Chronic Daily Headache

- with an emphasis on the medication overuse aspect of management

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Summary

- Purpose of review: Chronic daily headache, or "chronic headache" as now defined by the International Classification of Headache Disorders (ICHD) III, is any headache on more than 15 days per month.
- Most frequent and therefore clinically important sub-entities are chronic migraine, chronic tension-type headache and medication overuse headache (MOH).
- The current article provides a summary of the literature on the epidemiology of MOH, risk factors and treatment strategies.

The primary headaches of migraine and tension-type headache are common disorders which are associated with significant disability and economic burden. Chronic headache, defined as headache occurring on more than 15 days per month, accounts for most of the disability. In order to recognise the impact of regular use of any acute-relief medication the International Headache Society introduced the term "medication-overuse headache" (MOH).

Inappropriate use of acute-relief medication for headache may contribute to the development of chronic headache which is refractory to medical and non-drug treatments. Peters and Horton recognised this condition in the 1950s when describing chronic intractable headache in patients with migraine who used ergotamine frequently.[1,2] This was followed in the 1980s by reports of daily headache in patients, with migraine or tension-type headache, who were using analgesics or ergots on a regular basis. Importantly the chronic headache improved after discontinuation of regular acute-relief drug intake. The first International Classification of Headache Disorders (ICHD) of the IHS introduced the term 'drug-induced headache'. This was defined as a chronic headache in patients with migraine or tension-type headache following overuse of acute-relief medication (intake of analgesics or ergots on 15 days or more per month for at least 3 months) and resolving within one month of withdrawal.[3] Introduction of the triptans in the 1990s opened a new era in the treatment of migraine. Very soon it became clear that increasingly more patients used and overused triptans also. It has since been shown that triptan use on 10 days/month can lead to the development of chronic headache.[4] The second version of the ICHD introduced the term 'medication-overuse headache' (MOH) and decreased the critical threshold for triptan, ergot and opioid intake to 10 days/month. It further differentiated between MOH induced by triptans, ergots, opioids and analgesics, based upon clinical features.[5] This differentiation was widely criticised.[6] The committee of experts published appendix criteria introducing a broader concept of MOH where headache characteristics were eliminated. Moreover the definitions for chronic migraine were clarified to recognise that not all individuals improve following acute-relief drug withdrawal, but do become responsive to prophylactic medication, which had not been the case while they had been overusing.[7]

In the revised 3rd version of the ICHD three general principles have been adhered to: a) headache chronicity, b) overuse of any kind of acute-relief drugs and c) worsening of headache following overuse. The threshold for headache chronicity has been decreased from 15 days to 10 days per month. Specific MOH subgroups have been introduced: MOH following overuse of simple analgesics such as paracetamol, aspirin or other nonsteroidal analgesics, MOH due to combination drugs such as analgesics with caffeine, opioids or barbiturates, MOH due to ergots, triptans and opioids. For each of these groups the threshold of critical intake was defined between 10 and 15 days per month (personal communication, ZK is a member of the Classification Committee).

For the purpose of everyday clinical use it is essential to recognise potential MOH in patients with headache on 10 or more headache days per month with concomitant use of any kind of acute-relief drugs and treat them accordingly.

Clinical presentation

Patients with MOH are mostly women, aged 40 to 45 years. Most have migraine, but some have tension-type headache or a combination. On average they have suffered from primary headache for 20 years and overused acute-relief medication for about 5 years. Simple analgesics or combinations with caffeine are the most frequently overused drugs, followed by triptans. In the recent decade, use and overuse of ergots has decreased significantly worldwide. In Europe, very few patients overuse the combination of analgesics with barbiturates; this is much more frequent in the United States.[8,9]

