

Headache with medication overuse: treatment strategies and proposals of relapse prevention

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Abstract The diagnosis of medication overuse headache (MOH) is clinically important, because patients rarely respond to preventive medications whilst overusing acute medications. Properly treating medication overuse and preventing relapse require recognition of the different factors that contribute to its development and perpetuation, including some behaviours and psychological elements that are important in sustaining the overuse of medication. This article reviews current clinical experiences of MOH patients treated with different approaches. Moreover, initial outcomes and long-term durability of treatments are discussed.

Keywords Medication overuse headache · Withdrawal strategies · Pharmacological treatment · Behavioural therapies

Definition and diagnosis

Medication overuse headache (MOH) is the result of an interaction between excessive use of a therapeutic agent and a susceptible patient, and leads to considerable disability prior to treatment. In particular, medication overuse is often an exacerbating factor for migraine, which becomes chronic with a frequency of at least 15 days/month.

The proper diagnosis of this form of headache was disputed until the International Headache Society (IHS) committee published the new criteria for the classification of chronic migraine (CM) and MOH in 2004 [1]. Moreover, there are few investigations examining the natural course of these forms of headache.

Originally MOH was considered the “drug-induced headache” by the IHS in 1988 [2]. In order to emphasise the regular intake of drugs as the origin of this clinical form of headache, the IHS in 2004 introduced a new term, “medication overuse headache” and extended the definition to apply to different clinical symptoms induced by different drugs. Two Authors of the present article have previously published a review of this topic [3]. The present paper expands and updates the data reviewed there.

The diagnosis of MOH is based on the following criteria:

- A. Headache is present for 15 or more days per month fulfilling criteria C and D
- B. Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache (10 or more days per month for ergotamines, triptans, opioids or combination analgesics; 15 or more days per month for simple analgesics)
- C. Headache has developed or markedly worsened during medication overuse
- D. Headache resolves or reverts to its previous pattern

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within 2 months after discontinuation of overused medication

It is difficult to make a definitive diagnosis of MOH, as it is impossible to be sure of the diagnosis until a successful withdrawal has been completed. After withdrawal is completed, the diagnostician can then separate MOH from other headache disorders, such as CM or chronic tension-type headache (CTTH). On the other hand, it has been noted that not all patients with frequent headache overuse their acute medications, but if it happens, the diagnosis of MOH is clinically important, because patients rarely respond to preventive medications whilst overusing acute medications [4].

A general medical/neurological history and a detailed history of drug intake and intake frequency are the main methods for a correct diagnosis. A daily headache diary is always important for monitoring the precise drug intake, identifying the extent of overuse and arriving at an accurate diagnosis.

Epidemiological and clinical aspects

The prevalence of chronic headache associated with medication overuse is about 1% [5, 6]. It has been noted that the overuse of analgesics and chronic headache is not only prevalent in Europe and North America but also in Asian countries [7]. Moreover clinical evidence shows that overuse associated to chronic forms of headache can occur in childhood and early adolescence [8].

A potential problem for the development of this form of headache arises from the recommendations that drugs have to be taken as early as possible in migraine. This approach, although correct for specific medications like triptans, increases the risk that patients will take more of the drug than is necessary, thus increasing the risk of inducing medication overuse. Medication overuse is a major health problem all over the world, considering the potential secondary effects of chronic drug overuse on different organ systems (kidney, liver, etc.), so education about medication overuse is necessary for healthcare providers who treat patients suffering from headache.

Although the IHS classification offers explicit criteria, the diagnosis of MOH does not require any specific examination (examination is needed only to exclude a symptomatic origin of chronic headache). Several clinical characteristics may be helpful in identifying MOH in patients with primary headaches of this type. The headache is daily or nearly daily, and the headache may change in intensity, type and location from time to time. A patient's intake of symptomatic medication is daily or nearly daily and concomitant prophylactic treatment is typically ineffective while patients are taking excessive amounts of symptomatic medications [9].

Medication overuse may induce the onset of specific symptoms. For example, the symptoms arising from the

overuse of ergotamine are: cold extremities, tachycardia, hypertension and muscle pain in the extremities. These symptoms disappear after withdrawal therapy. Many, but not all, of these symptoms are observed with triptan overuse. For example, with triptans an increase of blood pressure values is often recorded and this disappears after triptans are withdrawn. It is not uncommon to note associated symptoms characterised by physical symptoms, such as asthenia, nausea and gastrointestinal problems, and also mental disturbances, such as anxiety, depression irritability and difficulty in concentration [9]. All of these symptoms may reveal a possible concomitant problem of comorbidity so it is often necessary to treat these patients by considering the psychological components. Psychiatric comorbidity is a significant moderator of treatment outcome and can be a prognostic indicator for some pharmacologic and behavioural treatments [10].

