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EFNS GUIDELINES/CME ARTICLE

Treatment of medication overuse headache – guideline of the EFNS headache panel

S. Evers[a] and R. Jensen[b]

[a]*Department of Neurology, University of Münster, Münster, Germany; and* [b]*Danish Headache Center, Department of Neurology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark*

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Background: Medication overuse headache is a common condition with a population-based prevalence of more than 1–2%. Treatment is based on education, withdrawal treatment (detoxification), and prophylactic treatment. It also includes management of withdrawal headache.
Aims: This guideline aims to give treatment recommendations for this headache.
Materials and methods: Evaluation of the scientific literature.
Results: Abrupt withdrawal or tapering down of overused medication is recommended, the type of withdrawal therapy is probably not relevant for the outcome of the patient. However, inpatient withdrawal therapy is recommended for patients overusing opioids, benzodiazepine, or barbiturates. It is further recommended to start individualized prophylactic drug treatment at the first day of withdrawal therapy or even before. The only drug with moderate evidence for the prophylactic treatment in patients with chronic migraine and medication overuse is topiramate up to 200 mg. Corticosteroids (at least 60 mg prednisone or prednisolone) and amitriptyline (up to 50 mg) are possibly effective in the treatment of withdrawal symptoms. Patients after withdrawal therapy should be followed up regularly to prevent relapse of medication overuse.
Discussion and conclusion: Medication overuse headache can be treated according to evidence-based recommendations.

Objectives

This guideline aims to give recommendations for the treatment of medication overuse headache (MOH) as classified by the International Headache Society (IHS) [1]. Although this headache disorder is frequent and a major problem in the treatment of patients with chronic headache, placebo- or sham-controlled double-blind trials for a specific treatment of this condition are almost completely missing. Nearly, all published trials are underpowered or have a high number of dropouts. Therefore, these guidelines are based on publications with a low level of evidence and on expert consensus. A brief clinical description of this potentially preventable and treatable type of headache disorder is included.

Correspondence: Prof. S. Evers, MD PhD, Department of Neurology, University of Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany (tel.: +49 251 8348196; fax: +49 251 8348181; e-mail everss@uni-muenster.de).

This is a Continuing Medical Education article, and can be found with corresponding questions on the Internet at http://www.efns.org/EFNS Continuing-Medical-Education-online.301.0.html. Certificates for correctly answering the questions will be issued by the EFNS.

Background

The classification of the IHS provides diagnostic criteria for chronic headache which is accompanied by the overuse of acute headache drugs such as analgesics, triptans, and opioids (Table 1). In the first edition of the IHS classification, this headache disorder was defined as drug-induced headache implicating that the frequent drug intake itself is the cause of the headache [2]. In the present classification, medication overuse with all its somatic and psychological implications is regarded as an association and possibly not the only cause of chronic headache [1]. However, it has soon become obvious that some subtypes were missing and that headache features of MOH cannot be defined in general. Therefore, a revision of these diagnostic criteria was published in 2005 [3]. These criteria are valid until today although a further revision developed for research purposes has been published in 2006 [4].

The purpose of this article is to give recommendations for the specific management of MOH including the treatment of withdrawal headache. The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by the

Table 1 Current diagnostic criteria of the International Headache Society for medication overuse headache (MOH)

