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Medication Overuse Headache: an Updated Review and Clinical Recommendations on Management

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Abstract

Overview Medication overuse headache (MOH) is highly prevalent among individuals with primary headache disorders.
Purpose of Review (1) Provide an update on epidemiology, risk factors, and treatment strategies of MOH and (2) provide recommendations on the management of MOH.
Recent Findings The prevalence of MOH ranges from 0.5 to 7.2%. Risk factors for MOH include female sex, lower socioeconomic status, some psychiatric conditions, and substance use disorders, among others. Recent large clinical trials support preventative therapy as an integral component of MOH management. Emerging clinical trial evidence supports anti-CGRP mAbs as effective preventative treatments among individuals with migraine and MOH. Among the large clinical trials, candesartan, topiramate, amitriptyline, and onabotulinumtoxinA were the most used preventative therapies, providing further support for these agents.
Summary MOH management requires a multifaceted and patient-centered approach that involves patient education, behavioral interventions, withdrawal of the overused medication, and initiation of preventative medication.

Keywords Medication overuse · Headache · Preventative · Withdrawal

Introduction

Primary headache disorders, including migraine and tension-type headache, are the second leading cause of years lived with disability [1]. Patients often turn to acute medications for relief. However, when used too frequently, some acute medications can paradoxically lead to a new headache or worsening headache.

Medication overuse headache (MOH) has previously been termed "drug-induced headache," "medication-misuse headache," and "rebound headache" [2]. The International Classification of Headache Disorders (ICHD-3) criteria define MOH as headache occurring on 15 or more days per month in a patient with a pre-existing primary headache disorder, that develops as a consequence of regular overuse of acute or symptomatic medication for more than 3 months, which is not better accounted for by another ICHD-3 diagnosis (Table 1) [2]. The frequency of analgesic intake required for the diagnosis is based on expert opinion and varies between medications, with opioids carrying a higher risk than simple analgesics [2].

MOH is both preventable and treatable. With growing awareness of MOH and global research efforts specific to MOH, our understanding of this entity continues to improve and is critical for providing optimal care of patients with chronic headache disorders. The aim of this review is to provide an update on epidemiology, risk factors, and management strategies of MOH. We conclude with recommendations on the management of MOH in clinical practice.

Epidemiology

Few studies have assessed the prevalence of MOH. A systematic review [3] across 27 studies found a prevalence of MOH among adults ranging from 0.5 to 7.2%, with the majority of studies reporting a range between 0.5 and 2.6%. In recent years, migraine has gone from the sixth leading cause of disability worldwide to the third leading cause [4],

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Table 1 International Classification of Headache Disorders third edition (ICHD-3) criteria for medication overuse headache (MOH)

ICHD-3 Diagnostic Criteria for MOH	
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	
Medications ≥ 15 days/month leads to MOH	Medications ≥ 10 days/month leads to MOH
• Paracetamol/acetaminophen • NSAIDs (including ASA) • Other non-opioid analgesics	• Opioids • Triptans (in any formulation) • Ergotamine • One or more combination-analgesic medication • Any combination (ergotamine, triptan, non-opioid analgesia, opioid) without overuse of a single drug or drug class alone

ASA acetylsalicylic acid, *ICHD-3* International Classification of Headache Disorders third edition, *MOH* medication overuse headache, *NSAIDs* non-steroidal anti-inflammatory drugs;

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which may be at least in part a consequence of the rise of MOH [5].

Headache disorders are both highly disabling and costly. The Eurolight project [6] found that MOH was among the most expensive headache disorders, with higher costs than both migraine and tension-type headache. The total annual cost of MOH was estimated at 37 billion euros amongst adults [6], with the mean-person annual cost for MOH 14 times higher than tension-type headache, and almost 3 times higher than migraine.

Characteristics of MOH

In order to prevent, identify, and treat MOH, it is critical to understand the typical presentation of MOH, risk factors, and associated comorbidities of this common headache disorder.

