

European Academy of Neurology guideline on the management of medication-overuse headache

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Abstract

Background: The frequent use of medication to treat migraine attacks can lead to an increase in migraine frequency and is called medication-overuse headache (MOH).

Methods: Based on the available literature in this guideline, the first step in patient management is education and counselling.

Results: Patients with MOH should be managed by a multidisciplinary team of neurologists or pain specialists and behavioral psychologists. Patients in whom education is not effective should be withdrawn from overused drugs and should receive preventive treatment with drugs of proven efficacy. Patients with MOH in whom preventive treatment is not effective should undergo drug withdrawal. 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 of these drugs is recommended. Withdrawal can be performed on an outpatient basis or in a daycare or inpatient setting.

Introduction

The frequent and regular intake of drugs to treat acute headache episodes, e.g. migraine attacks in patients with primary headache disorders, can result in an increase in headache frequency and finally lead to chronic headache. This condition is called medication-overuse headache (MOH) by the classification of the International Headache Society [1] (Box 1). The purpose of this guideline is to provide good practice advice to clinicians on the management of MOH in terms of primary and secondary prevention and treatment.

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Medication-overuse headache is a frequent problem in clinical practice and the majority of patients with MOH improve after discontinuation of the overused medication [2-4]. Unfortunately, there are very few placebo- or sham-controlled double-blind trials for a specific treatment of this condition.

In Europe, the prevalence of MOH in the general population is around 1–2% [5-7], with a preponderance in women (up to 93%) [8-10]. In patients with chronic headache, in particular chronic migraine, the prevalence of MOH is as high as 70% [7,9] and in headache clinics or tertiary-care centers, patients with MOH form one of the largest patient groups [11,12]. MOH is also amongst the most costly headache disorders for both the patient and society [13].

Box 1. ICHD-3 diagnostic criteria of MOH [1]

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

Migraine is the underlying primary headache disorder in 80% of patients with MOH [14]. Most of the remaining patients have tension-type headache or, more rarely, post-traumatic headache [15], new daily persistent headache [16] or other secondary headaches [17]. Among patients with cluster headache, MOH may occur in patients with co-morbid migraine or with a family history of migraine [18]. The phenotype of MOH usually depends on the primary headache and the type of overused medication [19]. For example, the triptan-overuse subtype of MOH is characterized by a high number of headache days that maintain the migrainous features [19].

Triptans, simple analgesics, combination analgesics and opioids are the drugs most commonly associated with MOH [2]. Most patients with MOH take more than one drug [10]. The number of days of medication intake considered to define overuse in the different subtypes of MOH [1] (Box 2) is based on expert opinion. Patients with MOH should be classified according to the 3rd edition of the International Classification of Headache Disorders (ICHD) on the basis of the specific medication(s) overused and the primary headache type [1]. Patients who overuse combination-analgesic medications should receive the diagnosis 'combination-analgesic-overuse headache' (ICHD 8.2.5). Patients overusing multiple drugs, even though no individual drug is overused, should be coded as 'Medication-overuse headache attributed to multiple drug classes not individually overused' (ICHD 8.2.6). Patients who are

Box 2. Subtypes of MOH [1]

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

not aware of the amount of distinct drugs possibly overused should receive the diagnosis 'Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes' (ICHD 8.2.7).

Risk factors for MOH include other types of co-morbid pain, a more aggressive type of migraine, use of tranquilizers, progressive increase in the days of use of acute medications for headache, psychiatric comorbidities, lifestyle-related factors and female gender [2,20-23]. The most frequent comorbidities of MOH are anxiety and depression [2] and patients with MOH may show dependence-type behavior [24,25]. Importantly, patients with episodic headache may develop MOH if they use pain medication for other causes such as arthritis [26]; however, the non-headache pain in these patients does not worsen and therefore the pathophysiology of MOH seems to be headache-specific. Medication overuse and MOH are therefore distinct conditions as patients taking analgesics for other pain conditions do not develop chronic headache *de novo* [27] and patients who overuse medication to abort headache attacks do not necessarily develop MOH.

Methods

We performed a systematic literature review with the terms 'chronic headache', 'medication overuse', 'medication-overuse headache', 'treatment', 'withdrawal', 'follow-up' and 'relapse' for the time period between January 2000 and May 2019. The full reports of observational studies and randomized clinical trials published in peer-reviewed journals were identified using PubMed/MEDLINE and the Cochrane Library. Only articles published in English were selected. Studies published only as abstracts were excluded. At the end of the process, 139 publications were available for full reading (Table 1). Data were extracted by each author for his or her PICO question. We were unable to find a guideline for the treatment of MOH in the English literature. The German Society of Neurology published a guideline in German [28].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the quality of evidence and to elaborate recommendations. The GRADE tables can be found in the online Appendix S1 to S7. Six consecutive drafts of the guideline were prepared and reviewed by all authors. The recommendations, quality of evidence and strength of evidence for each PICO question were put to a vote by each member of the writing group.