Psychological aspects and the disability problem

There is emerging evidence that a number of behavioural/psychological risk factors are associated with progression of headache from episodic to chronic, and that psychological distress may play an even greater role in the transformation and chronification of headache than does analgesic overuse or abuse [10–13]. Although large-scale, long-term studies are necessary to better understand the role and the influence of comorbid psychopathology on migraine history, it has been noted that psychiatric comorbidity is often an important factor in the transformation of episodic headache and a negative prognostic indicator for headache treatment [10, 14]. The identification of these psychological variables is a key component for establishing an adequate treatment regimen for patients suffering from MOH.

Previous studies reported [15] that family history data uncovered an elevated risk of mood disorders and substance use disorders (alcohol, drugs) in the families of MOH patients. MOH could be the result in part of a broad family-based vulnerability to addiction that increases the risk of abuse of acute migraine drugs and analgesics. The term addiction is used not referring to antisocial behaviour, but rather drug-dependent behaviour characterised by a lack of control and by its expression despite the patients' awareness of the negative consequences [15].

Further, until recently, no prospective reports had been published about the impact of this condition on ability to function subsequent to withdrawal treatment followed by appropriate prophylaxis [16, 17]. Mathew et al., in 2002 [18], noted a significant improvement in disability upon treating a number of patients with "transformed headache" by adjunctive use of topiramate. Grazi and colleagues [19] noted a significant improvement of functional impact assessed by the Migraine Disability

Assessment questionnaire (MIDAS) (disability score reduction >50% at one-year follow-up) [20, 21] in a group of CM patients treated with an in-patient withdrawal programme for analgesic overuse, followed by prophylaxis. The improvement was confirmed at one-year follow-up. Because of the potential high social and economic impact of this condition it is important to collect information beyond clinical aspects, such as disability, quality of life and psychological functioning [22]. This information can also be of value in developing more specific treatment strategies.

Treatment strategies

Patients with chronic headache and medication overuse are particularly difficult to treat. No clear consensus exists on treatment strategies to be used and few data exist about the functional impact of headache in these patients [4, 23].

Although several treatment studies have been published on chronic headache and medication overuse [9], it is difficult to make comparative statements about the studies. The main reason is because different diagnostic criteria have been used, leading to heterogeneous groups.

Sometimes patients refuse to reveal their true drug consumption, but it is important to explain to them the concept of MOH and how it develops [10].

Patients often use medication to avoid a disabling withdrawal headache or they may overuse other substances, such as tranquillisers, or medication prescribed for other conditions, all of which can contribute to MOH [24–26].

The therapeutic programme at the Neurological Institute Besta in Milan consists of:

- explaining to the patients the entity of the problem;
- selecting with the patients the best solution for the withdrawal therapy, according to his or her characteristics, motivation to stop analgesics and compliance;
- encouraging and supporting the patients towards the goals, from the beginning to the end of the therapeutic programme.

Explaining to the patients the entity of the problem

The first step is to ask the patients directly about the frequency and quantity of abortive or analgesic use. It is helpful to inquire about use patterns in a nonjudgemental tone of voice, and rephrase the same question two or three times. Sometimes it is helpful to interview other family members who can help to identify problems minimised by the patients. It is necessary that the patients realise perfectly and know the real consequences of this overuse behaviour in the sense of increase of headache episodes and risk of important side effects for organic tis-

sues. After this important step we can proceed to discussion of the first phase of the therapeutical programme.

In our opinion withdrawal from analgesics is essential and can be done with different modalities according to the personality of patients, and their general physical and psychological characteristics.

Selecting with the patients the best solution for the withdrawal therapy

Abrupt drug withdrawal seems to be the most appropriate first step in managing MOH. The necessity of withdrawal for chronic patients has been confirmed in a recent study where a comparison of the outcome between two groups of patients suffering from MOH was conducted: the first group was treated by inpatient withdrawal, while the second group did not receive any treatment to stop the overuse. In the first group the percentage of patients whose chronic headaches became less frequent or episodic after one year was 70.7% and in the second group was 15.3% [27, 28].