8.2 MOH
Diagnostic criteria
A. Headache[a] present on ≥15 days/month fulfilling criteria C and D
B. Regular overuse[b] for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[c]
C. Headache has developed or markedly worsened during medication overuse
D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication[d]
[a]The headache associated with medication overuse is variable and often has a peculiar pattern with characteristics shifting, even within the same day, from migraine like to those of tension-type headache.
[b]Overuse is defined in terms of duration and treatment days per week. What is crucial is that treatment occurs both frequently and regularly, i.e., on 2 or more days each week. Bunching of treatment days with long periods without medication intake, practised by some patients, is much less likely to cause MOH and does not fulfill criterion B.
[c]MOH can occur in headache-prone patients when acute headache medications are taken for other indications.
[d]A period of 2 months after cessation of overuse is stipulated in which improvement (resolution of headache, or reversion to its previous pattern) must occur if the diagnosis is to be definite. Prior to cessation, or pending improvement within 2 months after cessation, the diagnosis 8.2.8 Probable MOH should be applied. If such improvement does not then occur within 2 months, this diagnosis must be discarded.
Subtypes of MOH
8.2.1 Ergotamine-overuse headache
Ergotamine intake on ≥10 days/month on a regular basis for >3 months
8.2.2 Triptan-overuse headache
Triptan intake (any formulation) on ≥10 days/month on a regular basis for >3 months
8.2.3 Analgesic-overuse headache
Intake of simple analgesics on ≥15 days/month on a regular basis for >3 months
8.2.4 Opioid-overuse headache
Opioid intake on ≥10 days/month on a regular basis for >3 months
8.2.5 Combination analgesic-overuse headache
Intake of combination analgesic medications[a] on ≥10 days/month on a regular basis for >3 months
8.2.6 MOH attributed to the combination of acute medications
Intake of any combination of ergotamine, triptans, analgesics, and/or opioids on ≥10 days/month on a regular basis for >3 months without overuse of any single class alone[b]
8.2.7 Headache attributed to other medication overuse
Regular overuse[c] for >3 months of a medication other than those described earlier
8.2.8 Probable MOH
A. Headache fulfilling criteria A, C, and D for 8.2 MOH
B. Medication overuse fulfilling criterion B for any one of the subforms 8.2.1–82.7
C. One or other of the following:
1. Overused medication has not yet been withdrawn
2. Medication overuse has ceased within the last 2 months, but headache has not so far resolved or reverted to its previous pattern
[a]Combination typically implicated are those containing simple analgesics combined with opioids, butalbital, and/or caffeine.
[b]The specific subform(s) 8.2.1–8.2.5 should be diagnosed if criterion B is fulfilled in respect of any one or more single class(es) of these medications.
[c]The definition of overuse in terms of treatment days per week is probably to vary with the nature of the medication.

respective task force of the EFNS. The definitions of the recommendation levels follow the EFNS criteria [5].

Search strategy

A literature search was performed using the reference databases MedLine, Science Citation Index, and the Cochrane Library; the key words used were 'headache' together with the term 'medication overuse' or 'drug-induced' (last search in January 2011). All articles published in English, German, or French were considered when they described a controlled trial or a case report or series on the treatment of one of these headache disorders. In addition, a review book was considered [6].

Clinical aspects

The development of MOH is mainly reported in patients with a primary headache disorder such as migraine and tension-type headache but has also been reported in smaller series of secondary headaches [7–11]. For cluster headache, studies have been published showing that these patients can also fulfill the criteria for MOH [12,13]. However, most of these patients had migraine as a comorbid headache or mi-

graine in their family history, and many cluster patients with headache take analgesics, ergotamine derivatives, or triptans on a daily basis without MOH. Patients with other pain conditions such as rheumatic diseases and no headache disorder do not develop chronic headache de novo when taking analgesics because of their pain condition [14–17].

The population-based 1-year prevalence of MOH in different countries ranges from 0.7% to 1.7% with a female preponderance between 62% and 92% [18]. The incidence of MOH has not been studied in specific population-based studies. In a study on episodic migraineurs, the 1-year incidence of chronic headache including MOH was 14% [19]. Amongst all patients in headache clinics or centers of tertiary care, patients with MOH are one of the largest patient group. In Europe up to 30% and in the USA even more than 50% of the patients in such centers present with MOH [18,20]. In India, for example, only 3.1% of the patients in a headache clinic fulfill the criteria for MOH [21].

