

A narrative review on the management of medication overuse headache: the steep road from experience to evidence

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Abstract The management of medication overuse headache (MOH) is based essentially on the withdrawal of the overused drug(s). Drug withdrawal is performed according to widely differing protocols, both within and across countries; therefore, therapeutic recommendations for the acute phase of detoxification vary considerably among studies. Basically, the aims of MOH management are: (a) to withdraw the overused drug(s); (b) to alleviate withdrawal symptoms by means of a bridge therapy, which includes pharmacological and non-pharmacological support, designed to help the patient to tolerate the withdrawal process; (c) to prevent relapse. Today, there is extensive debate over the best strategies for achieving these goals and the different aspects of this debate are discussed in this review.

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The authors searched for the best available evidence relating to the following questions: should medication withdrawal be abrupt or gradual? Should patients receive replacement therapy? What are the most effective therapeutic programmes for controlling withdrawal symptoms? Should replacement therapy be administered routinely or as rescue therapy? Should preventive treatment be started before, during or after withdrawal? What are the most effective preventive treatments? Should patients be managed through inpatient or outpatient withdrawal programmes? What is the best approach to adopt in preventing relapses? Treatment of MOH is a difficult challenge, but may be very rewarding. Although there is still a lack of high-quality studies providing evidence-based answers to the many specific questions it raises, neurologists need to know that the combination of education with a rational use of selected therapeutic strategies may be beneficial to people with chronic headache and help to relieve their suffering.

Keywords Medication overuse headache · Therapy · Management · MOH · Review

Background

Over the past 15 years, clinical experience and scientific studies on medication overuse headache (MOH) have accumulated, providing the basis for revisions of the International Classification of Headache Disorders (ICHD-II) diagnostic criteria [1, 2] and for the proposal (the practical details of which remain to be worked out) of a pragmatic clinical distinction between simple and complicated MOH (Table 1) [3, 4]. The “New appendix criteria for a broader concept of chronic migraine” recently published by the International Headache Society (IHS) [2] no longer require

Table 1 Proposed criteria for simple or complex medication overuse headache (see references [3, 4])

Simple MOH	Complex MOH
Short duration of MOH (3 months–1 year)	Long duration of MOH (>1 year)
Relatively modest doses of drugs ^a	Daily opioids or combination medication with more than one prescription drug
Minimal psychiatric contribution ^b (one or two axis I clinical syndromes)	Multiple psychiatric comorbidities including personality disorders
No history of relapse after withdrawal	History of relapse following withdrawal

^a Up to two triptans and three analgesics per day

^b Psychological issues contributing to the perpetuation of MOH include: (a) the belief that drug(s) is(are) the only solution, (b) anticipatory fear of pain (cephalalgiphobia), (c) difficulty tolerating discomfort, (d) sedation seeking, (e) outside pressure, need to function, (f) axis I, clinical syndrome, (g) axis II personality disorders

headache resolution or a return to the previous headache pattern after drug discontinuation, to confirm the diagnosis. These simplified diagnostic criteria will help physicians to recognise MOH, thus removing the diagnostic barriers to proper care of affected patients. In this scenario, there is an increasing need for evidence-based and cost-effective drug withdrawal strategies.

Drug withdrawal is the treatment of choice for MOH [5–7]. Zeeberg et al. recently reported that mere discontinuation of regular drug intake had, after 2 months, reduced the mean headache frequency by 51% in migraine, 18% in tension-type headache (TTH) and 33% in patients with a combination of migraine and TTH [8]. They also found that MOH patients who had previously failed to respond to preventive treatment became responsive to medical prophylaxis after withdrawal of the acute headache drugs they had been overusing [9]. A survey of 22 studies dealing with the therapy of drug-induced headache revealed that most centres used drug withdrawal as the first-choice therapy [5]. Drug withdrawal, however, is performed very differently within and across countries and therapeutic recommendations for the acute phase of detoxification thus vary considerably among studies. Moreover, the IHS only recently published its guidelines for controlled trials of prophylactic treatment in chronic migraine, including MOH [10]. Currently, there is a lack of prospective, controlled trials in this field, and treatment effectiveness is basically inferred from the results of open-label trials, retrospective case reviews, anecdotal observations, clinical experience and generalisations from the literature on primary headaches. As a result, no formal evidence-based recommendations for optimal therapy can be made and, in general, published guidelines reflect the personal experience of the authors and/or the best available evidence [11–14].