Guideline questions

This European Academy of Neurology guideline addresses the following PICO questions (P = population, I = intervention, C = control O = outcome):

Table 1 Results of literature search

Section	Identified articles	Selected articles for full reading
PICO question 1 + 2	167	14
PICO question 3	51	2
PICO question 4	128	16
PICO question 5	151	40
PICO question 6	108	26
PICO question 7	39	21
Total	644	119

Articles can appear at different PICO questions. A systematic literature review with the terms ‘chronic headache’, ‘medication overuse’, ‘medication-overuse headache’, ‘treatment’, ‘withdrawal’, ‘follow-up’ and ‘relapse’ for the time period between January 2000 and May 2019 was performed. The full reports of observational studies and randomized clinical trials published in peer-reviewed journals were identified using PubMed/MEDLINE and the Cochrane Library.

- 1) Are information and education effective for the prevention of MOH in patients at risk?
- 2) Is pharmacological preventive therapy effective in the prevention of MOH in patients at risk?
- 3) Are education and counselling effective in the treatment of MOH?
- 4) Is preventive medical and non-medical treatment effective in MOH?
- 5) Is withdrawal from overused medication(s) effective in MOH?
- 6) Can the symptoms that subjects with MOH develop during medication withdrawal be treated?
- 7) Can relapse after successful treatment of MOH be prevented?

PICO question 1: Are information and education effective for the prevention of MOH in patients at risk?

Medication-overuse headache is, in principle, preventable. However, few studies have investigated preventive strategies among patients at risk of MOH. Based on epidemiological studies, suggested risk factors for the development of MOH are primary headache disorders, female gender, high headache frequency, frequent use of pain medication, inadequate acute headache treatment, use of tranquilizers, smoking, physical inactivity, obesity, dependency behavior, comorbid psychiatric disorders, other chronic pain conditions and lower socio-economic status [5,7,29-33]. Physicians can, theoretically, identify patients at risk of MOH in order to avoid MOH development. However, risk-factor modifications are not easy to apply for preventive purposes. Firstly, the identified risk factors cause MOH in only a minority

of those bearing them. Second, many of the suggested risk factors reflect complex socio-economic and health conditions that are not easy to modify. Based on the available evidence, it is not possible to conclude whether these risk factors represent an indirect rather than a direct association with MOH.

There is a lack of knowledge of MOH among the general population, patients, medical students, pharmacy staff and clinicians [34-37]. An increased awareness among the public and healthcare professionals could prevent MOH through education on the potential relationship between frequent use of acute pain medication and headache chronification. A Danish national awareness campaign (media, social media, information leaflets and scientific reviews) aimed at the general public, general practitioners and pharmacists showed an increase in the percentage of the public who were informed about MOH from 31% to 38% [38]. However, no data exist on whether such an awareness campaign was actually effective in reducing the prevalence of MOH.

Only one randomized study has evaluated the efficacy of non-pharmacological preventive strategies in MOH [39]. A German multi-center study compared the impact of written information alone with a brochure versus written information plus behavioral minimal-contact training in preventing MOH 1–2 years later in subjects with migraine ($n = 182$). The minimal-contact training had an additional focus on psychoeducation and pain-coping strategies. The subjects had an average of 11 headache days per month and 7 medication days per month at baseline. None of the patients developed MOH and the vast majority were able to reduce their medication-intake days throughout the study period without any significant differences between the two study groups. This observation, together with the known 3% (or higher) annual rate of transition from episodic to chronic migraine, supports the statement that an information brochure may be useful in preventing medication overuse in migraineurs.

Good practice statement

- MOH is, in principle, preventable.
- An increased awareness in the general population and among healthcare professionals of the relationship between frequent intake of medications to treat acute headache episodes and the possible increase in headache days is important and may prevent MOH.
- An information brochure and education about the potential relationship between frequent use of pain medications and the transition from episodic to chronic headache may be effective in preventing MOH in at-risk patients with migraine.

- Patients at risk of developing MOH should be followed up at shorter time intervals by their general practitioner or a neurologist (ideally every 3–6 months).
- These recommendations are based on the authors' experience, as controlled studies of high quality on these topics do not exist.

PICO question 2: Is pharmacological preventive therapy effective in the prevention of MOH in patients at risk?

