

From drug-induced headache to medication overuse headache. A short epidemiological review, with a focus on Latin American countries

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Abstract Medication overuse headache (MOH) is a daily or almost-daily type of headache that results from the chronicization, usually migraine or tension-type headache, as a consequence of the progressive increase of intake of symptomatic drugs. MOH is now the third most frequent type of headache and affects a percentage of 1–1.4% of the general population. The currently available data on the impact of chronic headache associated with analgesic overuse in specialist headache centres confirm, beyond doubt, the existence of a serious health problem. Limited amount of data exists on the burden and impact of MOH in

Latin American Countries. In this review, we summarise the reliable information from the literature on the epidemiological impact of MOH.

Keywords Drug-induced headache · Medication overuse headache · Epidemiological impact · Prevalence · Latin American countries

Introduction

Inappropriate use of acute headache medications by patients with frequent migraine or tension-type headache may contribute to the development of a chronic, daily (or almost daily) headache that is induced and maintained by the use of the painkilling drugs. This very aggressive and disabling type of headache, now labelled medication overuse headache (MOH), is a largely under-diagnosed health condition, although it may affect 1–1.4% of the general population [1–6].

The clinical complexity of MOH, formerly known by other names—such as drug-induced headache, painkiller headache, transformed migraine—or included in the group of chronic daily headache (CDH) [7], has probably contributed to difficulties in defining precise and widely accepted diagnostic criteria for the condition. Indeed, over the years different sets of diagnostic criteria have been proposed and the experts in the field have only recently reached a general consensus, which will probably favour the acquisition of the necessary information on this disabling disorder.

In this short paper, we discuss relevant epidemiological data available on MOH, focusing on the information regarding this condition in Latin American (LA) countries, as a preparatory initiative to a project funded by the

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Methods: search strategy and selection criteria

Data used for this review were extracted from the authors' files and completed with data obtained from scientific databases (i.e., PubMed or EMBASE) using the search terms “medication overuse headache”, “drug-induced headache” or “chronic daily headache”. Articles and citations were selected on the basis of their scientific validity, historical value, importance, relevance, and ease of access. All indexed papers in English, German and Spanish were included.

More than 140 articles in the above languages, published in the past three decades in indexed journals were identified. Of these, nearly 50 were included in the evaluation. Articles were excluded if they were not considered representative of the problem (single case reports, personal opinions of single researchers, MOH was not the main topic, etc.) or did not add important information or, again, had been already analysed in reviews included in this report.

MOH: the history

The clinical features of drug-induced headache were first described in 1951 in relation to excessively frequent or daily use of ergotamine [8]. Subsequently, the same authors described improvement after ergotamine withdrawal in 52 patients who had developed daily headache following daily intake of ergotamine [9]. As from 1970s, drug-induced headache was also described in patients using analgesics and other compounds [10]. There is now substantial evidence that all drugs used for the treatment of headache can cause MOH in patients with primary headache disorders [10]. The pattern of use of the drugs that can lead to MOH varies substantially from country to country and is influenced by cultural factors. In many patients, it is difficult to identify a single causal substance, since 90% of patients take more than one compound at a time and each of the single drug may, in theory, induce headache.

Many terms have been used to describe MOH; in 1988 the condition was defined “drug-induced headache” by the International Headache Society [11]. This term, however, was criticized since several drugs, other than painkillers, can cause headache, even after a single dose, (nitrates, for example). In addition, it has been questioned whether

headache can be primarily drug-induced [12]. Therefore, the headache associated with the use of symptomatic drugs was classified under the heading “Headache induced by chronic substance use or exposure”—to distinguish it from the group of headaches induced by the acute use of drugs—and included only two subtypes: headache induced by ergotamine and headache associated with analgesics. Studies conducted in the subsequent years, along with availability of new symptomatic drugs, suggested the need for a further revision of both the name and the diagnostic criteria [13–15]. In 2004, the term “medication overuse headache” was finally introduced into the second edition of the International Headache Society's Classification (International Classification of Headache Disorders—II edition, ICHD-II), also with the aim of emphasising excessive drug intake as the basis of this form of headache [16]. In ICHD-II, MOH is classified amongst the secondary headache, within group 8: “Headache Attributed to a Substance or its Withdrawal”. Together, the 2004 classification [16] and the two subsequent revisions of the diagnostic criteria for MOH [17, 18] refine and extend the definition of this condition on the basis of both its chronicity (headache on more than 15 days/month for more than three months) and the different types of drugs overused, thereby identifying main types of MOH. In the case of ergotamine, triptans, opioids and combination medications in particular, intake on ≥ 10 days/month for >3 months is required, whereas simple analgesics are considered overused when they are taken on ≥ 15 days/month for >3 months (Table 1).