Basically, the aims of MOH management are: (a) to withdraw the overused drug; (b) to alleviate withdrawal symptoms by means of a bridge therapy, including pharmacological and non-pharmacological support, designed to

help the patient to tolerate the withdrawal process; and (c) to prevent relapse [13, 15].

Today, there is extensive debate on the best strategies for achieving these goals and the different aspects of this debate are discussed in this review (Table 2).

Should medication withdrawal be abrupt or gradual?

No study has compared abrupt withdrawal with tapered withdrawal in prospective randomised trials; therefore, no formal evidence-based recommendation can be made. However, the majority of headache specialists consider drug withdrawal to be more effective if done abruptly [12–14, 16]. Abrupt withdrawal is possibly associated with less protracted suffering for the patient and faster resolution of the drug-centred pain-coping behaviour.

This is likely to apply particularly in overuse of triptans, ergots, paracetamol, aspirin and NSAIDs, for which outpatient withdrawal programmes can be appropriate. Conversely, due to the possibility of severe withdrawal symptoms, patients overusing opioids, barbiturates or benzodiazepines should have their medication withdrawn gradually (i.e. reduced by 10–20% every week or two, depending on the overused drug, the dose and the duration of intake), preferably in the context of an inpatient programme (clinical experience-based recommendation).

Should patients receive replacement therapy?

What are the most effective therapeutic programmes for controlling withdrawal symptoms?

Should replacement therapy be administered routinely or only as rescue therapy?

Symptomatic drug withdrawal leads to worsening of headache and the onset of drug withdrawal symptoms such as

Table 2 Clinical management of MOH: questions and answers

Should medication withdrawal be abrupt or gradual?	No formal evidence-based recommendation can be made. The majority of headache specialists consider drug withdrawal more effective if done immediately. In general, triptans, ergots, paracetamol, aspirin and NSAIDs should be stopped abruptly.
Should patients receive replacement therapy?	Evidence from available controlled trials suggest that non-complicated MOH patients may achieve successful drug withdrawal through the simple imparting of advice to withdraw symptomatic medications and the use of rescue medications with limits on intake.
What are the most effective therapeutic programmes for controlling withdrawal symptoms?	Patients overusing drugs containing opioids, barbiturates or tranquillisers usually require a replacement therapy (clinical experience-based recommendation).
Should replacement therapy be administered routinely or as rescue therapy?	Although this is not yet supported by scientific evidence, patients overusing analgesics, ergots, combination drugs or combinations of acute medications (especially those using multiple daily doses), who experience intolerable withdrawal symptoms or present medical and psychiatric illnesses that could complicate their withdrawal programme, should be considered for regular replacement therapy, whether symptoms are present or not (clinical experience-based recommendation). No evidence-based recommendation can be made on the most effective replacement therapy in these patients.
Should preventive treatment be started before, during or after withdrawal?	No evidence-based recommendation can be made on the use of preventive treatment (who, when and what) for the clinical management of MOH. In non-complicated MOH patients, the decision on whether or not to start a preventive treatment may be postponed until a follow-up visit performed 2–3 months after the start of the withdrawal treatment. Complicated MOH patients, especially those who already had a high headache frequency before development of medication overuse and who had tried more than one preventive treatment in the past, probably need early prophylaxis (clinical experience-based recommendation).
What are the most effective preventive treatments?	There are no evidence-based indications supporting the use of specific preventive drugs in MOH (valproic acid as well as topiramate have been shown to have beneficial effects in the prophylactic treatment of chronic migraine, complicated by excessive analgesic intake in open-label and double-blind trials).
Should patients be managed through inpatient or outpatient withdrawal programmes?	No evidence-based recommendation can be made. In non-complicated MOH patients, effective drug withdrawal may be obtained in an outpatient setting. MOH patients overusing opioids, barbiturates or benzodiazepines, or presenting psychological problems or medical illnesses liable to complicate withdrawal programmes undertaken on an outpatient basis, are candidates for hospitalisation, as are those who have previously failed as outpatients or who lack the motivation needed to undertake an outpatient withdrawal programme (clinical experience-based recommendation).
What is the best approach to adopt to prevent the relapse?	The fact that a large proportion of MOH patients are at risk of relapse after withdrawal provides an indication of the lack of effective strategies for preventing this outcome. The most practical strategy in MOH is to prevent medication overuse through education and early and appropriate headache prophylaxis in patients who present a high headache frequency (author's personal view).

nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety and nervousness [5, 6]. Seizures and hallucinations have only rarely been observed, even in patients overusing butalbital-containing agents. Drug withdrawal symptoms typically last 2–10 days (average 3.5 days), but can persist for up to 4 weeks [7, 14]. Withdrawal symptoms are usually relieved by further intake of the overused medication, but this could lead to perpetuation of the overuse.