A survey of 22 studies dealing with therapy of drug-induced headache shows that most centres use drug withdrawal as the primary therapy [29]. The typical withdrawal symptoms last 2–10 days (mean 3–5 days) and include withdrawal headache, nausea, vomiting, hypotension, tachycardia, sleep disturbances, anxiety and rebound headache. Seizures or hallucinations, although rare, are observed in patients who overuse barbiturates containing anti-migraine drugs. Patients often show signs of physical and emotional dependence and some form of psychological involvement. Moreover, sustained improvement following treatment can be difficult to achieve and at the moment there is no consensus on what approach is most effective [29–32].

There are different drug withdrawal strategies. In particular, in-patient withdrawal seems the most helpful. Inpatient therapy should be performed in patients who take barbiturates, those who are not able to stop taking medications as outpatients or those with high levels of depression [4]. Treatments for the acute phase of drug withdrawal vary considerably between studies. They generally include fluid replacement, analgesics when strictly necessary for severe rebound headache, tranquillisers, sometimes neuroleptics and steroids. Steroids effectively reduce withdrawal symptoms, including rebound headache [19, 33].

In the hospital all pain killer medications are stopped abruptly. Fluids should be replaced by infusion if vomiting occurs frequently. Vomiting can be treated by an antiemetic, such as metoclopramide [19].

In some cases, intravenous dihydroergotamine has been used when the headache has migraine characteristics and if the patient has never used ergots previously [34]. Analgesics, such as naprosen and ASA, have been used dur-

ing the withdrawal phase [35], or steroids, as already mentioned [33]. Some cases have been treated by subcutaneous sumatriptan [36] and some patients require anxiolytics.

Other clinical experiences support the hypothesis that an outpatient treatment can be helpful in patients who are highly motivated and who do not take barbiturates [4, 37–39].

Outpatient treatment is a viable alternative for self-disciplined patients who take a single drug or analgesic not containing barbiturates, and who do not have a high level of depression or anxiety [36, 37].

Another helpful alternative can be performing drug withdrawal infusion therapy within a day hospital setting [40, 41]. This approach, which is most effective in patients who are highly motivated and self-disciplined, gives patients the possibility to stay in the hospital for at least 6 h during the infusion therapy, and to stay at home for the last part of the day and during the night (or at a local motel). In this case too, instructions have to be clear so that the patients avoid using medications for the rebound headache during the time they spend at home. Pini et al. showed encouraging results, but the follow-up period was too short (4 months) to make definitive conclusions [40]. More encouraging results were noted in our clinical experience after 1 and 2 years' follow-up from withdrawal performed in the Day Hospital setting: the patients regularly followed the therapeutic sessions and the clinical results were significant at 1 and 2 years' follow-up. Unfortunately the group of patients is too limited to draw definitive conclusions [41].

After the acute phase of the withdrawal therapy is completed, a prophylaxis for migraine or tension-type headache can be started, and it is necessary to follow the patients for an extended time with specific therapies to avoid the risk of relapsing to former medication overuse [19].

Physical and psychological characteristics of the individual and comorbid situations that are present (hypertension, depression, anxiety, tachycardia, sleep disturbances, obesity and so on) need consideration when designing treatment [4, 19].

Encouraging and supporting the patients

Proper instructions, careful education and appropriate surveillance are necessary in order to avoid relapse. In particular, patients who suffer from migraine and tension-type headache have to be instructed to use antimigraine agents only for a migraine attack. Adequate time has to be dedicated to encourage patients to follow the instructions carefully in order to obtain the best clinical results from the withdrawal and the subsequent prophylactic therapy. The headache diary is important to record attacks and medications consumed. Also several follow-up appointments at regular intervals are necessary to monitor the clinical course [19].

Most patients need to be supported and encouraged by the physician, nurses, allied health care providers and family members to follow the instructions carefully to stop the vicious cycle between medication overuse and headache increase in order to be effectively treated by prophylactic agents for migraine.