In principle, all acute drugs for the treatment of headache have been described to cause MOH (i.e., ergotamine derivatives, barbiturates, triptans, analgesics both simple and combined, opioids, benzodiazepines; possibly also caffeine). Today, simple analgesics and triptans are the most frequent drugs taken by patients with MOH [20,22].

Withdrawal treatment

There is evidence, although not overwhelming and unanimously shown in prospective trials, that withdrawal therapy is the best treatment for MOH. However, all experts and headache centers agree that withdrawal therapy should be offered to patients with MOH. The goal of this treatment is not only to detoxify the patients and to stop the chronic headache but also, probably, to improve responsiveness to acute or prophylactic drugs [23].

Withdrawal procedure

The recommended procedures for withdrawal of patients with MOH vary, and no study has compared abrupt withdrawal treatment with tapered withdrawal in prospective randomized trials. Most headache specialists favor the abrupt discontinuation of pain medication under the impression that abrupt withdrawal is associated with faster resolution of the drug-induced pain-coping behavior [24]. However, tapered withdrawal seems to be recommendable for opioids, for barbiturates, and for benzodiazepines. Main withdrawal symptoms are worsening of the headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. These symptoms normally last between 2 and 10 days but can persist for up to 4 weeks. The withdrawal headache was shorter in patients having taken triptans (mean 4.1 days) than ergotamine derivatives (mean 6.7 days) or NSAIDs (mean 9.5 days) [25].

The outcome of withdrawal therapy in patients with MOH followed up by a neurologist as compared to a primary care physician did not differ significantly for calculated mean headache and improvement of headache days [26]. Therefore, it is suggested that a primary care physician can follow these patients after detoxification, which was made in this study in hospital, as well as a neurologist or a pain specialist.

With regard to non-pharmacological approaches of treating MOH, combined short-term psychodynamic psychotherapy and pharmacological therapy improved headache in MOH, and the combination of both had been superior to pharmacological therapy alone for reducing long-term relapses and reduction in quality of life in a non-randomized study [27]. In another study, 120 uncomplicated patients with MOH were treated with three different modalities: (i) only strong advice to withdraw overused medication; (ii) standard outpatient detoxification programme (rapid withdrawal of overused medication plus oral prednisolone for 8 days plus personalized prophylactive drugs); (iii) inpatient programme (rapid withdrawal of overused medication plus oral prednisolone for 8 days plus personalized prophylactive drugs plus parenteral fluid and antiemetics plus close observation for 8 days). The percentages of patients achieving successful withdrawal and the headache frequency were not different between the groups during the follow-up period of 60 days after withdrawal [28].

A direct comparison between inpatient withdrawal and outpatient withdrawal treatment showed that both methods revealed a significant decrease in headache days per month after 12 months and a reduction in the scores of migraine disability without superiority of one method [29]. Following this study, the outpatient withdrawal is less expensive and as successful in a motivated patient group than inpatient withdrawal. Advantages of the inpatient withdrawal are the close monitoring of medication intake and the clinical state, professional psychological support, an immediate treatment of withdrawal symptoms, and eventually the administration of intravenous drugs. Overusing opioids, barbiturates, or benzodiazepines, psychological problems, severe medical comorbidities, severe withdrawal symptoms (e.g., vomiting, status migrainosus), or previous medication withdrawal failure are reasons for inpatient treatment according to expert consensus or national

guidelines [30–32]. However, this recommendation is not supported by randomized prospective trials.

A recent prospective, multicenter study investigated three relatively small groups: (i) only personalized preventive medication from day 1 ($n = 17$); (ii) abrupt withdrawal plus rescue medication ($n = 20$); (iii) no preventive medication plus no advice to stop overused drugs ($n = 19$) [33]. The primary end-point, change in headache days, did, however, not differ significantly between all three groups. Because of the more pronounced reduction in the headache index of the first group in comparison with the second group, there might be an advantage for a personalized preventive medication without abrupt withdrawal. In another study, advice alone was successful as withdrawal therapy in nearly all patients with simple MOH but significantly less successful in patients with complicated MOH [34]. Further larger, prospective trials are necessary to answer these questions.