Withdrawal symptoms vary greatly depending on the overused medication. The duration of the withdrawal headache is shorter in patients overusing triptans (4.1 days) than in those overusing ergots (6.7 days) or NSAIDs (9.5 days) [17]. Withdrawal from triptans is generally

achieved in a short period of time (approximately 80% of patients are headache-free 4 days after starting the therapy) and without serious withdrawal symptoms [17, 18].

Many different replacement strategies for treating medication withdrawal symptoms in MOH have been proposed and found to be effective, almost exclusively in uncontrolled, unblinded studies that employed a variety of outcome measures [12, 19]. The proposed treatments include different drug classes (used alone or in combination), such as antiemetics, analgesics, triptans, sedatives, narcoleptics, central muscle relaxants and corticosteroids (the drugs suggested include intravenous dihydroergotamine, lidocaine, intravenous valproic acid, tramadol, clonidine, phenobarbital and amitriptyline), and other

preventive medications, oxygen, electrical stimulation and fluid replacement [12, 19, 20].

These treatments have been tested both in inpatient and in outpatient regimens. However, the fact that they are often used in combination with preventive and educational interventions makes it difficult to understand the efficiency of the treatments per se, as well as their reproducibility in other settings. Bridge therapies are regularly prescribed, usually administered for short periods, in other cases administered on demand (rescue treatment) and in some cases with limits on intake.

Because all drugs used for the acute treatment of headache can cause MOH, corticosteroids are an attractive option for the treatment of withdrawal headache. In a large open-label trial investigating patients with chronic daily headache and medication overuse, oral prednisone (60 mg as a starting dose, then tapering down by 20 mg every second day), as part of an outpatient regimen, effectively reduced withdrawal symptoms, including rebound headache [21]. Conversely, a recent Norwegian placebo-controlled study showed that prednisolone (60 mg as a starting dose, then tapering down by 20 mg every second day), given as part of an inpatient regimen for 6 days, was ineffective in treating withdrawal headache [22]. This latter study included patients with both TTH and migraine. In a very recent study, intended as a proof-of-concept uncontrolled study, prednisone 100 mg, given once a day for the first 5 days of withdrawal as part of an inpatient strategy, was effective in reducing medication withdrawal headache in 20 MOH patients with migraine as a primary headache [23]. Thus, in the only high-quality study available, steroids administered in the acute phase of drug withdrawal seem ineffective. High-quality randomised placebo-controlled trials using higher dosages and taking into account the clinical heterogeneity of MOH are needed.

Three recent prospective randomised controlled trials (two open-label and one double-blind) compared the efficacy of different therapeutic regimens following abrupt withdrawal of the overused medication [22, 24, 25].

Rossi et al. [24] randomly allocated 120 simple MOH patients (no previous detoxification treatments, no coexistent, significant and complicating medical illnesses, no current psychiatric comorbidity, no overuse of agents containing opioids, benzodiazepines or barbiturates, migraine as primary headache) to one of three groups, each of 40 subjects: Group A received only strong advice to withdraw overused medication(s); Group B underwent a standard outpatient detoxification programme based on advice to withdraw, abruptly, overused medication(s) + oral prednisone for the first 8 days+ personalised preventive treatment starting on day 1; Group C underwent a standard inpatient drug withdrawal programme based on the abrupt discontinuation of overused medication(s) + oral prednisone for

the first 8 days+ personalised preventive treatment starting on day 1 + parenteral fluid replacement and administration of antiemetics + close observation and support for 8 days.

Krymchantowski and Moreira [25] randomised 150 MOH outpatients (diagnosed according to the Silberstein–Lipton criteria), who were moderate overusers of acute drugs (excluding opioids, barbiturates and tranquillisers), to a tapering course of prednisolone, regular naratriptan or no regular medication for 6 days, in addition to advice and rescue medication (indomethacin or chlorpromazine). All the patients were started on prophylaxis on day 7 (atenolol, nortriptyline or flunarizine).