Whether or not an adequate preventive headache medication in episodic headache prevents MOH has not been formally tested in randomized controlled trials (RCTs). However, the effect of topiramate in preventing the conversion from episodic migraine to chronic migraine over 6 months was evaluated in a *post hoc* analysis with pooled data ($n = 756$) from three RCTs of topiramate versus placebo [40]. There was a significant reduction in both headache days/month and analgesic days/month in the topiramate versus placebo group. Furthermore, fewer patients in the topiramate group developed chronic headache and MOH. Based on this pooled analysis, it may be suggested that adequate preventive medication is effective to prevent the development of MOH over a 6-month period. However, properly designed and powered RCTs focused specifically on this aim are warranted.

Research recommendation

- There is insufficient evidence that preventive medical therapy in patients with frequent migraine may prevent the transition from episodic to chronic migraine and the development of MOH.
- The question of whether preventive therapy in episodic headache may prevent chronification and MOH is important and clinically relevant. Researchers are therefore encouraged to conduct randomized controlled studies on this topic.
Quality of evidence: low.

PICO question 3: Are education and counselling effective in the treatment of MOH?

A double-blind, pragmatic and cluster-randomized controlled study performed in south-eastern Norway compared general practitioners' brief intervention (BI) with 'business as usual' (control group) [41]. Out of 75 randomized patients with MOH, 60 were included in the study. BI was significantly better than business as usual for the primary outcome measures with the number of headache days and days of acute

medication intake per month being reduced by 7.3 and 7.9, respectively, in the BI compared with the control group ($P < 0.001$). Headache reverted to an episodic pattern in 50% of the patients in the BI group and 6% of the control group [73]. Rossi *et al.* [42] compared the effectiveness of advice with either outpatient or inpatient withdrawal in patients with MOH and migraine as primary headache and low medical needs, defined as no previous detoxification failures, psychiatric comorbidities and overuse of opioids or barbiturates. The study was a randomized, prospective, open-label study that compared the effectiveness of an educational strategy based on advice to withdraw the overused medication(s) with two different structured pharmacological detoxification programs: (i) advice + steroids + preventive treatment or (ii) advice + steroids + fluid replacement and antiemetics + preventive treatment. The drugs used for preventive treatment were not specified. The study was performed in a tertiary headache center and included 120 patients [42]. Advice alone was as effective as the other two interventions, with a success rate after 2 months of >70%. Success was defined as transition from the chronic pattern of headache to an episodic one and reduction of the days of intake of symptomatic medications to <10 days/month.

In a subsequent study, the authors used a similar design but targeted 137 patients suffering from complicated MOH, defined by comorbidity load, previous failure of detoxification, presence of psychosocial and environmental problems and daily or almost daily use of multiple doses of symptomatic medication. The success rate, defined as no medication overuse and no headache or headache with an episodic pattern at 2 months, was 60% for the patients in the first two groups and 89% for those in the third group. A systematic review and meta-analysis that compared the outcome of outpatient withdrawal with inpatient treatment found no difference in terms of responder rates or reduction in headache days [43].

A prospective cohort study in Norway conducted on 109 participants with chronic headache (mostly tension-type headache) and MOH evaluated the impact of short information about the possible role of medication overuse in headache chronification [44]. Patients were followed for 18 months. At baseline, the mean duration of chronic headaches was 8–18 years, mean duration of medication overuse was between 5 and 10 years and mean medication days per month were 22. At follow-up, the mean medication days dropped to 6 per month with 76% of subjects no longer overusing [44]. It must be noted that this was not a controlled study. The approach of providing advice also seems feasible in general practice [45].

Krause *et al.* [46] performed a prospective cohort study on 379 patients with chronic headache to examine the impact of a 3-week outpatient interdisciplinary program that included medical interventions addressing long-term preventive medications, intravenous bridge therapies such as intravenous dihydroergotamine and optimization of acute migraine and headache management strategies. Outcome parameters were physical functioning and psychological impairment. Assessments of headache severity, psychological status and functional impairment were completed by 371 subjects (97.8%) at the time of admission. At discharge, 340 subjects (89.7%) provided assessment data and 152 (40.1%) provided data at 1-year follow-up. At entry, subjects' mean headache pain intensity was 6.1, declining to 3.5 at discharge and to 3.3 at follow-up. As a measure of functional impairment, the Headache Impact Test-6 score improved from 66.1 at baseline to 55.4 at the end of 3-week treatment and 51.9 at follow-up. Depression and anxiety also showed a marked improvement, although depression scores lapsed back toward admission levels at the 1-year follow-up.