Headache Presentation in MOH

Individuals with MOH have previously been diagnosed with or concurrently receive a diagnosis of a pre-existing headache disorder, which is most often chronic migraine or tension-type headache. Increasing headache frequency in pre-existing primary headache disorders leading to increased use of medications, as well as baseline frequent use of these medications, can both lead to MOH. Multiple studies report that MOH is more common in migraine compared to other headache disorders [7, 8, 9•]. Although headache characteristics and duration can vary depending on the underlying primary headache disorder, those with MOH have been reported to have more headache days [7, 10], endorse more allodynia [9•, 10], and endorse greater pain intensity [10] compared to those without MOH.

Risk Factors and Comorbidities in MOH

Across MOH epidemiological studies, Westergaard and colleagues [3] found a higher prevalence in females than males in 10 out of 11 studies. A more recent study [9•] similarly found that 85.6% of individuals with MOH were female.

MOH has been associated with multiple markers of lower socioeconomic status, including lower educational attainment [7, 8], lower household income [8], and lower full-time employment [11]. Specifically, Westergaard and colleagues [11] found that fewer individuals with MOH worked full time (44.1%) as compared to both those with chronic headache without overuse (51.9%) and those without chronic headache (64%).

Lifestyle factors, including higher body mass index and physical inactivity [7, 10], are associated with MOH. Furthermore, those with MOH have higher rates of cardiovascular risk factors [7, 9•], gastrointestinal symptoms [7], fibromyalgia and musculoskeletal complaints [7, 9•], and insomnia [7].

Psychiatric comorbidities have consistently been reported as a risk factor for MOH, particularly anxiety and depression [7, 9•, 10–13]. The Eurolight Project [13] found that comorbid depression and anxiety were high in both migraine and MOH, but this association was stronger for MOH. Adverse Childhood Experiences (ACEs), including abuse, neglect, or exposure to household dysfunction [14], have also been shown to be associated with chronic migraine and chronic daily headache [15]. A recent study [16] found that 54.4% of those with MOH reported ACEs. These studies highlight the

importance of screening for ACEs and psychiatric comorbidities among those with MOH.

Common Medications in MOH

Across recent studies, simple analgesics (e.g., acetaminophen and ibuprofen) were the most commonly used medications among patients with MOH in 3/5 studies (RELEASE, MOTS, COMOESTAS-Europe, COMOESTAS-Latin) [9•], ranging from 28.4 to 62%, with the other two studies reporting combination analgesia (33.3%) and ergotamines (72.3%) as the most common. The prevalence of triptan use ranged from 6.2 to 41%, combination analgesia 18.1–33.3%, and ergotamine 1–72.3%. Opioids were the least common, ranging from 0 to 4% [9•]. The Medication Overuse Treatment Strategy (MOTS) trial [17•] similarly found that the most overused mediations were simple analgesics (62% of patients), followed by combination analgesics (41%), triptans (21%), opioids (4%), and ergotamines (1%).

The MAST study directly compared medications used among patients with and without MOH, and those with MOH were more likely to be taking triptans (31.3% versus 14.2%), followed by opioids (23.8% versus 8.0%) and barbiturates (7.8% versus 2.7%), than ergotamines (3.1% versus 0.6%) compared to those without MOH [10].

Importantly, opioids and barbiturates are thought to carry a higher risk of MOH than triptans or NSAIDs [18]. Patients taking regular opioids or butalbital are often excluded from clinical trials, including those mentioned above, since these medications may be difficult to safely stop quickly, making MOH due to these categories of medication more difficult to study and an important area for future research.

Management of MOH

Successful management of MOH requires a holistic and patient-centered approach. Treatment is multi-dimensional, including non-pharmacological management through patient education and behavioral interventions. Pharmacological strategies involve discontinuation of the overused medication and initiation of acute and preventative medications that target both MOH and the underlying primary headache disorder.