Boe et al. [22] evaluated 100 MOH inpatients, who had no psychiatric or physical comorbidity and were not overusing opioids or barbiturates; these patients received prednisolone or placebo and pre-withdrawal advice, and were allowed to take antiemetics, antihistaminic drugs and antipsychotics, if necessary.

After a follow-up period ranging from 8 days to 2 months, none of these three studies found any between-group differences in:

- the percentage of patients achieving successful withdrawal [24, 25];
- headache frequency [24, 25];
- headache intensity [25];
- calculated mean headache [22].

It is worth noting, however, that in the study by Krymchantowski and Moreira [25], the patients not receiving bridge therapy experienced more symptoms and required more rescue medication.

The findings of available randomised controlled trials indicate that in patients with simple MOH, especially in those with migraine as the primary headache, effective drug withdrawal can be achieved through the imparting of advice alone, although the use of medication (on a routine or rescue basis) can be effective as well. This may have important economic implications, if we consider the costs, per detoxified patient, of the different strategies emerging in the study by Rossi et al.: the simple imparting of advice, €40; the outpatient programme (including replacement therapy), €116; and the inpatient programme, €2,876 (Rossi et al., unpublished data).

In summary:

- (a) Simple MOH patients may achieve successful drug withdrawal through the simple imparting of advice to withdraw symptomatic medications and the use of rescue medications with limits on intake (evidence from available randomised controlled trials). Effective education of MOH sufferers is crucial to proper management, and information should be imparted to

all patients in accordance with the principles summarised in Table 3. Rescue treatment should be tailored to the patient on the basis of his or her medical history, headache characteristics and previous therapeutic experiences, and adherence to the rule that patients should not be prescribed, as a rescue drug, the drug that they had been overusing.

- (b) Patients overusing drugs containing opioids, barbiturates or tranquillisers require a replacement therapy regimen, which may include the short-term use of long-acting opioids, phenobarbital, clonidine (depending on the overused drug), hydration and, if necessary, antiemetics [12–14, 20]. No formal recommendation on support therapy in these patients can be made and placebo-controlled studies are needed.
- (c) Although this is not yet supported by scientific evidence, patients overusing analgesics, ergots, combination drugs or combinations of acute medications (especially those using multiple daily doses), who experience intolerable withdrawal symptoms or present medical and psychiatric illnesses that could complicate their withdrawal programme, should be considered for regular replacement therapy, whether symptoms are present or not. No formal recommendation can be made on the most effective replacement therapy in these patients. A single course of naproxen or tapered steroids, with or without antiemetics, and adequate hydration are the therapeutic measures most frequently included in guidelines suggested by experts [12–15, 19, 20]. Again, well-designed, double-blind controlled trials are needed.

Should preventive treatment be started before, during or after withdrawal?

High-quality studies investigating the usefulness of preventive treatment in the acute phase of drug withdrawal are lacking. In the study by Rossi et al. [24], personalised preventive therapy started on day 1 did not improve the outcome of withdrawal therapy. In the Danish study of 175 MOH patients [8], preventive therapy was initiated after a 2-month withdrawal period and actually found to be

necessary in only 47% of the patients; in the other 53%, headache frequency was markedly reduced simply by discontinuation of the overused medication (in this study, 36% of the patients failed to remain drug-free after receiving advice to withdraw the overused medication). Hagen et al. [26], in a recently published prospective, multicentre study, investigated the effect of early introduction of prophylactic treatment in three groups of MOH patients. In the prophylaxis group ($n = 17$), patients received personalised preventive medication from day 1; the abrupt withdrawal group ($n = 20$ patients) received advice to withdraw abruptly the overused medication plus rescue therapy, whilst the controls ($n = 19$) received no preventive medication and no explicit advice to withdraw the overused medication. The primary outcome measure, i.e. the change in headache days/month, was not found to differ significantly among groups. The prophylaxis group recorded the most consistent reduction in headache days/month at months 3, 5 and 12, though the mean headache frequency continued to be greater than 15 days/month in all the groups. All three groups recorded significant reductions in days with use of acute medication per month, when compared with baseline, the change being greatest in the abrupt withdrawal group versus the controls (-19.1 vs. -6.9 at month 3, $p = 0.002$). The prophylaxis group, compared with the withdrawal group, showed significantly more pronounced reductions in total headache index at months 3 and 12, and in sick leave days/month at months 5 and 12. During the follow-up, the proportion of responders, defined as patients no longer overusing symptomatic medications or with a greater than 50% reduction in headache days, tended to be higher in the prophylaxis group. The authors concluded that early introduction of preventive treatment, in the absence of previous detoxification reduced total headache suffering more persistently than abrupt withdrawal, challenging the notion that drug withdrawal is necessary to obtain reduced headache frequency and a response to prophylactic treatment. Unfortunately, the results of this study are weakened by several methodological flaws. First, all the patients received written information on MOH and the therapeutic importance of withdrawing the acute medication, and this may have influenced the behaviour both of the prophylaxis group members and the controls (indeed, 26% of the controls

