Medication overuse headache (MOH) is a clinically important entity and it is now well documented that the regular use of acute symptomatic medication by people with migraine or tension-type headache increases the risk of aggravation of the primary headache. MOH is one of the most common causes of chronic migraine-like syndrome. Because of easy availability and low expense, the greatest problem appears to be associated with barbiturate-containing combination analgesics and over-the-counter caffeine-containing combination analgesics. Even though triptan overuse headache is not encountered with great frequency, all triptans should be considered potential inducers of MOH. There are several different theories regarding the aetiology of MOH, including: (i) central sensitisation from repetitive activation of nociceptive pathways; (ii) a direct effect of the medication on the capacity of the brain to inhibit pain; (iii) a decrease in blood serotonin due to repetitive medication administration with alteration of serotonin receptors; (iv) cellular adaptation in the brain; and (v) changes in the periaqueductal grey matter. The principal approach to management of MOH is built around cessation of overused medication. Without discontinuation of the offending medication, improvement is almost impossible to attain. Thus, the best management advice is to raise awareness and strive for prevention. In this article, we analyse also the possible mechanisms that underlie sensitisation in MOH by comparing these mechanisms with those reported for other forms of drug addiction.

**Key words** Medication overuse headache • Migraine • Sensitization • Drug abuse • Obsessive-compulsive behaviour
headache medications, especially the triptans, provided increased migraine relief. Nevertheless, the emergence of triptan overuse headache has also gained interest. Similarly, others symptomatic drugs for headache relief such as ergots, analgesics, opioids, morphinomimetics and barbiturates can cause MOH [1–5].

MOH is an interaction between a therapeutic agent used excessively and a susceptible patient. Awareness of MOH and familiarity with the diagnosis and treatment of this disorder are important to physicians who treat patients with headache. Features of migraine and tension-type headache often coexist in MOH. The diagnosis of MOH is clinically extremely important because patients rarely respond to prophylactic medications whilst overusing acute medications [6]. Furthermore, the understanding of the pathophysiological mechanisms underlying MOH may help to explore appropriate therapeutical strategies. The general term of MOH encompasses those headaches presenting more than 15 days per month [2].

Patients suffering from MOH represent a great number of patients referring to headache specialist centres. Moreover, these patients have high frequencies of psychiatric comorbidity or psychologic distress in clinic-based studies [7]. The presence of psychologic distress contributes to poor quality of life in patients with MOH.

Overuse of various compounds frequently leads to a state of dependency. This kind of headache can be caused by the intake of combination analgesics, opioids, ergot alkaloids, aspirin, non-steroidal anti-inflammatory drugs, caffeine and triptans [1–6].

The most frequent cause for the transformation of a periodic headache into a chronic disabling headache is substance abuse. Substance abuse and drug dependency have multiple causes, and the aetiology resides with the compounds that are used to excess.

The problem may arise as a result of poor instructions from the physician, improper diagnosis with gradual escalation in amounts of drug consumed, or a reinforcement mechanism and a brain stimulation-reward effect. Frequent use (≥15 times/month) of medication for the treatment of acute migraine attacks may cause MOH. The delay between first intake and daily headache is shortest for triptans (1–2 years), longer for ergots (3 years) and longest for analgesics (5 years) [1].

Analgesic and ergot alkaloid combinations with caffeine often lead to a relapse. However, patients overusing opioids have the highest relapse rate after withdrawal treatment.

Some studies have suggested that triptan overuse may increase migraine frequency to that of chronic migraine. Evidence suggests that this occurs sooner with triptan overuse than with ergotamine overuse.

Complete withdrawal from headache medication is the treatment of choice for MOH. Discontinuation of the overused headache medication, however, results in the development of withdrawal headache, often associated with nausea, vomiting and sleep disturbances [1–6].

**Drug-induced sensitisation and MOH**

Sensitisation is the enhanced response to a stimulus that occurs with repeated exposure to that stimulus. Psychostimulants are perhaps the best-studied drugs of abuse in terms of producing sensitisation. Behavioural sensitisation is the augmented motor-stimulant response that occurs with repeated, intermittent exposure to cocaine and amphetamine. Sensitisation is hypothesised to underlie the craving associated with drug abuse that may lead to relapse following a period of abstinence. In addition, cross-sensitisation occurs between drugs of abuse, suggesting that common mechanisms may underlie the development of sensitisation to drugs targeting different neurotransmitters [8, 9].