Non-Pharmacologic Approaches to MOH Management

Patient Education Proper patient education represents the fundamental foundation for successful MOH management. There continues to be a lack of knowledge about MOH among both the general population and healthcare professionals [19]. Although most studies combine both education and behavioral interventions as treatment for MOH, one early study of patients with migraine showed that, when provided information alone, patients were able to reduce the number of medication days and none developed MOH [20]. This suggests early education may be critical for preventing MOH. Importantly, many of the behavioral interventions discussed in the section below use comparison groups involving some form of patient education, and all of these studies show some degree of benefit among the education (comparison) groups.

Behavioral Interventions Most behavioral interventions combine patient education, motivational interviewing strategies to promote patient self-efficacy, and exploration of pain control strategies. Results show a reduction in headache frequency [21–23], number of medication-used days [21, 23], and number of patients meeting criteria for MOH [22] with behavioral intervention. A recent clinical trial showed a 75.9% reduction in headache days among patients receiving treatment as usual (education, medication withdrawal, initiating pharmacologic prevention) combined with mindfulness, compared to 54.4% of patients receiving only treatment as usual.

Taken together, comprehensive patient education and empowerment are critical in the treatment of medication overuse. Implementation of dependence-focused intervention [23] and mindfulness therapy [24•] may yield additional benefit.

Pharmacologic Approaches to MOH Management

Withdrawal of the Overused Medication Withdrawal of overused medications has been widely accepted as an important step in treating MOH and is reflected across international guidelines [25••, 26••]. However, the approach to withdrawal remains under debate. Some clinicians worry that abrupt withdrawal may reduce adherence, and opt for restricting the use of the overused medication or switching to a similar class of medication. A third option of "bridge theraphy" involves using a temporary bridging medication with a low risk of MOH to reduce acute medication intake and medication withdrawal symptoms.

Multiple recent randomized controlled trials (RCTs) have compared complete withdrawal of acute medications to the restriction of these medications to 2 days per week. Although both approaches are effective, complete withdrawal was more effective across multiple outcomes [27–29], including reducing disability and headache burden [27], headache days (by 46% versus 22%) and migraine days per month (by 7.2 days versus 3.6 days) [29], reverting

to episodic headache [29], reducing headache-related anxiety (32% versus 11%) [28], and reducing dependence (44% versus 26%) [28]. Complete withdrawal was also viewed as more feasible by patients in a Danish study [28]. In practice, patient involvement is crucial in determining the best approach.

For most patients with MOH, successful withdrawal can be achieved in an outpatient setting with education. However, evidence supports an inpatient setting for withdrawal among patients with complex MOH [30]. Specifically, for those with concurrent mental health disorders, substance use and addiction, relapse from previous detoxification treatment, and social and environmental stressors, withdrawal in an inpatient setting was more effective than education alone or an outpatient withdrawal approach. This suggests that patients with complex MOH likely benefit from a more supportive environment, removal from social and environmental triggers, and more strict control of medication access [30]. Furthermore, in those with overuse of opioids or tranquillizers, a controlled tapered approach is typically required.

Bridge Therapy The goal of bridge therapy is to provide a temporary treatment to help manage pain and optimize functioning during the withdrawal period. It is critical that the over-used medication is not the chosen bridging agent. Despite the important role that bridge therapy can play in treatment, no recent studies have investigated the utility of bridge therapy in the acute management of MOH. Recent guidelines have put forward recommendations based on expert consensus.

The majority of studies investigating the utility of corticosteroids (methylprednisolone or prednisone) found no effect on withdrawal headache in patients with MOH [31, 32]; however, there may be some utility in IV methylprednisolone in reducing headache intensity [33]. Anti-emetics and neuroleptics (e.g., prochlorperazine, promethazine, metoclopramide, and chlorpromazine) may also be effective in the management of MOH [25••, 26••, 34]. There is some evidence for the use of NSAIDs in bridge therapy, including naproxen, indomethacin, and ketorolac [34]. Expert opinion recommends the discontinuation of short-acting NSAIDS and initiation of a short course of long-acting NSAIDs (e.g., naproxen, nabumetone, celecoxib) over a 10–14-day period. Intravenous sodium valproate may also be an effective bridge treatment [26••].