Table 3 Pillars of the educational approach to MOH sufferers

Explanation of the role of medication overuse in making headache chronic and in reducing the effectiveness of preventive and behavioural treatments
Explanation in detail of the phenomenon and symptoms of withdrawal headache
Emphasis on the beneficial long-term effects, on headache natural history, of reducing symptomatic medication intake (including reduction of the disease-reinforcing properties of short-term pain relief)
Discouragement of anticipatory use of medication
Emphasis on the need for a detoxification programme prior to other therapeutic options

spontaneously reduced their drug intake considerably). Second, since 72% of the patients in the withdrawal group received a preventive therapy at month 3, the differences observed from month 5 to 12 may be only poorly attributable to the different initial therapeutic strategies. Furthermore, in view of the heterogeneity of MOH, the number of patients included in the study, which was below the power calculation, was too low. In addition, almost 30% of the MOH patients included in this study overused opioids (vs. 42% of the controls); opioid overusers are usually excluded by studies of this kind, investigating the effectiveness of different treatment strategies in MOH, because they can present withdrawal symptoms liable to complicate the withdrawal process, and this aspect may have contributed to determining the low success rate observed in this study. Finally, with regard to the differences in the outcome measures observed at month 3, only the reduction in headache index showed a statistical difference among groups in favour of the prophylaxis group; for all the other parameters, only non-significant differences were observed. For all the above reasons, the authors' conclusions appear speculative. There is still a need for further prospective, large-scale randomised trials to establish the usefulness of early preventive treatment for MOH.

In summary:

- (a) In simple MOH patients, the decision on whether or not to start a preventive treatment may be postponed until a follow-up visit performed 2–3 months after the start of the withdrawal treatment (clinical experience-based recommendation). This approach may help patients to feel more in control of their headache, and it also fits better with what is known about the natural history of the disease.
- (b) An alternative approach is to start preventive and withdrawal treatments simultaneously, or to start preventive therapy during the washout period, making it clear to the patient that the treatment may not become fully effective until MOH has been eliminated. This approach has two potential advantages: first, it may help to reduce reliance on symptomatic medications, and, second, the prophylactic treatment may improve the withdrawal symptoms and headache frequency.

Complicated MOH patients, especially those who already had a high headache frequency before medication overuse developed and who had tried more than one preventive treatment in the past, probably need early prophylaxis. But, currently no formal evidence-based recommendation can be made on the use of preventive treatment (who, when and what) for the clinical management of MOH.

What are the most effective preventive treatments?

In the absence of evidence-based indications, the choice of preventive agent in MOH patients should be based on the primary headache type (migraine or TTH), the drug side-effect profile, the presence of any comorbid and coexistent conditions, and the patient's preferences and previous therapeutic experiences [15].

In clinical practice, a monotherapy approach is preferable, selecting from the possible first-line treatments: beta-blockers, tricyclic antidepressants, calcium antagonists, tizanidine or anticonvulsants. It seems reasonable to start with low dosages, to reduce the risk of adverse events, and then to increase the dose progressively until a therapeutic effect or adverse events appear [12–14]. Only when such a first-line monotherapy approach fails does it become advisable to look for an alternative second- or third-line treatment.