Studies on a specific preventive therapy of MOH are missing. Therefore, the choice of the preventive agent in MOH should be based on the primary headache (e.g., migraine vs. tension-type headache), the possible side effects of the drugs, the comorbidities, and the patient's preference and previous therapeutic experience. Several open-label trials showed positive effects of different substances such as valproic acid and topiramate in the prophylactic treatment of chronic daily headache with excessive medication intake. A double-blind trial in patients with the specific diagnosis of chronic migraine and medication overuse showed a significant reduction in the mean number of migraine days per month by topiramate (range 50–200 mg/day) in comparison with placebo (-3.5 ± 6.3 vs. -0.2 ± 4.7; $P < 0.05$). However, side effects were reported by 75% of the patients in the topiramate group compared with 37% in the placebo group [35]. The headache reduction was nevertheless not big enough to change the chronic headache into an episodic form. In a similar study on chronic migraine, topiramate achieved a significant reduction in migrainous days per month by 6.4 as compared to placebo which achieved a reduction by 4.7 days/month [36].

In a large-scale study of 335 patients with MOH from the Danish Headache centre, where abrupt detoxification was initiated, the headache frequency was reduced by 67% in migraine patients and by 37% in those with combined migraine and tension-type headache after a 2-month observation period without prophylactic medication [37]. In a recent project with two large studies on the efficacy of onabotulinum toxin A in the treatment of chronic migraine, also patients with medication overuse were treated [38]. Although no specific data on the efficacy of onabotulinum toxin in this specific group of patients (between 63% and 69% of all patients in the different treatment arms) is given, the studies give evidence that onabotulinum toxin A is efficacious in the reduction of headache days in MOH. In summary, it is suggested that detoxification prior to initiating prophylactic therapy may not be required in all patients with MOH [39], whereas other studies support the importance of initial detoxification [20,23,37].

Treatment of withdrawal headache

Because most drugs helpful for the treatment of withdrawal headache can cause MOH themselves, corticosteroids were regarded as an option for the treatment of withdrawal headache [40,41]. The only controlled, randomized, double-blind study that investigated oral prednisolone during the first 6 days after medication withdrawal revealed no effect on a combined primary end-point. Of total 97 patients, 49 received prednisolone (60 mg on days 1 and 2, 40 mg on days 3 and 4, and 20 mg on days 5 and 6) and 48 placebo [42]. Conversely, a large open-label trial on patients with chronic daily headache and medication overuse showed that treatment with 60 mg prednisone for 2 days and tapering down by 20 mg every other day effectively reduced rebound headache and withdrawal symptoms [43]. Recently, in a small proof-of-concept study, nine patients each with MOH received either placebo or 100 mg prednisone for 5 days [44]. The duration of withdrawal headache was significantly lower in the prednisone group as compared to the placebo group. Taken these results together, there might be an efficacy of corticosteroids on withdrawal symptoms in patients with MOH but high-quality placebo-controlled trials are needed.

There are no other controlled trials on the specific treatment of withdrawal headache or of other symptoms during withdrawal therapy. One open study suggested the combination of intravenous hydration, dexamethasone, metoclopramide, and benzodiazepines for 7–15 days [41]. Very early studies suggested that also (subcutaneous) sumatriptan, naproxen (500 mg), and amitriptyline (10–50 mg) were effective in ameliorating withdrawal headache [40,45,46]. However, all these studies were not placebo controlled. Therefore, by expert consensus, headache drugs and analgesics are not recommended for the treatment of headache during withdrawal therapy except single intravenous administrations in very severe cases.