Taken together, across recent European guidelines, there is consensus for the use of anti-emetics/neuroleptics [25••, 26••] in the acute withdrawal period of MOH. Danish guidelines recommend no further management aside from methadone in cases of opioid or barbiturate over-use [25••]. Other guidelines suggest that corticosteroids [35••], long-acting NSAIDs [34], sodium valproate [26••], dihydroergotamine (DHE) infusion (in complex cases) [36, 37], and tricyclic antidepressants [35••] may be clinically useful as bridge therapy. Most of these recommendations are based on expert consensus given the lack of current studies in bridge therapy, pointing to a major gap in the current MOH literature.

Preventative Therapy With multiple recently published clinical trials, there is growing evidence supporting the use of preventative medications in the treatment of MOH. Two large recent clinical trials were a Danish clinical trial led by Carlsen and colleagues [38••, 39••] which included 720 patients with MOH, and the Medication Overuse Treatment Strategy Trial (MOTS) trial in the USA which included 120 patients with MOH [40••].

Carlsen and colleagues [38••, 39••] found that a combination of complete withdrawal with concurrent initiation of preventative medication was superior to withdrawal or preventative medication in isolation at a 6-month follow-up. Specifically, at 6-month follow-up, 96.8% of those in the withdrawal plus preventative group no longer had MOH compared to 74.3% in the preventative group without withdrawal, and 88.9% in the withdrawal without preventative treatment group. The authors concluded that this translated to a 30% increased chance of eliminating MOH in the withdrawal plus preventative group compared to preventative management alone. At 1-year follow-up, when comparing the three groups (withdrawal with early preventative treatment, preventative treatment with potential withdrawal after 6 months, and withdrawal with delayed potential preventatives at 2 months), there were no significant differences in treatment effect between the three groups. Monthly headache days were reduced by 10.3 days in the withdrawal plus preventative group, 10.8 days in the preventative plus potential withdrawal at 6 months, and 7.9 days in the withdrawal with delayed potential preventative group. Thus, all three strategies were effective in treating MOH. However, since withdrawal with simultaneous initiation of a preventative medication may lead to the fastest effective response, the authors concluded that this strategy should be recommended.

The MOTS trial compared two groups: preventative medication with switching the overused medication to a medication from a different class (limited to 2 days per week), versus preventative medication with continuation of the overused medication [40••]. The authors found that preventative medication plus the continuation of the overused medication with no maximum limit was not inferior in reducing moderate to severe headache days compared to preventative medication with switching from the overused medication [40••].

There are important methodological differences in both study design and withdrawal approach between these two clinical trials, which may account for the seemingly conflicting results, and which render direct comparisons difficult. Carlsen and colleagues [39••] had three study groups

(preventative + withdrawal, preventative, withdrawal), whereas Schwedt and colleagues [40••] had two study arms (preventative + switching, preventative with no switch). Carlsen and colleagues [39••] had patients undergo complete withdrawal, with discontinuation of analgesics for 2 months. In contrast, the MOTS trial [40••] switched medications to an alternative analgesic from a different class while limiting its use to 2 or less days per week. Overall, both trials support preventative therapy as an integral component of the successful management of MOH [38••, 39••, 40••]. Initiating preventative therapy simultaneously with complete withdrawal from analgesic medication may lead to the fastest effective response in the treatment of MOH [39••]. Finally, preventative therapy may be more important than withdrawal in the management of MOH. This is further supported by earlier trials [41, 42] suggesting that while both preventative therapy in isolation and out-patient detoxification in isolation are effective in decreasing headache days per month, preventative medication led to the greatest reduction in headache days per month (50% versus 25% reduction).

The approach to choosing a preventative therapy should be similar to the approach in any primary headache disorder—based on empirical evidence, patient comorbidities, and patient preference. Across large recent clinical trials, the most common preventative medications in the MOTS trial [40••] were topiramate, followed by onabotulinumtoxinA and amitriptyline. These medications were used for over 50% of the sample. The remaining preventatives used were not documented. In the Danish trial [38••, 39••], the most common preventative treatment was candesartan (33.3%), followed by amitriptyline (14.6%), metoprolol (10.4%), lisinopril (3.1%), topiramate (2.1%), and mirtazapine (1%).