In open-label trials, both valproic acid and topiramate have shown beneficial effects in the prophylactic treatment of chronic daily headache complicated by excess analgesic intake [27, 28]. More recently, a double-blind trial tested the efficacy and safety of topiramate in patients with a diagnosis of chronic migraine and MOH [29]. A total of 32 patients in the intent-to-treat population received topiramate and 27 patients received placebo for a period of 16 weeks (78% of these subjects met criteria for MOH). Topiramate was titrated (25 mg weekly) to a target dose of 100 mg/day, allowing dosing flexibility from 50 to 200 mg/day, according to patient need. Topiramate produced a significant reduction in the mean number of migraine days/month compared with placebo (-3.5 ± 6.3 vs. -0.2 ± 4.7 , $p < 0.05$). There emerged no significant between-group differences in health-related quality of life. The MIDAS questionnaires showed improvements in the topiramate treatment group ($p = 0.042$ vs. placebo). Treatment-emergent adverse events were reported by 75% of the topiramate-treated patients (vs. 37% in the placebo group). This randomised, double-blind, placebo-controlled trial demonstrated that topiramate is effective, although associated with a higher incidence of side effects when used for the preventive treatment of chronic migraine, even in the presence of MOH. However, the reported improvement in terms of headache frequency appears poor and not sufficient to constitute a reversion of the headache to its previous episodic form.

There is thus a need for further well-designed, double-blind, controlled trials investigating the effectiveness of other preventive treatments, and prolonged, longer follow-up periods.

Single injections of the greater occipital nerve with anaesthetics or corticosteroids have been reported as helpful in providing temporary relief from headache even

Table 4 Published recommendations for outpatient and inpatient withdrawal from headache medication

	Inpatient	Outpatient
Pamelaire et al. [12]	Drugs (opioids/barbiturates) Status migrainosus Severe vomiting/dehydration Social situation Previous failure as outpatient Psychiatric comorbidity Physical comorbidity Fear of drug interactions	Motivated patients Mild-moderate overuse
German Migraine and Headache Society (1999)	Drugs (codeine, barbiturates, tranquillisers) Depression	Drugs (monosubstances, analgesic mixture not containing barbiturates or codeine)
Obermann and Katzarava [14]	Previous medication withdrawal failure	Highly motivated patients Possibility of daily follow-up visits Overall good compliance
British Association for the Study of Headache (2007)	Drugs (overuse of high doses of opioids/barbiturates/benzodiazepines) Presence of psychiatric/behavioural disturbances (in these cases the authors recommend referral to specialist units or pain management clinics offering neurological and psychiatric services)	No specific indication (the authors state that admission to a hospital is rarely necessary)

in MOH patients, but further controlled studies are needed to confirm these findings [30].

Should patients be managed in inpatient or outpatient withdrawal programmes?

Rossi et al. [24], in their study of 120 patients with migraine plus MOH, low medical needs and no previous detoxification therapy, found simple advice to be as effective as structured inpatient and outpatient detoxification programmes in achieving withdrawal from the overused medication (approximately 75% of patients in all groups). In addition, the level of adherence to treatment was comparable with all three strategies (almost 90% of the initial sample completed the study). These results are in line with those of a previous German study, which suggested that outpatient and inpatient programmes could be equally effective [31]. Sick leave of 1 or 2 weeks may be needed when patients are detoxified in an outpatient setting.

The inpatient therapeutic setting offers at least three indisputable advantages. Namely, it allows: (1) close monitoring of the patient's medication intake and clinical conditions, (2) prompt and adequate treatment of withdrawal headache and associated symptoms; (3) the administration of drugs that need continuous medical monitoring (e.g. lidocaine, intravenous ergot derivatives). As discussed in the previous paragraphs, different supportive medication regimens have been proposed.

Headache experts and academic societies have published recommendations that offer criteria for deciding between in- and outpatient approaches (Table 4). It is generally agreed that MOH patients overusing opioids, barbiturates or benzodiazepines, or presenting psychological problems or medical comorbidities, liable to complicate withdrawal programmes undertaken on an outpatient basis, are candidates for hospitalisation, as are those who have previously failed as outpatients or who lack the motivation needed to undertake an outpatient withdrawal programme.

These recommendations are not evidence based and reflect, essentially, the authors' experience and beliefs, as well as basic principles of good clinical practice. Furthermore, the indications are not sufficiently specific. For example, psychiatric comorbidity and socio-environmental problems need better categorical and dimensional definition. Finally, these recommendations are the result of experience accumulated in headache clinics. Thus, the reproducibility in other settings (e.g. primary care) of the protocols they suggest remains uncertain. Data from literature indicate that the strategy chosen (outpatient vs. inpatient) is not a significant predictor of the long-term success of withdrawal therapy [31, 32].