Clinical features of MOH seem to depend on the pharmacology of the overused substances. Unlike migraine patients with MOH following ergot or analgesic overuse, migraine patients (but not patients with tension-type headache) who overused triptans did not develop a daily tension-type headache with

superimposed migrainous exacerbations. Instead they developed a migraine-like daily headache or, a significant increase in migraine frequency. The delay between frequent medication intake and the development of daily headache is shortest for triptans (1.7 years), longer for ergots (2.7 years), and longest for analgesics (4.8 years). Hence, triptans not only cause a different spectrum of clinical features but are also able to cause medication overuse headache faster and with lower dosages than other substance groups.[4]

Epidemiology

From epidemiological studies 1-2% of the general population suffer from chronic daily headache associated with the overuse of headache medication.[9,10]

Thanks to the efforts of the Global Campaign Against Headache and World Health Organisation (WHO), there have been several large scale population based studies addressing prevalence and burden of chronic headache in Russia, Eastern Europe, China and India.[11] Chronic headache and MOH, in particular, are an important medical and societal problem both in the developed and developing countries. The prevalence of chronic headache in developing countries is higher, e.g. 6% in Brazil[12] and 10% in Russia,[13] providing an argument against the view that headache is a problem of developed countries.

Use, and overuse, of acute-relief drugs in migraine varies between different parts of the world and depends mainly on local medical, societal and economic factors. Analgesics are most frequently used worldwide.[14] Use of triptans is more frequent in wealthy countries and fairly rare in developing countries.[22,26] Overuse of ergots has significantly decreased worldwide, especially in US and Europe.[15]

Risk factors and pathophysiology

MOH is an interaction between an excessively used acute-relief drug and a susceptible patient. The assumption of genetical susceptibility is supported by the fact that patients with migraine and tension-type headache have a higher potential for MOH than patients who use similar drugs for other diseases, such as arthritis. Patients with arthritis have a large consumption of analgesics but do not necessarily show an increased incidence of headache.[16] Patients with cluster headache usually do not develop MOH despite daily use of triptans, unless they also have a history or family history of migraine.[17]

Medication overuse is the most important risk factor and the driving force in the development of MOH. This statement seems self evident, but is difficult to confirm, because daily headache itself causes patients to use frequent painkillers. The argument for considering medication overuse as a main pathophysiological factor for headache chronicity is the fact that in the majority of cases withdrawal of the offending drug results in the improvement of headache. Furthermore, several longitudinal population-based studies have clearly demonstrated that overuse of any kind of acute-relief drugs bears a risk to developing chronic headache in the predisposed.[18] Whether some drugs bear a higher risk than the others is unclear. A recent population-based study demonstrated that regular caffeine may present a modest risk factor for the development of headache chronicity.[19] Thus caffeine combinations might also bear a higher risk for MOH. This could be compounded by a reluctance to withdraw given that caffeine withdrawal is not only associated with rebound headache but also with irritability, nervousness and restlessness.[20] A large population-based prospective study in Norway demonstrated that regular use of tranquilisers is also associated with a higher risk of MOH.[21]

Psychological co-morbidities such as depression and anxiety have been demonstrated to increase risk for MOH.[21,22] Low socioeconomic status has been identified as a further risk factor. This association has been shown in the US[23] and Europe,[24] particularly in Eastern Europe.[13]

Another important issue is the correlation between chronic headache and other body pains. Chronic headache is frequently associated with chronic back pain,[25] fibromyalgia[26] and facial pain.[27] Moreover, a bi-directional relationship between chronic headache and musculoskeletal pain has been demonstrated.[28] These findings suggest that the pathophysiology of chronification of headache and pain elsewhere in the body is likely to be interelated and to involve the entire central pain matrix.