Previous studies support the use of onabotulinumtoxinA [43, 44], sodium valproate [45], and topiramate [46–48] as preventative therapy in MOH.

More recent evidence from subgroup analyses from the anti-calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) clinical trials supports this class of medications in the treatment of MOH [49•, 50•, 51•, 52•, 53•, 54]. In the PROMISE-2 trial, 29% of patients with MOH treated with eptinezumab (100 mg or 300 mg) did not meet the criteria for chronic migraine or MOH across the 6 months of treatment compared to 6.3% of placebo-treated patients [52•]. Among patients with MOH at baseline, 50.5% (100 mg) and 49.5% (300 mg) of those treated with eptinezumab did not meet the criteria for MOH consistently for all 6 months compared to 27.1% of placebo controls [51•]. Similarly, in a subgroup analysis across three trials of galcanezumab for episodic (EVOLVE-1 and EVOLVE-2) and chronic (REGAIN) migraine, galcanezumab (both 120 and 240 mg) led to a significant reduction in monthly migraine days and monthly medication overuse rates compared to placebo among those with MOH [53•]. Furthermore, in a prospective study, after 6 months of treatment with erenumab or galcanezumab, 60.6% of patients with baseline MOH no longer met MOH criteria [50•]. There were no differences found between erenumab and galcanezumab. A subgroup analysis of a clinical trial investigating the utility of erenumab (70 mg or 140 mg) in patients with MOH showed that treatment with erenumab led to greater reductions in monthly migraine days and acute medication days compared to placebo. A 50% reduction in monthly migraine days was achieved in 36% (70 mg group) and 35% (140 mg group) of patients treated with erenumab compared to 18% of patients in the placebo group [54]. In another study, more patients treated with fremanezumab had 50% or more reduction in headache days compared to placebo, including patients with MOH (monthly 39.4%, quarterly 34.8% versus 13.8% in placebo). More patients treated with fremanezumab no longer had MOH compared to the placebo group (60.6% monthly, 55.2% quarterly versus 46.3% in placebo) [49•].

Taken together, these results support the use of anti-CGRP mAbs as effective preventative treatments among migraine patients with MOH and were shown to reduce both monthly migraine days and medication overuse.

Several recent clinical trials have investigated the use of oral CGRP receptor antagonists (gepants) in migraine prevention. Although not yet published, a recent conference abstract of a subgroup analysis of patients with MOH from the PROGRESS trial found that more patients with MOH treated with atogepant as compared to placebo achieved a 50% or greater reduction in migraine days per month [55].

Nerve Blocks A few RCTs have investigated the utility of greater occipital nerve (GON) blocks in the treatment of MOH. In combination with medication withdrawal, GON blocks have been shown to significantly improve headache characteristics, including severity, frequency, and duration [56•, 57]. Karadas and colleagues [57] additionally reported decreased need for triptans in those who received multiple GON blocks compared to those who only received one GON block.

What Is the Best Approach to MOH Management?

There is a lack of consensus on the optimal approach to MOH treatment, with variability in recommendations across international guidelines (Table 2) as well as in practice between local institutions. The most recent European guidelines recommend education and counselling followed by withdrawal of overused medications and initiation of preventative medication [26••]. Similarly, French recommendations [58••] suggest education, followed by discontinuation or at least reduction of overused medication, combined with preventative therapy. Previous Danish guidelines

Table 2 Recommendations from current European expert guidelines in the management of MOH