In summary, effective drug withdrawal may be obtained simply in an outpatient setting, at least in MOH patients presenting low medical needs and no previous experience of detoxification therapy. Future controlled studies are needed to establish whether outpatient programmes may be considered as the first step in a step-care approach to MOH

management, in which patients progress through a sequence of treatments (determined by a combination of perceived effectiveness, safety and cost) until they find an effective one, or as just one of the therapeutic options in a stratified-care approach, in which patients, on the basis of the extent of their medical needs, are assigned to different treatments.

What is the best approach to adopt in preventing relapses?

As stated by Obermann and Katsarava [14], the long-term management of MOH is definitely more challenging than acute drug withdrawal. Several studies have investigated the long-term outcome of MOH following detoxification and carefully evaluated possible relapse predictors.

MOH following successful drug withdrawal has a variable, but mainly good, prognosis [5]. Success is usually strictly defined as no headache at all or an improvement (in terms of headache days/month) of more than 50%. In a review of 17 studies (1,101 patients), the mean success rate of withdrawal therapy, within a time window of 1–6 months, was found to be 72.4% [5]. Three further studies considered a longer observation period (9–35 months) [31–33] and recorded success rates of 60, 70 and 73%, respectively. Longer-term follow-up studies (4–6 years) found relapse rates of between 40 and 60% [34–40]. These studies are largely heterogeneous with regard to the definition of MOH, populations under study, types of medication overused, types of original primary headache, therapeutic approaches and many other variables. Furthermore, most of them were designed retrospectively.

Recent prospective studies that included patients with triptan-induced MOH reported relapse rates after successful drug detoxification therapy of 38% in the first year and around 42% at 4 years [38, 41]. Patients with TTH had higher relapse rates than migraine patients (77 vs. 23%, respectively), and analgesic overusers had higher relapse rates than ergot and triptan overusers (58 vs. 18 and 22%) [41]. In a recent study, from Serbia, of patients not overusing triptans, 39.6% of 240 patients had relapsed at the 1-year follow-up [32]. The frequency of the primary headache disorder, ergotamine overuse and pre-treatment disability as measured by MIDAS were all found to be predictors of relapse (the reported OR values and CIs actually raise some question marks over the statistical interpretation of the results). These, and older studies investigating rates and predictors of relapse in MOH, were conducted on non-selected populations of headache patients [5, 31, 40]. In a recent publication, Rossi et al. [42] evaluated the rates and predictors of relapse after successful drug withdrawal in a previously studied population of simple MOH patients with

migraine as primary headache. The patients were followed up prospectively for 1 year: relapsers were defined as patients fulfilling, at follow-up, the new ICHD-II appendix criteria for MOH. At the 1-year follow-up, the relapse rate was found to be 20.5%, which is consistent with that reported in the subgroup of patients with MOH plus migraine studied by Katsarava et al. [41]. A binary logistic regression analysis was performed and three variables emerged as significant predictors of relapse: years with more than eight migraine days per month (OR = 1.57, $p = 0.01$), higher frequency of migraine attacks after drug withdrawal (OR = 1.48, $p = 0.04$), and a greater number of previous preventive treatments (OR = 1.54, $p = 0.01$). This study suggests that in patients with migraine plus MOH and low medical needs, the occurrence of relapse seems to depend on a greater severity of baseline migraine. In the study by Hagen et al. [26], the reduction in monthly headache days was more pronounced in the individuals who had tried only one or no preventive medications before inclusion than in those who had tried two or more (6.1 vs. 1.3 days, $p = 0.02$).

In short, the main findings of the investigations addressing the long-term prognosis of MOH may be summarised as follows:

- the literature data are heterogeneous due to the use of different patient populations;
- relapse after withdrawal therapy is an important concern even in patients with simple MOH;
- TTH patients are more likely to relapse than those with migraine, probably due to the lack of effective TTH prophylactics;
- the majority of patients who relapse do so in the first year after withdrawal (many patients relapse within the first 6 months);
- the withdrawal therapy strategy [31, 33], the use of preventive treatment, the duration of migraine and the duration of drug overuse, as well as socio-demographic variables, have no impact on the outcome [31, 32, 39, 41], whereas discrepancies have emerged with regard to the influence, on MOH prognosis, of the type of drug overused;
- the role of additional factors, such as psychological and social ones, on MOH prognosis has not been adequately investigated;
- in MOH that has evolved from migraine as the primary headache, relapse seems to depend on a greater severity of migraine at baseline.