Recommendation

- Advice alone is an appropriate initial treatment approach in patients who overuse triptans or simple analgesics and who do not have major psychiatric comorbidity.
 - Advice alone can be provided by trained headache nurses, general practitioners and neurologists in private practice.
 - Advice alone is not appropriate for patients who overuse opioids, tranquilizers or barbiturates or who have experienced previous relapses into overuse or who failed to stop overuse following advice. These patients need to be referred to a headache specialist or to specialized care.
- Quality of evidence: low.
Strength of recommendation: moderate.

PICO question 4: Is preventive medical and non-medical treatment effective in MOH?

For many years it was thought that preventive treatments were not effective in patients with MOH. In the last decade, this concept has changed, thanks to the prospective randomized studies with topiramate and onabotulinum toxin A and, more recently, to the RCTs on the efficacy of calcitonin gene-related peptide (CGRP)-targeting monoclonal antibodies. Most patients with MOH accessing headache centers have

already failed preventive therapy with beta-blockers, flunarizine, valproic acid or amitriptyline.

Topiramate was investigated in a European study and included patients with chronic migraine who were randomized to topiramate or placebo for a 16-week period in a double-blinded trial. A total of 32 patients in the intent-to-treat population received topiramate and 27 received placebo. A total of 78% of patients met the criteria for medication overuse at baseline. Topiramate also reduced the mean number of monthly migraine days by 3.5 in this latter group, which was significantly better than placebo (+0.8 days) [47]. A second trial conducted in the USA compared topiramate with placebo for the prevention of chronic migraine [48]. A subgroup analysis of the patients with MOH at baseline showed a non-significant reduction in mean monthly migraine/migrainous days compared with placebo [49]. This trial differed from the European trial as regards inclusion criteria and the classes of overused medications [48,50,51]. Overall, it is reasonable to conclude that topiramate is effective in the treatment of patients with chronic migraine and MOH [50].

The SAMOHA study was a randomized, double-blind, placebo-controlled study that enrolled patients with MOH for a 3-month treatment period with sodium valproate (800 mg/day) or placebo after a 6-day outpatient detoxification regimen, followed by a 3-month follow-up [52]. The 3-month 50% responder rate was higher with sodium valproate (45.0%) than in the placebo arm (23.8%) with an absolute difference of about 20% ($P = 0.0431$).

About 65% of the population included in the two pivotal trials comparing onabotulinum toxin A with placebo injections in patients with chronic migraine in the PREEMPT program fulfilled criteria for MOH [53-55]. Patients with opioid overuse were excluded. At week 24, statistically significant results favoring onabotulinum toxin A versus placebo were observed for headache days (primary endpoint: -8.2 vs. -6.2 ; $P < 0.001$). Significant benefit was observed for secondary endpoints such as frequencies of migraine days ($P < 0.001$), moderate/severe headache days ($P < 0.001$), cumulative headache hours on headache days ($P < 0.001$), headache episodes ($P = 0.028$) and migraine episodes ($P = 0.018$) [56].

A *post hoc* analysis of the pooled data obtained from these two pivotal studies evaluated the effect of onabotulinum toxin A in the subgroup of subjects with medication overuse and showed that the efficacy was also maintained in this subgroup [46]. Onabotulinum toxin A has been investigated against placebo in the prophylactic treatment of migraine without aura and MOH in combination with early

discontinuation of acute medication(s) [57]. No significant differences between onabotulinum toxin A and placebo were detected in the primary endpoint, i.e. headache days (12.0 vs. 15.9, respectively; $P = 0.81$). A significant reduction was, however, recorded in the mean acute pain drug consumption at 12 weeks (12.1 vs. 18.0, respectively; $P = 0.03$). It is worth noting that, in this latter study, the toxin dose was lower, the number of injection points fewer and the sample size smaller in comparison with the pivotal trials.

In an open long-term study in patients with chronic migraine and MOH, onabotulinum toxin A produced a clinically meaningful improvement in headache days with a mean reduction of -15.9 days at the 12-month follow-up (mean number of headache days at baseline 21.6) and a parallel reduction in the intake of acute medications [58].

Silberstein *et al.* [59] assessed the effect of fremanezumab, a monoclonal antibody against CGRP, versus placebo on medication overuse and intake of acute headache medications in patients with chronic migraine. Fremanezumab treatment was associated with a significant reduction in the overuse of acute medications and a decrease in days of acute medication intake. Fremanezumab significantly reduced the frequency of headache days of at least moderate severity by -4.7 days ($P < 0.0001$) and -5.2 days ($P < 0.0001$) in the groups with quarterly and monthly injections, respectively, compared with -2.5 days in the placebo group. It is of note that the patients with medication overuse included in this study did not undergo any withdrawal procedure at baseline.