	Danish 2020 Guidelines [25••]	European Academy of Neurology [26••]	S1 Expert Guidelines [35••]	French Guidelines [58••]
Education/behavioral	• Counselling on MOH, rationale for withdrawal, and treatment of withdrawal symptoms • Counselling precedes withdrawal therapy	• Advice alone is an appropriate initial approach for triptan or simple analgesic overuse in the absence of major psychiatric comorbidity • Advice alone is not appropriate for opioid, tranquilizer overuse, history of previous relapses, failure to stop overuse after advice • Advice should precede preventative therapy	• Counselling/education alone are sufficient in a proportion of patients • Education alone not sufficient in opioid overuse, previous relapse after withdrawal treatment; requires multimodal care in headache centers or inpatient setting • Relaxation techniques, exercise, CBT, and biofeedback may be beneficial	• Simple advice is sufficient for many individuals • Short psychotherapy for inpatient withdrawal is effective
Withdrawal	• Complete stop/withdrawal of all short-term medications for 2 months OR reduce intake to a maximum of 2/days per week (less effective) • Inpatient setting for comorbidities or risk of severe withdrawal symptoms • Recommended 2–3 weeks of sick leave	• Withdrawal is effective in stopping overuse and restoring an episodic pattern of headache	• Withdrawal combined with preventative therapy is recommended • Medication pause, withdrawal, and controlled reduction (with education) are effective and equivalent to preventative therapies • Medication pause can be abrupt for analgesics or triptans; slow taper in opioids or tranquilizers • Outpatient withdrawal for no comorbidities; inpatient for comorbidities*	• Discontinuation or at least reduction of the overused medication is recommended • There is no difference between inpatient versus outpatient setting, except for complex MOH** • Higher withdrawal success with support and ability to contact headache team
Preventative	• Start preventative medication with withdrawal (previously would wait 2 months after withdrawal) • For diagnostic clarity, can delay preventative therapy for 2 months when the underlying headache disorder is not clear • Choice depends on underlying headache disorder	• Topiramate, Onabotulinum toxin A or anti-CGRP mAbs/gepants are effective in patients with chronic migraine • Beta-blockers, flunarizine, amitriptyline may be used, although efficacy has not been shown in RCTs • Low evidence: topiramate • Moderate evidence: Onabotulinum toxin A, erenumab	• If education is not sufficient, patients should receive preventative medication • Topiramate, Onabotulinum toxin A, and the CGRP and CGRP-receptor antibodies are recommended for migraine • Amitriptyline is recommended in tension-type headache • Medication should be supplemented with non-pharmacologic therapy	• Preventative/ prophylactic medication must be started with withdrawal therapy • Topiramate, possibly sodium valproate, Onabotulinum toxin A, and CGRP mAbs may be effective treatment options
Bridging	• Rescue medication in week 1–3 may be needed • Recommendations include: A. levomepromazine or promethazine B. Metoclopramide or domperidone for nausea C. For opioid or barbiturate overuse: methadone (only in-patient care)	• Many medication classes can be used, including diphenhydramine, dihydroergotamine, antidopaminergic drugs, valproic acid, ketorolac, magnesium, or corticosteroids • Rescue therapy for a different class can be used at higher frequency during initial withdrawal	• Tricyclic anti-depressants, neuroleptics/ antiemetics, and steroids are recommended for treatment of withdrawal symptoms	None

CBT cognitive behavioral therapy, *CGRP mAbs* calcitonin gene-related peptide monoclonal antibodies, *gepants* calcitonin gene-related peptide (CGRP) receptor antagonists, *MOH* medication overuse headache, *RCT* randomized control trial

*Depression, anxiety, severe internal disease, abuse of other substances, and previous, unsuccessful withdrawal from medication

**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

recommended education with complete discontinuation of analgesia for 2 months and preventative therapy being postponed to after the 2-month period as patients may not need preventative therapy after the withdrawal period [25••]. However, with the recent publication of the Danish clinical trial [38••, 39••], it is now recommended to start preventative therapy simultaneously with withdrawal [25••]. In contrast, recent expert guidelines put forward by Diener and colleagues [35••] recommend education as a first step in the management of MOH, followed by the initiation of preventative treatment targeting the underlying headache disorder. If education and prevention are not adequate, then medication withdrawal is recommended.

