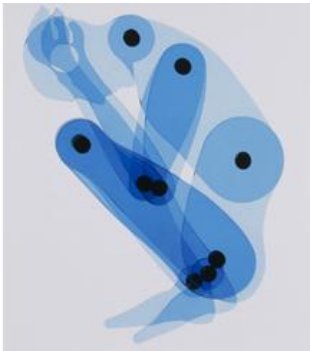




## MOH

### MOH pathogenesis and pathophysiology

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The underlying mechanisms that lead to the development of Medication Overuse Headache (MOH) are still widely unknown and the clarification of their role is hampered by the lack of experimental research or suitable animal models.

Various pathophysiological abnormalities have been reported and they seem to have an important role in initiating and maintaining chronic headache: genetic disposition, receptor and enzyme physiology and regulation, psychological and behavioural factors, physical dependencies, recent functional imaging results.

In the following paragraphs, the possible pathophysiological mechanisms will be briefly presented and analyzed.

**Genetic disposition:** According to the 2<sup>nd</sup> edition of the International Classification Headache Disorders, MOH is an interaction between a therapeutic agent used excessively and a susceptible patient (ICHD-II, 2004). Various clinical observations and studies concluded that MOH may be restricted to individuals who already have headache disorders, suggesting a genetic predisposition to this form of headache. As a matter of fact, the association between overuse of analgesics and headache has been studied in other disorders, apart from primary headaches. For example, chronic overuse of analgesics for arthritis is not associated with an increased incidence of headache in patients without migraine (Lance, 1988). Moreover, migraineurs who take analgesics for the treatment of other pain types are significantly more likely to develop MOH than patients without headache (Bahara A et al., 2003).

**Receptor and enzyme physiology and regulation:** Regular exposure to a substance can induce significant changes in expression and sensitization of receptors as well as changes for the threshold of receptors activation. The entity of these changes and their speed depend on the receptor type, duration of overuse and concentration of drugs exposure. In rats, chronic exposure to triptans,



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particularly sumatriptan and zolmitriptan, alters 5-HT receptors in trigeminal ganglion and generates a down-regulation, a reduction of receptor function (Reuter et al., 2004), and, also, decrease of the 5-HT synthesis in the dorsal raphe nuclei of the brainstem (Tohyama et al., 2002; Dobson et al., 2004). Enzyme regulation, however, needs a prolonged exposure to high concentrations of drugs (Weksler, 1987). These hypotheses are supported by clinical experiences; as a matter of fact, Katsarava and colleagues showed that MOH develops faster with triptan overuse than with analgesic overuse, while the withdrawal phase is significantly milder and shorter with triptans (Katsarava et al, 2001). A decrease in the levels of 5-HT in platelets has been observed in patients with chronic tension type-headache and migraine with MOH. An up-regulation of pronociceptive 5HT<sub>2A</sub> receptors was observed in platelets of patients with drug-induced headache (Srikiatkachorn and Anthony, 1996). Thus, these alterations of the 5-HT-dependent pain control system might facilitate the process of sensitization and, consequently, favour the development of chronic headache.

**Psychological and behavioural factors:** Psychological factors include the reinforcing properties of pain relief by drug consumption, a powerful component of positive conditioning. Many patients take symptomatic migraine drugs with a preventative modality to avoid headache attacks that might interfere with daily activities that cannot be postponed (work or important social events). Patients are often instructed by physicians or by the instructions supplied with the medication to take against migraines when the feeling of pain starts, to avoid a severe and disabling headache attack. This behaviour, which can be considered correct to a certain extent, may, on the other hand, facilitate the regular and daily assumption of headache medications and the maintenance of the chronic overuse state. Moreover, migraine drugs such as barbiturate, codeine, other opioids, and caffeine have a stimulating action or psychotropic effects (sedation or mild euphoria) that may lead to drug psychological dependency. Also caffeine - a compound frequently associated to various anti-migraine drugs (such as acetylsalicylic acid and acetaminophen) for enhancing the analgesic action - increases vigilance, relieves fatigue, and improves performance and mood. The typical symptoms of caffeine withdrawal, i.e. irritability, nervousness, restlessness, and "caffeine withdrawal headache" (which may last for several days) encourage patients to continue the overuse. Withdrawal headache, as a consequence of the discontinuation of the overused headache medication, is an additional factor. When the patient tries to stop or reduce the medication, the pre-existing headache worsens and, often, causes nausea, vomiting and sleep disturbance.



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**Physical dependencies:** the development of physical dependence on codeine or other opioids has been reported by headache patients (Fisher et al., 1997; Ziegler, 1994). Ergotamine and dihydroergotamine may lead to physical dependency and many migraineurs take ergotamine as prophylactic treatment (Saper and Jones, 1986). The reason for the physical dependency on ergotamine remains obscure.

**Central sensitization:** sensitization is the enhanced response to a stimulus that occurs with repeated exposure to the same stimulus. Growing evidence shows that central sensitization may play an important role in the pathophysiology of headache chronification. Repetitive activation of the trigemino-vascular system can cause biologic and functional changes in the nociceptive neurons of the trigeminal nucleus caudalis. These alterations are characterized by a decrease in nociceptive threshold and by its temporary facilitation at a supraspinal level. Both alterations normalize the following withdrawal of analgesics. Suppression of the endogenous pain control system can facilitate the process of central sensitization through a reduction in descending inhibition, which underlies the craving associated to drug abuse that can lead to relapse following a period of abstinence. Nevertheless, one can postulate that behavioural correlates associated with MOH might partially resemble some features of the behavioural sensitization to psychostimulants. This process might underlie the development of sensitization to drugs, suggesting that MOH shares some pathogenetic mechanisms with other types of drug addiction.

**Imaging studies:** Imaging studies provide further insights into the pathophysiology of MOH. Recently, Fumal and colleagues conducted the first functional imaging study in MOH (Fumal A et al., 2006) and observed metabolic changes in several brain areas, including brain stem nuclei that are usually involved in pain network. In addition, glucose metabolism was abnormal in the medial orbitofrontal cortex, which may be related to dependence on the analgesic drugs and the high recurrence rate associated with MOH. Moreover, the orbitofrontal cortex showed persistent hypometabolism before and after drug withdrawal, which was also demonstrated in individuals with substance abuse, suggesting a role for this area in promoting ongoing medication overuse and in predisposing the patient to a relapse of MOH.

The exact way in which medication overuse transforms an episodic headache into daily or, sometimes, continuous headache remains unclear. Central sensitization appears to have a pivotal role in the pathogenesis of MOH. Repeated migraine attacks in susceptible patients may lead to a state of chronic central sensitization of trigeminal pain-pathway, resulting in continuous and chronic



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headache. Whether sensitization occurs 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 attacks, is still unclear. Overuse of analgesics, and specially opioids, may also sensitize central-pain pathways. Although some of these findings about the pathogenesis of MOH may help to understand the chronic pain, they offer no explanation for several clinical observations, suggesting that dependency and genetic predisposition might play a role in MOH suffers associated to other unknown factors. Clinical and neurochemical similarities between MOH and drug addiction have also been emphasized (Calabresi and Cupini, 2005) and partially supported by the recent neuroimaging results, although there is not current and direct evidence available for a common underlying mechanism

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