In a study evaluating the efficacy of erenumab, a fully human monoclonal antibody targeting the CGRP receptor, monthly migraine days were reduced by 6.6 days after 12 weeks in 667 patients with chronic migraine, 41% of whom had medication overuse [60]. In a pre-defined subgroup analysis, patients were stratified by region and medication-overuse status. Data from patients with medication overuse at baseline ($n = 274$) were used to assess changes in monthly migraine days, acute migraine-specific medication treatment days and proportion of patients achieving $\geq 50\%$ reduction from baseline in monthly migraine days [61]. Groups treated with erenumab 70 or 140 mg had greater reductions than the placebo group at month 3 in monthly migraine days [mean (95% confidence intervals), -6.6 (-8.0 to -5.3) and -6.6 (-8.0 to -5.3) vs. -3.5 (-4.6 to -2.4)] and acute migraine-specific medication treatment days [-5.4 (-6.5 to -4.4) and -4.9 (-6.0 to -3.8) vs. -2.1 (-3.0 to -1.2)]. In the placebo and 70- and 140-mg groups, $\geq 50\%$ reductions in monthly migraine days were achieved by 18%, 36% [odds ratio (95% confidence intervals), 2.67 (1.36–5.22)]

and 35% [odds ratio, 2.51 (1.28–4.94)]. Erenumab 70- and 140-mg treatment arms had statistically significant and clinically meaningful improvements in headache-related disability measured both by the Headache Impact Test-6 and Migraine Disability Assessment Scale. These data support the use of erenumab in patients with chronic migraine, including those with MOH [62].

Observational and small randomized trials investigated valproic acid [52], cannabinoids, pregabalin, occipital nerve stimulation and acupuncture for the treatment of MOH (summarized in [63]). Due to the methodological shortcomings, the results of these studies have no impact on the practical treatment of patients with MOH. Antidepressants and especially amitriptyline are widely used drugs and even recommended by some guidelines in the treatment of chronic migraine [64]. However, there is no study that shows clear evidence of their efficacy, especially in patients with MOH. However, given the prevalence of depressive symptoms in patients with MOH, they could be useful in this group of patients.

From a theoretical point of view, the effect of preventive treatment of MOH with topiramate, onabotulinum toxin A or monoclonal antibodies targeting CGRP may be potentiated by the adoption of non-pharmacological treatments [64]. There are, however, no randomized trials investigating the combination of non-pharmacological therapy (stress-management, relaxation therapy, exercise) with medical treatment.

Recommendations

- Topiramate, onabotulinum toxin A or a monoclonal antibody targeting CGRP or the CGRP receptor are effective in patients with chronic migraine and medication overuse. Topiramate should not be used in women of childbearing potential.
- In clinical practice, advice to stop overuse should be provided before starting patients on these treatments (see also PICO question 5).
- Other preventive medications such as beta-blockers, flunarizine or amitriptyline may be used, although their efficacy has not been shown in randomized, placebo-controlled trials.

Quality of evidence: low for topiramate, moderate for onabotulinum toxin A and erenumab.

Strength of recommendation: weak.

PICO question 5: Is withdrawal from overused medication(s) effective in MOH?

Overuse of analgesics and/or acute migraine medications is one of the most important risk factors for the

transition from episodic to chronic headache. For decades, withdrawal of overused medications has been reported to be the initial step in treating MOH and is also recommended in several national and European guidelines [65-68] but there is still lack of consensus on how to perform this withdrawal and the long-term effect. Different approaches have been suggested with abrupt or tapered withdrawal and simultaneous or postponed preventive medication [69,70]. Overall, there is a lack of randomized placebo-controlled studies dealing with this aspect of MOH management and most studies are observational and/or uncontrolled and/or involve small sample sizes. The available larger studies are reviewed and summarized in the GRADE tables.

Most of the withdrawal programs allowed restricted intake of acute headache medications during the withdrawal period in order to relieve the withdrawal symptoms [71-73], whereas others used abrupt withdrawal [74-79]. Some physicians may be reluctant to recommend abrupt withdrawal and some patients may be less motivated to follow such a strict withdrawal program. Therefore, different strategies have been suggested to increase patient compliance. Withdrawal could be more feasible with a less strict approach where some doses of acute headache medication are allowed. In the COMOESTAS study, 46% of the Intention-to-Treat population stopped overuse and their headache reverted to an episodic pattern using a consensus protocol that limited, but did not forbid, the use of acute headache medications [74]. A randomized study comparing abrupt withdrawal not allowing acute headache medications with a program that restricted the use of acute headache medication to 2 days/week showed that abrupt withdrawal is the most effective approach in terms of reduction of headache days (-42% vs. -22%; $P < 0.005$), but not of days of intake of acute medications (21.2-6.9 with abrupt withdrawal; 22.1-9.3 when usual acute headache medications were allowed 2 days/week; $P = 0.33$) [79]. Self-efficacy and confidence may play an important role in the management of MOH. In this study, the positive effect on headache frequency was maintained after 12 months in both groups, although it was still better in the abrupt-withdrawal group. A similar long-lasting reduction in headache frequency after withdrawal has also been achieved in several other studies, varying from 46% in the most recent Danish study [79], 63% in the Norwegian study in primary care after BI [80,81] to 77.5% in the Italian outpatient study [42]. Likewise, a headache frequency reduction between 40.2% and 49.8% was reported in so-called complex patients with refractory MOH from Denmark and Italy [3,75,77]. A randomized study in