Although Danish guidelines [25••] did not recommend specific preventative therapies, European and French guidelines recommended onabotulinumtoxinA, CGRP-targeted therapies, topiramate, and valproate (French recommendations only) [58••] as preventative options in patients with MOH with migraine. Furthermore, beta-blockers, flunarizine, and amitriptyline may be effective, but more evidence from clinical trials is needed. Diener and colleagues [35••] additionally recommended amitriptyline specifically in tension-type headache.

Conclusions and Recommendations

MOH is highly prevalent among individuals with primary headache disorders. MOH is associated with further disability and is highly costly for the healthcare system. MOH was first described in the 1950s [59]; however, it remains an under-recognized and under-treated entity. Although there is more recent research focused on MOH, increased awareness among both the general population and healthcare professionals is important in preventing and treating MOH [19].

While the ICHD-3 criteria for MOH are widely accepted, controversy remains around both the terminology and diagnostic criteria for MOH. The term "medication overuse" headache may imply blaming the patient; however, MOH can be a consequence of inadequate patient education from healthcare professionals as well as lack of awareness from patients, healthcare professionals, or both, and often signals a disabling underlying primary headache disorder. Furthermore, the strict cut-offs of medication-use days have been selected based on expert opinion rather than large-scale studies. Variability exists between patients, and it is possible to see MOH emerge with frequency of use that is both less than and above these cut-offs. This may be due to underlying genetic differences in predisposition as well as the presence or absence of risk factors. Finally, the criteria do not specify cut-offs for maximum daily doses. It is hoped that these issues will be addressed in future iterations of the ICHD criteria.

All patients with any primary headache disorder should be regularly screened for MOH. It is important to understand the factors associated with MOH, which are of value in identifying patients at increased risk. Female sex, lower socioeconomic status, some psychiatric conditions, and substance use disorders are all risk factors for MOH [3, 11, 13, 16]. A current gap in both the MOH and migraine literature is an understanding of sex and gender, including the influence of sex hormones in the symptomatology, pathophysiology, and treatment of headache. Although estrogen withdrawal has been established as a trigger for migraine, there are limited studies investigating the influence of other hormones, including testosterone and progesterone [60]. Additionally, the effect of gender-affirming hormone therapy on migraine pathophysiology and treatment remains unclear [60]. Further research is required to better understand the importance of sex and gender in both migraine and MOH.

Any physician or healthcare professional prescribing or recommending acute medications for headache or other pain conditions (post-operative pain, arthritis, chronic pain, etc.) should always screen for underlying primary headache disorders. Among those with comorbid primary headache disorders, counseling on MOH is essential when prescribing acute treatment for any condition. Furthermore, certain medications such as opioids and barbiturates carry an increased risk of MOH [18] and should be avoided or prescribed with caution in patients with comorbid primary headache disorders.

MOH management requires a multifaceted and patient-centered approach. Based on recent clinical trials and international guidelines, the following approach is recommended (Fig. 1):

1. Education: the most important first step in management of MOH is patient education. This is critical for patient understanding, acceptance, and ultimately, treatment success.
2. Medication withdrawal: ideally, as a second step, patients should undergo withdrawal from overused medications. However, in opioid and barbiturate overuse, a tapered withdrawal is often required. Withdrawal can often be effectively achieved in an outpatient setting; however, an inpatient setting is typically recommended for patients with complex MOH, including opioid use, concurrent substance use, significant environmental and social stressors, as well as psychiatric comorbidities.
3. Prevention: initiation of preventative therapy is essential. Preventative therapy may even be superior to medication withdrawal, as supported by the MOTS trial [40••], although a combination of preventative therapy with withdrawal may lead to the quickest effective treatment in MOH as supported by the Danish trial [38••, 39••]. There is growing evidence from clinical trials supporting the use of CGRP mAbs as preventative treatment options