The epidemiological impact

MOH is a largely under-diagnosed health condition, but its prevalence is increasing worldwide. Indeed, it is now the third most frequent type of headache [10, 19].

According to epidemiological surveys performed in the '80s, between 1 and 3% of the general population take analgesics on a daily basis, and up to 7% take them at least once a week [20, 21]. Cross-sectional, population-based and epidemiological studies in Europe and Asia indicate that the prevalence of chronic headache associated with medication overuse is about 1–1.4% in the general population [1–6], with the prevalence peaking in women in their 50s. In this age range, indeed, 5% of women meet the diagnostic criteria for MOH [3, 22]. A meta-analysis of 29 studies involving 2,612 patients with chronic headache and analgesic overuse [23] confirmed the females predominance (F/M ratio: 3.5/1) and reported, in these patients, the simultaneous use of an average of between 2.5 and 5.8 (range 1–14) different pharmacological agents. The mean duration of primary headache at the time of diagnosis was 20.4 years, the mean duration of drug overuse was

Table 1 Medication overuse headache: its subtypes and diagnostic criteria [16–18]

8.2 Medication overuse headache (Previously used terms: rebound headache, drug-induced headache, medication-misuse headache)
Subtypes
8.2.1 Ergotamine overuse headache
8.2.2 Triptan-overuse headache
8.2.3 Analgesic overuse headache
8.2.4 Opioid overuse headache
8.2.5 Combination analgesic overuse headache
8.2.6 Medication overuse headache attributed to combination of acute medications
8.2.7 Headache attributed to other medication overuse
8.2.8 Probable medication overuse headache
Diagnostic criteria:
A Headache present on >15 days/month fulfilling criteria C and D ^a
B Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache.
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 ^a

^a Removed in latest revision [18]

10.3 years, and the mean duration of daily headache (>15 days per month) was 5.9 years.

It is worth noting that the vast majority of these epidemiological studies investigated chronic headache following the overuse of analgesics or ergots diagnosed according to the International Headache Society's 1988 criteria [11] and, in part, the revised criteria of Silberstein et al. [15, 24]. Therefore, data from these studies must be interpreted cautiously, since they were conducted prior to the development of the ICHD-II criteria, and it is not possible to ascertain whether all the cases described really were MOH (improvement within 2 months of discontinuation of the overused medication now being required for a definite diagnosis of MOH).

The situation will probably become clearer over the next years as a result of application of the International Headache Classification diagnostic criteria published in 2004 and alternative framing of data on the basis of the "new appendix criteria" for the diagnosis of MOH, which, proposed for research purposes, no longer require the headache to improve after withdrawal [18].

Having outlined these premises, the currently available data on the impact of chronic headache associated with analgesic overuse in specialist headache centres confirm, beyond doubt, the existence of a serious health problem. In US specialist headache clinics, 60–80% of patients who presented with CDH used analgesics on a daily or near-daily basis [25–27]. More recently, a retrospective study conducted in a large, tertiary care headache centre in the United States (US) showed that the relative frequency of probable MOH in this setting had remained remarkably stable over the past 15 years [28], varying from 64% of all cases seen in the centre in 1990 to 59.3% in 2005. At

variance with these findings, in European headache centres, only 5–10% of patients presented with drug-induced headache [29–31]. MOH may also be a high-impact disease in general practice, as suggested by the results of a survey of 174 general practitioners in the US, which showed that chronic headache with overuse of symptomatic drugs is the third most common form of headache [32]. There is increasing evidence that the overuse of analgesics leading to MOH is a major epidemiological issue not only in Europe and North America, but also, more and more, in Asian countries, too; indeed, the prevalence of MOH in China and Taiwan is the same as that recorded in Europe [1, 2, 5, 21, 33, 34].

MOH in Latin American countries

Unfortunately, the epidemiological impact of MOH in LA countries is little known.

Indeed, some studies aiming at determining the prevalence of CDH have been conducted in Latin American [35, 36]. These studies point to a prevalence of CDH in Brazil that is higher than the prevalence recorded in countries outside of Latin America. However, it must be noted that these studies were about CDH, but did not take into account the actual epidemiological impact of MOH.

Indirect information can be derived by the study of Morillo et al. [37] where the authors describe the clinical characteristics and pattern of medication use of migraineurs in 12 LA urban communities and report a total of 13% patients using symptomatic medication on at least 16 days per month.