The pathophysiology of MOH is still unknown. There is growing evidence that central sensitisation may play an important role in the pathophysiology of headache chronicity. A series of investigations using psychophysical and electrophysiological techniques demonstrated facilitation of trigeminal pain processing in patients with chronic migraine, chronic tension-type headache and MOH.[29] It is possible that each class of acute-relief drug may cause MOH via a different mechanism. Lasting changes in the serotonergic system, following exposure to painkillers, has been demonstrated in humans and animals,[30,31] while pre-treatment with opioids in rats can induce an enduring hyperalgesia, involving the peripheral and central trigeminal nociceptive system, in response to typical migraine triggers.[32]

Structural imaging studies in chronic pain, including chronic headache, have most consistently shown a decrease in grey matter volume in the pain matrix, in particular the anterior cingulate cortex [for review see 33]. An 18-FDG PET study was performed before and after acute-relief drug withdrawal.[34] Prior to withdrawal there was hypometabolism in regions of the pain matrix – bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula, ventral striatum and right inferior parietal lobule. All recovered glucose uptake following withdrawal except the orbitofrontal cortex, This occurred in patients overusing combination acute-relief preparations. In behavioural 18-FDG PET studies the abnormal activation within the striato-thalamo-orbitofrontal circuit underlies the maladaptive behaviour of substance abuse. This would be consistent with the clinical correlate that in patients who cannot maintain abstinence from overusing acute-relief drugs this is not related to severity of the disorder but behavioural, with a proportion fulfilling Diagnostic and Statistical Manual of Mental Disorders' criteria for Substance abuse disorder.[35]

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Treatment and outcome

Treatment of MOH patients should include a) education on the nature of the disorder, risk factors and treatment options, b) withdrawal, c) preventive treatment and d) multimodal approach including psychological support.[36]

Patient education is an important step in the treatment of MOH. An Akershus population based study in Norway identified people with possible MOH. A letter was provided with educational material and advice. This intervention alone resulted in improvement of headache in many cases.[37] An Italian study compared advice alone with a structured detoxification programme in patients with

MOH and without psychological co-morbidity; both arms were similarly effective.[38] The withdrawal headache usually lasts about 2-10 days and may be accompanied by a number of additional withdrawal symptoms depending on the type of acute-relief drugs overused. The withdrawal phase is much shorter for isolated triptan overuse.[39] Treatment recommendations for the acute phase of drug withdrawal has varied considerably. They include fluid replacement, rescue medication with limited amount of analgesics or triptans, tranquilisers and neuroleptics. Two independent placebo-controlled randomised studies from Norway and Germany revealed that oral prednisone (60 or 100mg per day) were not superior to placebo.[40,41]

There have been varied approaches to drug withdrawal. However the majority of patients can be withdrawn as an outpatient. Those with greater psychiatric comorbidity may need greater support and a more structured withdrawal programme.[36]

A multidisciplinary approach, involving medical, psychological and physiotherapy input has proven effective in the management of primary headaches including MOH.[42] This approach requires an initial investment in resources. Therefore, for the time being such an approach may be limited to patients with high medical needs, thus those who relapse after initial successful withdrawal and those with concomitant psychiatric co-morbidity.

Several studies have dealt with the long-term outcome of patients with MOH after successful withdrawal, defined as no headache or improvement of at least 50% in terms of headache days. The success rate over an observation period up to six months is up to about 75%. Long-term (four years) follow-up studies found relapse rates between 30-60%. Patients with migraine, rather than tension-type headache, and those who used triptans compared to other drugs had a significantly lower relapse rate.[43-45]

Conclusion

The most important measure to prevent MOH is proper general information as well as clear instruction and appropriate surveillance of patients. Migraine patients at risk often have a phenotypic mixture of migraine and tension-type headaches and should be carefully instructed to use specific antimigraine drugs for migraine attacks only. The number of doses of triptans should be limited to eight days/month based upon the work which shows that triptans used on 10 days a month can lead to the development of MOH. Drugs that contain barbiturates, caffeine, codeine, or tranquilisers, as well as mixed analgesics, should be avoided. Early and appropriate migraine prophylaxis, medical and behavioural, are important preventive measures to avoid medication-overuse headache. ◆

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