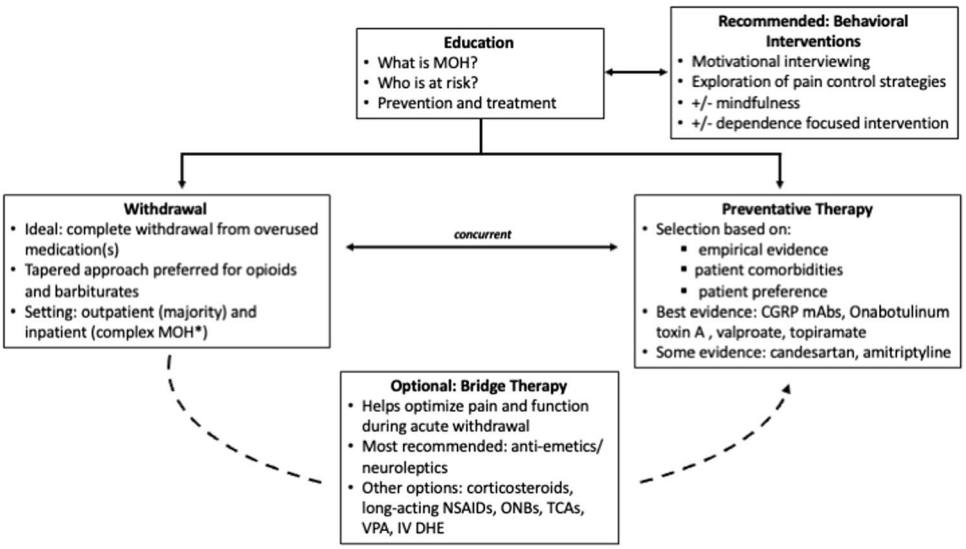

Fig. 1 Recommendations for the management of MOH. CGRP calcitonin gene-related peptide, DHE Dihydroergotamine, mAbs monoclonal antibodies, MOH medication overuse headache, NSAIDs non-steroidal anti-inflammatories, ONB occipital nerve block, TCA tricyclic antidepressant, VPA sodium valproate. *Complex MOH: opioid use, psychiatric comorbidities, complex medical comorbidities, environmental and social stressors, substance use

in MOH. Additional agents with evidence for benefit are onabotulinumtoxinA, sodium valproate, and topiramate. Furthermore, in the MOTS and Danish trials, candesartan and amitriptyline were widely used, and to a lesser extent, metoprolol and lisinopril, as preventative treatments in MOH. Patient comorbidities and preference should always be considered when selecting a preventative medication.

4. Bridge therapy: although evidence is limited, bridge therapy can be offered during the acute withdrawal period to better optimize pain management and patient function. Bridge therapy options include anti-emetics/neuroleptics (currently the most supported by guidelines), corticosteroids, long-acting NSAIDs (nabumetone, naproxen), sodium valproate, dihydroergotamine (DHE) infusion (in complex cases), and tricyclic antidepressants. Procedural interventions including occipital nerve blocks may also be beneficial.
5. Behavioral: the addition of behavioral interventions to patient education, particularly motivational interviewing strategies to promote patient self-efficacy, and exploration of pain control strategies, are effective treatment strategies in MOH. Behavioral interventions that include dependence-focused intervention and mindfulness therapy may lead to additional benefit.

In order to advance the management of MOH, it will be critical for future clinical trials investigating treatment options among patients with episodic and chronic migraine (including acute, preventative, and non-pharmacological interventions) to perform secondary analyses investigating the utility of these treatment options in MOH. Many of the recent GCRP mAb trials have performed these sub-group analyses and it is important that this be continued in future clinical trials, including (but not limited to) the gepant trials. Further research investigating the utility of bridge therapy is essential, as current recommendations are largely based on expert opinion. Addressing these gaps in the current literature will be important for the development of empirically validated guidelines in the management of MOH.

Declarations

Conflict of Interest MAH: no conflicts to declare. CHS: Abbvie, Eli Lilly, Lundbeck, Miravo, Novartis, Teva (Advisory Board); Eli Lilly, Novartis (Consulting), Novartis (Speaking).

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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