the Netherlands investigated the use of onabotulinum toxin A against placebo in addition to drug withdrawal [82]. In this setting of combination therapy, onabotulinum toxin A was not superior to placebo.

Some studies also report a very high percentage of patients with MOH who were 'cured' from overuse, ranging from 81% to 91% of all patients, which is a very positive outcome and also cost saving for both patients and society [4,79,83,84]. The 50% responder rate is reported in some studies and ranges from 26% in the complex patients from Italy [3] to 70% in the most recent study [79].

Overall, there is consensus that withdrawal of acute medications is highly effective and very important for the individual patient. Despite the lack of RCTs, withdrawal from overused drugs apparently has a much better outcome than most existing preventive headache drugs.

Most of the studies were conducted as outpatient programs in patients overusing simple analgesics with or without triptan overuse. Some patients with MOH may suffer from more complicated forms such as MOH in post-traumatic headache, MOH due to overuse of opioids, barbiturates or benzodiazepines, or with severe co-morbidities [3]. In these cases and when previous outpatient trials have failed, inpatient management may be the optimal setting. Even in such complex patients, Rossi *et al.* reported very positive outcomes after inpatient detoxification and preventive therapy with a 73% frequency reduction and a 38% responder rate after 14 weeks [3].

In conclusion, the available evidence is in support of the efficacy of interrupting the intake of overused medications. This can be achieved simply with adequate advice or with outpatient or inpatient structured programs. Abrupt outpatient withdrawal is usually effective in simple MOH, whereas the presence of relevant comorbidities, opioid or poly-drug overuse and/or previous withdrawal failures may require an inpatient regimen. The medication withdrawal can be accompanied by rescue medication, patient education and close follow-up to prevent relapse although the optimal composition thereof is not yet supported by strong evidence.

In the large COMOESTAS multicenter and open-label study conducted on 694 patients with MOH from seven different countries, preventive medication was started in parallel with the medication withdrawal and a very fast headache frequency reduction of 44% was seen within the first month, with a further reduction to 59.9% after 6 months [4,85]. Here, 68% of those patients who completed the protocol reverted to episodic headache and coexisting depression, anxiety, disability and quality of life

were markedly improved. In addition, costs of medication and use of healthcare services were also dramatically reduced [83]. These findings demonstrate that, although MOH represents a burden for the patients and society, its appropriate treatment is very rewarding and cost-effective. A comparative and randomized study of the effect of early or late preventive medication is presently ongoing (<https://clinicaltrials.gov/show/NCT02993289>).

It is of note that preventive drugs were only indicated in half of the patients after detoxification in the previous MOH study by Zeeberg *et al.* [8], as more than half of their patients had reverted to episodic migraine or tension-type headache and were no longer in need of preventives. Those findings are, however, controversial and acceptance of preventive medications is probably closely related to cultural traditions and various healthcare systems. In this frame, it is important to consider that the compliance to most existing oral drugs for migraine prevention is poor as only 14% adhere to the recommended preventives after 1 year due to intolerable side effects, costs and lack of consistent effect [86]. The good tolerability profile of the new CGRP antibodies, together with the first signals suggesting their capability to reduce the use of acute headache medications, suggests the possibility that they might be effective in the preventive treatment of MOH [60], ideally in synergy with overused medication withdrawal.

Recommendation

- Withdrawal from overused acute medications is effective in ceasing overuse and restoring an episodic pattern of headache for prolonged periods in a high percentage of subjects.
- Withdrawal is associated with documented improvements in healthcare costs, quality of life, coexisting depression and anxiety.
- Uncertainty remains as to whether preventive medications should be added early or late and this problem awaits further investigations.

Quality of evidence: moderate.

Strength of recommendation: strong.

PICO question 6: Can the symptoms that subjects with MOH develop during medication withdrawal be treated?