Owing to this substantial lack of published data on the impact of MOH in LA countries, we planned a pilot study

in collaboration with our LA partners (Argentina and Chile). The aim of this study was to estimate the impact of MOH in specialised headache centres. To this end, we developed a clinical report form for the diagnosis of MOH and the collection of relevant data from patients. This report form was administered to 100 consecutive patients referred to the Headache Centre of the Fleni Institute in Buenos Aires (Argentina) and to the Headache Centre of the Pontificia University of Santiago (Chile). According to the data supplied by our partners (Fadic R and Goicoichea MT, personal observations), in LA countries MOH accounts for between 55% (the Chilean centre) and 70% (the Argentinean centre) of headache patients seen in specialist centres. These findings, which will be better analysed by the COMOESTAS consortium, confirm the higher prevalence of MOH in subjects attending headache clinics; moreover, this result is similar to that found in tertiary headache clinics in US [28]. Of course, as in other studies, MOH patients who seek specialist care are likely to differ from MOH sufferers in the general population.

MOH has changed over time

The acute treatment of migraine has changed substantially over the past 15 years, following the marketing of the triptans, and so, too, has the type of MOH. Four studies [30, 38–40] investigating the frequency of the headache associated with the use of various drugs were performed prior to the publication of the ICHD-2 diagnostic criteria for MOH. In a US study, combination analgesics containing butalbital (a short-acting barbiturate), caffeine, and aspirin with or without codeine emerged as the medications most likely to cause MOH [39]. Until the mid 1990s, combination analgesics with codeine or caffeine, or ergots combined with codeine were the most common headache therapies in many European countries [30, 38, 40].

However, the introduction of the triptans and the recent withdrawal of ergots from some markets (e.g., Germany) is changing this picture. In fact, since 1994, clinical reports have suggested that the triptan overuse, too, may lead to the development of MOH [41, 42]. Sumatriptan-induced MOH was first recorded in patients who had previously overused ergotamine [41, 43]. MOH was later reported [44] in patients using naratriptan, zolmitriptan, or rizatriptan. Typically, triptan-induced MOH appears 1 year after a drug has been commercialised [44]. Triptan-induced MOH shows more migrainous features, it develops more rapidly than that associated with other classes of symptomatic drugs, and is associated with a lower mean critical monthly dosage [45]. Increasing body of evidence suggests that all the available triptans can cause MOH [45, 46] and reports on MOH induced by the newer triptans (eletriptan,

frovatriptan, almotriptan) will probably appear in the next future.

A study based on the prescription register in Denmark revealed that the prevalence of sumatriptan use in the Danish population, in 1995, was 0.78%. Of these users, up to 5% overused sumatriptan on a daily basis [47]. Evers and colleagues found that 4.7% of 320 sumatriptan users overused the drug by taking it at least every other day [48]. A recent population-based study in France revealed that triptans are used in a low percentage (7.5%) of migraine patients, but in a definitely higher proportion (25%) of patients with CDH [49]. This latter observation suggests a potential causal relationship between triptan misuse and development of daily chronic headache, although future studies are needed to address this issue.

MOH in children and adolescents

Several studies have addressed the prevalence of chronic headache in early adolescence and even in childhood [50, 51]. Hering-Hanit and Gadot [51] reported daily or near-daily headache related to excessive consumption of caffeine in a group of 36 children and adolescents aged from 6 to 18 years; in this study, the mean age of the subjects was 9.2 years, with a mean duration of headache of 1.8 years; thus, indicating that overuse may also begin very early. Adolescents with analgesic-induced headache responding to withdrawal treatment have also been reported [52]; however, conclusive data are missing on the real dimension of the problem. The scarce data available from the literature seem to suggest that MOH in children and adolescents may be less frequent than in adults. In one population-based study conducted in Taiwan, the authors reported a prevalence of 1.5% of CDH in a population of adolescents (12–14 years of age) and MOH was present only in 1/5 of these subjects [53]. Furthermore, a study from Canada, conducted in a general paediatric neurology ambulatory practice, showed that daily chronic headache prevalence was 3% in a group of 1,669 children seen because of headache. In this small subset of children suffering from chronic headache, medication overuse was present in 50% of cases [54].

Conclusion

The data illustrated confirm that MOH is a chronic disorder and major health problem that affects a huge number of subjects, including youngsters. Although scientific data is limited, MOH, on account of its clinical characteristics, is clearly a cause of disability and, if not adequately treated, of co-morbidity due to the excessive intake of drugs.

MOH can be treated through withdrawal of the overused drug(s) and adopting specific approaches that focus on the development of a close doctor–patient relationship in the post-withdrawal period.

Conflict of interest None.

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