The possibility of using behavioural approaches can be considered, as these treatments are very helpful for patients and some encouraging results have been obtained during follow-up in terms of avoiding relapses in medication overuse [42]. Behavioural techniques, such as relaxation therapies and stress management, should be started as soon as possible after the acute withdrawal phase to increase the efficacy of any prophylaxis and to encourage and teach patients to manage the pain and the stressful events which often induce or increase the migraine episodes [43]. Grazi et al. have shown that the addition of behavioural treatment can enhance outcome over drug treatment alone, with respect to both symptom reduction and relapse prevention [42]. Behavioural treatments do not necessarily provide the immediacy of headache reduction, however patients undergoing biofeedback or behavioural therapy often learn to restructure their cognitive approach to pain, in essence learning how to tolerate discomfort, reduce pain-related emotional distress, stop the overly frequent pharmacological treatment and reduce the escalation to the pain experience. If learned and maintained over time, this behaviour can help reduce the likelihood of overusing pain medication and MOH relapse [15].

Concluding remarks

Criteria for determining success of withdrawal therapy have varied across studies. It has been suggested that success can be defined as no headache at all or an improvement of more than 50% in terms of headache days [4].

In the outcome studies that have been completed, follow-up intervals have varied considerably [19, 23, 37, 38, 40, 44].

Several studies have reported outcomes for periods of 12 months or less. Lake et al. [44] and Grazi et al. [42] showed clinically significant results after inpatient treatment at 8 and 12 months' follow-up respectively and also after 3 years' follow-up [28].

All of these studies show that this category of patients requires intensive treatment and careful analysis of their clinical condition. On the other hand, the follow-up periods have been fairly brief for adequately assessing the risk of relapse and new chronicisation. The treatment can be considered successful when clinical improvement is confirmed after at least 1 year of follow-up after withdrawal [4].

Recently other authors have been able to conduct studies with longer-term follow-up in order to provide a more thorough analysis of relapse and clinical course [28].

Findings observed from recent studies suggest that patients have greatest risk for relapse within the first 12

Table 1 Studies published in the last decades on treatment for MOH with their follow-up (longest follow-up interval)

Authors	Year	Tr	Follow-up (months)	% improvement
Baumgartner	89	inpt	12	61
Diener	89	inpt	35	67
Silberstein	92	inpt	24	87
Lake	93	inpt	8	50
Pini	96	DH/outpt	4	60
Schneider	96	inpt	60	50, <8 days/month
Monzon	98	inpt	12	57
Grazzi	02	inpt	36	58–69
Grazzi	04	inpt	12	59
Andrasik	07	inpt	36	59.8
Zidverc-Trajkovic	07	inpt/outpt	12	8.6

months but have a decreased risk of relapse when they have avoided medication overuse for 12 months after withdrawal therapy [28] (see Table 1 for a summary of results for these long-term follow-up studies).

A meta-analysis has been performed on 27 papers or abstracts on treatment for different forms of chronic headache [23]. Thirteen studies in particular concerned chronic daily headache and medication overuse. The authors point out a difficulty with the meta-analysis because of the different methodologies employed, but the results are encouraging, with a high percentage of clinical success after inpatient treatment.

Although the findings concerning the clinical results after withdrawal are highly encouraging, with a long follow-up period, they are by no means definitive. The major limitation is the absence of a control or comparison condition. On the basis of these reports, comparative outcome investigations, incorporating appropriate control and/or comparison conditions, appear warranted. Further it may prove fruitful to compare different treatment approaches (inpatient vs. outpatient, pharmacological alone vs. pharmacological augmented by behavioural and related procedures) [45] and examine whether response is related to the type of medication overused and also to determine if there are categories of medication that when overused make patients more susceptible to CM. Future studies need to incorporate improved methodologies in order to provide firmer conclusions about patient treatment interactions.

Sommario La diagnosi di Medication-Overuse Headache è impegnativa e presenta implicazioni clinico-terapeutiche importanti poiché questa categoria di pazienti difficilmente risponde alle terapie di profilassi comunemente usate nei pazienti emicranici. Un trattamento adeguato ed una attenta prevenzione delle recidive di abuso richiedono una valutazione dei diversi fattori di rischio che contribuiscono allo sviluppo e alla degenerazione delle forme emicraniche episodiche in forme croniche. Anche i fattori psicologici e comportamentali sono riconosciuti come determinanti per la induzione del “Medication-Overuse”. In questo lavoro vengono descritte diverse esperienze cli-

niche condotte in pazienti affette da forme emicraniche cronicizzate e Medication-Overuse; sono descritti i diversi approcci terapeutici e le possibili strategie terapeutiche a partire dalla “disassuefazione” da sintomatici alla impostazione di una eventuale profilassi. Sono inoltre menzionati e discussi i risultati derivanti dalle diverse esperienze cliniche con relativi follow-up.

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