Withdrawal symptoms after termination of overused medications include withdrawal headache, various degrees of nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, anorexia, restlessness, anxiety and nervousness [87]. Seizures or

hallucinations have been only rarely observed, even in patients who were overusing caffeine or barbiturate-containing migraine drugs [88,89]. Withdrawal symptoms usually last for 2–10 days (average 3.5 days). The withdrawal phase is much shorter in patients overusing triptans alone (~4 days) than in patients overusing ergotamine (~7 days) or analgesics (~10 days) [90,91].

Treatment recommendations for the acute phase of drug withdrawal vary considerably between studies and include pharmacological and non-pharmacological approaches. General rules include simple advice, availability of the physician in 'off' hours, 24-h nursing support and psychological and behavioral support. Some patients on withdrawal require hospital-level care because of excessive headache and behavioral and emotional escalation, as well as sleep disturbances and other withdrawal symptoms.

In order to ease the withdrawal symptoms, there may be differences between abrupt withdrawal versus tapering of the overused drug(s). However for opioids, barbiturates and benzodiazepines, a tapered inpatient withdrawal is prudent to prevent withdrawal symptoms [65]. In these cases, a careful monitoring for changes in metabolic parameters, blood pressure, drug adjustments for pain control, fluid replacement, sedation and other rescue efforts are generally required. Sometimes, analgesics or triptans, tranquilizers and antidopaminergic drugs may be required [87,92].

Rescue treatments (an analgesic if triptans are overused and vice versa) can be used for symptomatic relief and can be proposed at greater-than-usual frequency during the initial withdrawal period without the fear of causing rebound MOH. The drugs proposed for the treatment of headache during withdrawal as a bridging therapy are those recommended for the acute migraine attack, e.g. diphenhydramine [93], dihydroergotamine [94], antidopaminergic drugs (chlorpromazine, prochlorperazine, metoclopramide, droperidol) [95–98], valproic acid [99], ketorolac [10], magnesium [11] or corticosteroids [12,103].

Many medications have been studied as short-term therapy in a limited number of case series. Pascual and Berciano [14] concluded that naproxen, a long-acting non-steroidal anti-inflammatory drug, was beneficial as a rescue medication for patients with MOH. Tizanidine has been studied as an adjunct to a long-acting non-steroidal anti-inflammatory drug and was shown to be helpful [15]. Patients overusing opiates, barbiturates and tranquilizers may require long-acting opioids, phenobarbital and clonidine as a transition during detoxification [71]. In an uncontrolled study

dealing with subjects with MOH who did not overuse opioids, the COMOESTAS group suggested rescue therapy from day 1 to day 7 with analgesics in triptan overusers or triptans in analgesic overusers [71], in addition to metoclopramide 10 mg i.m. or p.o. tid, chlorpromazine 25–50 mg i.m./o.s., prochlorperazine 10 mg oral/i.m., domperidone 30 mg rectal or 10 mg oral and levopromazine 6–25 mg oral or parenteral. Recommended analgesics include acetaminophen 1000 mg p.o., p.r. or i.v. on demand and naproxen 500 mg p.o. with a maximum of 3 days within the first week. Oral administration may not be as effective as parental use.

Taghdiri *et al.* compared the efficacy of celecoxib 400 mg/day for the first 5 days, then decreased at a rate of 100 mg every 5 days vs. prednisone 75 mg/day for the first 5 days, then tapered off every 5 days in 97 patients with MOH [16]. Although patients treated with celecoxib had slightly lower headache intensity, headache frequency and use of rescue medications, which were the primary endpoints, were not different between groups [23]. To the best of our knowledge, the other withdrawal protocols are as follows. Two placebo-controlled randomized studies from Norway and Germany revealed that oral prednisone (60 or 100 mg/day for 5 days) was not superior to placebo [17,108], although patients in the prednisone group requested rescue medication less frequently than those in the placebo group. Cevoli *et al.* [19] showed that methylprednisolone 500 mg i.v. and paracetamol (acetaminophen) 4 g/die i.v. were not superior to placebo at the end of the detoxification program. Methylprednisolone and paracetamol, a well-tolerated simple analgesic, have the same efficacy in controlling withdrawal headache but might be superior to placebo (fluid replacement) in reducing the intensity of rebound headache only during the second day of withdrawal.

Recommendation

- Several types of symptomatic medications can be used to attenuate withdrawal symptoms.
Quality of evidence: low.
Strength of recommendation: weak.

PICO question 7: Can relapse after successful treatment of MOH be prevented?