The fact that a large proportion of MOH patients are at risk of relapse after withdrawal provides an indication of the lack of effective strategies for preventing this outcome. Even though many authors are in favour of starting first-line preventive treatments as soon as possible [13, 14],

these treatments have no influence on the prognosis. It is generally agreed that behavioural and psychological factors could potentially influence the induction, maintenance and outcome of MOH [3, 4, 6, 7, 43]. Consequently, many authors consider the following to be essential aspects of long-term management of MOH (clinical experience-based recommendation):

- patient education (e.g. suggestions on how to improve self-management of attacks, information on maximal monthly dosages of symptomatic drugs, on what to expect from preventive treatments, etc.);
- continuous support in the first year after withdrawal (frequent follow-up visits, also involving, if necessary, patients' family);
- continuous monitoring by means of a headache diary, and behavioural therapies aiming to correct aberrant pain-coping strategies and psychological factors contributing to MOH [4, 13–15, 44, 45].

Currently, data on the effectiveness of these measures are limited. In a quasi-randomised controlled trial ($n = 61$) the addition of biofeedback-assisted relaxation therapy to preventive medication did not increase the success rate at 3 years and, though the patients in the combined group were less likely to relapse, this finding did not reach statistical significance when subjected to an intention-to-treat analysis [46]. Recently, in a very limited number of MOH patients ($n = 27$) having migraine as primary headache, it was shown at the 12-month follow-up that the decrease in headache frequency and medication intake was greater, and the relapse rate lower, in patients receiving psychoanalysis-based psychotherapy in addition to prophylactic treatment than in those receiving only pharmacotherapy [47]. Of course, these findings need to be confirmed in further randomised controlled studies enrolling a larger number of patients.

All these data highlight the urgent need for future research into effective relapse prevention strategies and strengthen the notion that the most practical strategy in MOH is to prevent medication overuse through education and early, appropriate headache prophylaxis in patients with high headache frequency.

Conclusions

Management of medication overuse can be very rewarding, but it is, in general, difficult. This is due to a number of inter-related factors. The first, as illustrated, is the lack of high-quality studies providing evidence-based answers to the various specific questions pertaining to the treatment of MOH, which is essentially based on drug withdrawal. MOH is not simply a highly frequent migraine or TTH and, consequently, efforts to treat MOH by applying the basic

principles of primary headache therapy are often unsuccessful. Second, the pathophysiological mechanisms underlying MOH are poorly understood. Indeed, MOH is an extremely heterogeneous disorder with regard to many factors, such as type of primary headache, genetic predisposition, pattern and severity, types of drug overused, psychiatric and physical comorbidities, socio-environmental pressures on individual patients and individual patients' past therapeutic experiences. As a result, there probably exists no single therapeutic strategy that is effective in every patient. Future studies should consider the heterogeneity of MOH, to promote the development of therapeutic strategies that can be tailored to the clinical peculiarities of every single patient. Finally, MOH is underestimated and, in some way, encouraged by those physicians who instruct patients with a high frequency of attacks to take the symptomatic drug as early as possible, thereby reinforcing a drug-centred pain-coping strategy that is very difficult to reverse.

Currently, the only reasonable strategy is to prevent the development of MOH by educating patients and providing them with adequate and accurate general information, drawing their attention to the information given in the instructions leaflets contained in the packages of all potential risk drugs and monitoring them closely. More specifically, targeted education and information programmes could effectively increase awareness of this largely underestimated clinical entity. Patients seeking treatment should be informed of the risks of overusing symptomatic headache drugs, the consumption of which should be restricted to a maximum prescribed monthly dosage. As a general rule, a preventive medication should be started when a patient regularly requires acute treatment on more than 2 days a week. Early initiation of headache prophylaxis, either a medical or a behavioural approach, is a powerful means of avoiding MOH. Headache drugs containing barbiturates, caffeine, codeine or sedatives, as well as mixed analgesics, are the worst offenders and should be avoided. The main problem is that these compounds are available as over-the-counter drugs and those who use them may not seek professional and more adequate treatment. International and national institutions should step up their efforts to spread the message that frequent use of acute attack medication constitutes misuse. Future longitudinal population-based studies will help us to identify the patients who are at risk of developing MOH and to adjust preventive strategies accordingly.

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Conflict of interest None.

Appendix

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