OnabotulinumtoxinA and CGRP monoclonal antibodies might be effective in reducing headache, migraine frequency, and acute drug consumption, even in the absence of active drug withdrawal.

As anxiety and depression are frequently comorbid with chronic migraine, it is recommended to propose behavioral therapies (relaxation, biofeedback and cognitive behavioral therapies) or mindfulness-based stress reduction as add-on therapy to pharmacological treatments if those comorbidities are present.

New evidence is needed and will help clinicians to make the right choices for patients suffering from MOH and comorbidities.

Disclosure of interest

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Box 1. ICHD-3 of MOH [1]

A. Headache occurring on 15 or more days/month in a patient with a pre-existing headache disorder.

B. Regular overuse for more than three months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

C. Not better accounted for by another ICHD-3 diagnosis.

Box 2. Subtypes of MOH [1]

Intake on 10 or more days/month:

- Ergotamine-overuse headache
- Triptan-overuse headache
- Opioid-overuse headache
- Combination-analgesic-overuse headache
- MOH attributed to multiple drug classes not individually overused
- MOH attributed to unspecified or unverified overuse of multiple drug classes
- MOH attributed to other medication.

Intake on more than 15 days/month:

- Non-opioid analgesic-overuse headache (paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, others).