Prognosis of withdrawal therapy

The relapse rate of MOH is about 30% (range between 14% and 41%) after 1 year regardless whether inpa-

Table 2 Recommendations for the treatment of medication overuse headache (MOH). The level of recommendation is classified as follows

Level A: established as effective, ineffective, or harmful by at least one convincing class I study or at least two consistent, convincing class II studies
Level B: probably effective, ineffective, or harmful by at least one convincing class II study or overwhelming class III evidence
Level C: possibly effective, ineffective, or harmful by at least two convincing class III studies
Good practice point: lack of evidence but consensus within the task force

1) Patients with MOH should be offered advice and teaching to encourage withdrawal treatment. (B)
2) There is no general evidence whether abrupt or tapering withdrawal treatment should be preferred. For the overuse of analgesics, ergotamine derivatives, or triptans, abrupt withdrawal is recommended. For the overuse of opioids, benzodiazepines, or barbiturates, tapering down of the medication should be offered. (good practice point)
3) The type of withdrawal treatment (inpatient, outpatient, advice alone) does not influence the success of the treatment and the relapse rate in general. (A)
4) In patients with opioid, benzodiazepine, or barbiturate overuse, with severe psychiatric or medical comorbidity or with failure of a previous outpatient withdrawal treatment, inpatient withdrawal treatment should be offered. (good practice point)
5) Individualized preventive medication should be started at the first day of withdrawal treatment or even before if applicable. (C)
6) Topiramate 100 mg (up to 200 mg maximum) per day is probably effective in the treatment of MOH. (B)
7) Corticosteroids (at least 60 mg prednisone or prednisolone) and amitriptyline (up to 50 mg) are possibly effective in the treatment of withdrawal symptoms. (good practice point)
8) Patients after withdrawal therapy should be followed up regularly to prevent relapse of medication overuse. (good practice point)

tient, outpatient, or advice alone treatment were applied [18]. Further, the relapse rates do not differ significantly when a short or a long observation period is used, and most studies indicate that the eventual relapse occurs at an early stage (i.e., within few months) after detoxification. In one study, for example, the relapse rate was 23% both after 2 months and after 1 year in the same sample; [47] in another example, the relapse rate was 41% after 1 year and 44% after 4 years [48]. Overall, the detoxification is fairly successful in most patients, and all patients with MOH should be informed and encouraged to discontinue their overuse. In the general population, simple advice regarding MOH was sufficient to result in a successful treatment of MOH in 76% of all patients after 1.5 years [49].

In an Italian study on different ways of withdrawal therapy, a long duration of migraine before medication overuse, a higher frequency of migraine after withdrawal therapy, and a greater number of previous preventive treatments were associated with a higher risk for relapse of MOH [50]. In other studies, predictors of relapse were male sex, intake of combination analgesics after withdrawal therapy, nicotine and alcohol consumption, and taking the former medication again after withdrawal therapy [51,52]. Recently, use of codeine-containing drugs, low self-reported sleep quality, and high self-reported bodily pain as measured by the quality of life tool SF-36 were predictors for a poor outcome [53]. In some studies, the prognosis was better for patients with migraine as the underlying primary headache disorder than for patients with tension-type headache and for ergotamine or triptan withdrawal than for analgesic withdrawal [37,48]. It is likely that the different results in these studies with respect to predictors of relapse are because of different study designs and different background populations.

Specific pattern in children and adolescents

Several studies showed that MOH also exists in children and adolescents [18]. Population-based epidemiological studies detected a 1-year prevalence of 0.3–0.5% in adolescents all of them overusing over the counter (OTC) analgesics (mainly combined analgesics) [54,55].

Children also benefit from withdrawal therapy [56]. However, only very few data are available on the best treatment in this age group. One month after withdrawal therapy, about 53% of all children had a reduction in headache frequency by more than 90% regardless whether they were on preventive medication or not; the only predictor for a poor outcome after withdrawal therapy was a duration of MOH longer than 2 years [57].

Conclusion

As described earlier, only very few controlled and/or randomized trials are available to give evidence-based recommendations for the treatment of MOH. Therefore, the conclusions of this guideline are of low evidence or are good practice points as agreed by expert consensus. A summary of our clinical recommendations are presented in Table 2.

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