Certain features of MOH, namely, increased headache frequency, expansion of headache area and cutaneous allostodynia, may imply sensitisation of central nociceptive neurons in the trigeminal pathway as well as in cells of the periaqueductal grey (PAG).

Repetitive activation of the trigeminal nerve can lead to a biologic and functional change in trigeminal nucleus caudalis neurons, characterised by a decrease in nociceptive threshold and receptive field expansion. Suppression of the endogenous pain control system can facilitate the process of central sensitisation [10]. A similar process might be also involved in the sensitisation induced by medication overuse in tension-type headache patients [8].

Sensitisation underlies the craving associated to drug abuse leading to relapse following a period of abstinence. In support of this hypothesis, sensitisation may last months to years following the cessation of drug exposure. Whether sensitisation may occur as a consequence of medication overuse in headache patients or it is caused by the repetitive occurrence of episodes of stressful events such as headache episodes is still unclear [11]. Nevertheless, behavioural correlates associated with MOH might partially resemble some of the more characteristic features of the behavioural sensitisation to psychostimulants. Among these features the most important are the requirement of repeated administrations during a certain period of time, the tendency to have a “craving” in the early phase of abstinence, and the occurrence of cross-sensitisation among different drugs used to treat headache. In addition, the tendency to reach a status in which the assumption of the drugs is induced by a “compulsive” and stereotypical behaviour rather than by real
medical needs, and the possibility to observe a relapse after relatively long periods of abstinence may resemble the characteristics of drug addiction [12].

The first step among the several biochemical changes required to induce synaptic plasticity and central sensitisation is an increased extracellular level of glutamate [8, 13]. A significant increase in glutamate levels has been detected in the cerebrospinal fluid of patients with chronic forms of headache [8].

Central sensitisation and storage of information at a cellular level also require changes at maintained transcriptional level. Several different intracellular signal transduction cascades converge on mitogen-activated protein kinase (MAPK), activation of which appears to be a master switch or gate for the regulation of central sensitisation via transcriptional regulation of key gene products. Thus, memory traces of painful events can be retained as a form of long-term increase in the efficacy of excitatory synaptic transmission [8, 10, 11].

Are MOH patients sharing an obsessive-compulsive profile with other addictions?

Psychiatric comorbidity, especially major depression, anxiety and panic disorders, has been found to be highly prevalent in patients with chronic headache and MOH [7, 14]. Comparing psychiatric comorbidity between migraineurs with and without chronic drug overuse a significantly higher prevalence of major depressive disorder, panic disorder and social phobia has been found in the patients with a history of chronic substance use.

Drug dependence disorders have been found to be associated with various comorbid psychiatric disorders including panic attacks, social phobia, specific phobia and obsessive-compulsive disorder (OCD) [15, 16].

Although neuropsychological and neuroimaging studies of OCD have implicated cortical areas, subcortical structures (i.e., the ventral and dorsal striatum) seem also to play a major role in the pathophysiology of the disorder. Accordingly, neuropsychological studies have demonstrated that patients with OCD showed specific cognitive deficits on tasks of executive and visual memory function [8, 15, 16].

Patients with chronic headaches and MOH bear similarities to drug or substance abuse patients, for whom genetic liability loci have been implicated. Molecular genetic studies in this field are, however, still few and preliminary.

Shared neurobiological features characterise substance use disorders and other compulsive behaviours (alcoholism, pathological gambling, compulsive shopping, compulsive sexual behaviours, compulsive computer use). Thus, future clinical and genetic studies on the comorbidity between MOH patients, other forms of addiction and OCD are needed.

The common pathogenetic role of 5-HT in both MOH and OCD can establish an additional link between these two disorders. Moreover, it is worth noting that selective serotonin reuptake inhibitors (SSRI) are effective in the treatment of OCD but they may also represent a therapeutic option in MOH [8].

Conclusions

In recent years, advances in brain research have resulted in a striking strategic shift in studies designed to develop new, effective treatments for MOH as well as for related neuropsychiatric disorders. This involves a multidisciplinary approach with recursive interactions among respective disciplines with the ultimate goal of contributing to treatment development. New common perspectives for treatment of MOH, drug abuse and other related psychiatric disorders may arise from brain imaging and molecular and pharmacogenetic studies, showing a shared pathophysiological base among these disorders. Translational components of this research include the potential for integrating advances in brain imaging and molecular and pharmacogenetic assessments as they may potentially relate to neurodiagnostic assessment and treatment development.

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