The observational periods ranged from 6 months to 9 years. In most studies, no significant predictors of relapse were found. Relapse rates after 6 months were evaluated in one RCT [80] and seven non-randomized open-label observational studies [72–

73,85,110–113] and ranged from 0% to 41%. Relapse rates after 12 months were evaluated in 10 non-randomized observational studies [73,76,111,114–120] and varied from 13% [117] to 41% [111]. Two observational studies of continuous treatment with only onabotulinum toxin A or in combination with oral preventive treatment indicated no relapses at 2 years [119,121]. In two non-randomized observational studies with a 6-year follow-up, relapse rates were between 21% and 45% [120,122]. The 9-year follow-up was the longest recorded period after inpatient detoxification; the relapse rate in this study was 32% [117]. The relapse rates did not differ significantly when a short or a long observation period was used [122]. The majority of relapses occur within the first year after withdrawal [120,122]. No new relapses were recorded during a 3–5-year follow-up in one study [123].

The following risk factors were identified as predictors of relapse: type of headache (more frequent relapses in migraine combined with tension-type headache than in migraine alone), overused medication (more frequent relapses in analgesic versus triptan overuse) [111], frequent migraine/headache before and after withdrawal [115,120], greater number of previous preventive treatments [115], history of withdrawal in the previous 3 years, headache frequency, admission to emergency room after discharge, high score on Beck Depression Inventory [124], smoking and alcohol consumption [116].

The importance of counselling was evaluated in two studies [80,81]. A randomized trial ($n = 60$, complete follow-up 100%) evaluated the relapse rate after a brief intervention (BI) given by a trained general practitioner at the beginning of the study (early BI) or after 6 months (late BI) as compared with business-as-usual care [81]. The relapse rate in the early BI group was 4% at 6 months and 8.3% at 16 months. No relapses were seen in the late BI group. A low relapse rate (15%) was achieved in patients with unsuccessful previous detoxification attempts using a multidisciplinary treatment program with participation of specially trained nurses and a close follow-up [76].

The importance of psychological therapy was analyzed in two small prospective observational studies. The relapse rate was significantly lower in the group receiving short-term psychodynamic psychotherapy and medical prophylaxis compared with the group that received only medical prophylaxis after 6 ($P = 0.016$) and 12 ($P = 0.047$) months of follow-up [114]. However, mindfulness-based training had no significant effect on the relapse rate when compared with only medical prophylaxis group after 6 and 12 months of follow-up [113].

Two observational studies of continuous MOH treatment with only onabotulinum toxin A or in combination with medical preventive treatment indicated no relapses after 2 years of follow-up [119,121]. The studies, however, varied by patient numbers and completed follow-up. A very low relapse rate (6.5%) was achieved by monitoring the drug intake with paper headache diary and e-diary and close follow-ups (every 2 months, including phone calls) [85].

Good practice statement

- The relatively high relapse rate after initially successful treatment warrants the identification of risk factors for relapse and regular follow-up of patients.
- Monitoring of drug intake (paper headache diary or e-diary) is probably effective. Short-term psychodynamic psychotherapy and mindfulness-based training after detoxification can possibly reduce early and late relapse rate.
- Continuous treatment with onabotulinum toxin A may be effective in the prevention of relapse.
- The evidence for the different procedures to prevent relapse is insufficient.
- Monitoring of drug intake, different types of short-term psychotherapy and continuous treatment with onabotulinum toxin A are able to prevent relapse and should be used in patients at risk of MOH relapse.

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Box 3. Conclusions regarding the management of MOH

- Patient education is essential in the management of MOH.
- Uncomplicated patients with MOH can be successfully managed in general practice.
- Patients with more complex MOH should be managed by a multidisciplinary team of neurologists or pain specialists and behavioral psychologists.
- Patients in whom education is not effective should be withdrawn from overused drugs with the most appropriate program that applies to their clinical condition and the overused drug(s) and should receive preventive treatment with drugs of proven efficacy.
- Patients with MOH who do not respond to preventive therapy should undergo drug withdrawal. 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 of these drugs is recommended.
- Withdrawal can be performed on an outpatient basis, in a daycare setting or an inpatient setting. All settings have a similar success rate because of the different complexities suited for each setting. Headache history may help to assign patients to a particular setting.

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Data availability statement

The data that support the findings of this study are available in the Supporting information of this article.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PICO2_Should Topiramate vs. Placebo be used for Prevention of MOH

Appendix S2. PICO4_Should Botulinum toxin vs. Placebo be used for preventive treatment in MOH patients

Appendix S3. PICO4_Should Erenumab vs. Placebo be used for preventive treatment in MOH patients

Appendix S4. PICO4_Should Topiramate vs. Placebo be used for preventive treatment in MOH patients

Appendix S5. PICO6_Should corticosteroids vs. no treatment be used for treatment of withdrawal symptoms in MOH

Appendix S6. PICO7_Should Counselling vs. usual care be used for MOH prevention after detoxification

Appendix S7. PICO7_Should Onabotulinumtoxin vs. baseline be used for prevention of MOH after detoxification

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