▪ Headache Medicine 2025, 16(4):224-234 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2025.36

Review

Medication overuse headache: from brain alterations to disease burden

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Edited by:
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Introduction
Medication-overuse headache is a secondary headache that develops in patients with a pre-existing primary headache, most often migraine, who experience daily or near-daily headaches as a result of excessive intake of symptomatic medications. According to the ICHD-3 criteria, diagnosis requires ≥15 headache days per month and ≥10–15 days per month of medication use, depending on the drug class, for at least three months.

Objective
To review the pathophysiological mechanisms, risk factors, clinical impact, and regional characteristics, highlighting therapeutic implications and current research gaps.

Methods
A narrative review of recent high-quality literature indexed in PubMed was conducted, integrating clinical, epidemiological, and experimental data, to ensure comprehensive coverage of emerging evidence.

Results
Pathophysiology involves dysregulation of the trigeminovascular system, cortical hyperexcitability, maladaptive neuroplasticity, and dysfunction of dopaminergic reward circuits, showing parallels with addictive disorders. Major risk factors include female sex, high baseline headache frequency, psychiatric comorbidities, socioeconomic vulnerability, and genetic predisposition. Alterations in CGRP and endocannabinoid systems may further increase susceptibility. In Latin America, ergotamine remains the most frequently overused drug, unlike triptans and simple analgesics in developed countries, underscoring regional disparities and safety concerns.

Conclusion
Medication-overuse headache is a preventable yet underdiagnosed disorder with major personal and socioeconomic impact. Early diagnosis, patient and physician education, and effective withdrawal management are essential. Persistent gaps in pathophysiology, biomarkers, and tailored therapies demand further collaborative and multicenter research.

Keywords:
Medication overuse
Migraine disorders
Central sensitization
Trigeminovascular System
Chronic headache

Received: October 13, 2025
Revised: October 24, 2025
Accepted: December 9, 2025

Introduction

Medication-overuse headache (MOH) is a condition in which treatment of the headache may become the cause of the disease (1). Inappropriate use of acute headache medications, particularly among patients with frequent migraine or tension-type headache, can contribute to the development of chronic daily or near-daily headaches, induced and sustained by the repeated intake of analgesics (2). According to the current International Classification of Headache Disorders (ICHD) 3rd edition, MOH is categorized as a secondary headache (3). Epidemiological studies report that it affects up to 2% of the general population, making it a common and clinically relevant disorder (4).

Historical background

The first U.S. National Institutes of Health (NIH) ad hoc committee classification of headache, published in 1962, did not mention medication overuse (MO) as a cause or associated factor (5). In 1986, a group of experts proposed the first definition of "drug-related headache" (6).

The first ICHD edition, published in 1988, described "headache induced by consumption or chronic exposure to substances" (7). In 1994, Silberstein et al. introduced criteria that categorized four types of daily or near-daily primary headaches with or without MO (8), known as CDH-1994. The ICHD 2nd edition, published in 2004, incorporated the diagnosis of "medication-overuse headache" (9).

Reaching a practical definition of MOH that is “valid, reliable, and consensual” has remained a challenge (10). As Ferrari et al. noted in 2008, “in such a complex disorder, it is difficult to obtain a classification that is easily applicable and unequivocal” (11).

Since 2018, in the ICHD 3rd edition, MOH is categorized as a secondary headache and includes a more precise definition of ‘‘pre-existing headache disorder” as a criterion to diagnose MOH properly (1,3).

Definition of MOH

A considerable proportion of patients with chronic migraine (CM) also present with comorbid MOH (12,13). CM is a highly disabling migraine subtype with a global prevalence of approximately 2–4% (14,15). According to ICHD 3rd edition, CM is defined as a headache occurring ≥15 days per month for ≥3 months, of which ≥8 days have typical migraine features or respond to specific migraine therapies (3).

MOH is defined as a headache occurring on 15 or more days per month in a patient with a pre-existing primary headache, as a consequence of the regular overuse of acute or symptomatic headache medication (≥10 or ≥15 days/month, depending on the drug class) for a period longer than three months. Symptoms usually improve upon withdrawal of the overused medication (3). Table 1 shows proposed clinical categories for MOH (16).

Table 1. Medication overuse headache classification according to severity (16)

Clinical categories	Characteristics
Complicated MOH	Opioid overuse, failure of previous detoxification protocols, or clinically significant psychiatric comorbidities.
Uncomplicated MOH	Patients without the above characteristics

Clinically, MOH sufferers may have migraine, tension-type headache, or other primary headache disorders, which may have started in the second or third decades and progressed over time, leading to, or because of, a pattern of symptomatic headache overuse. In some subpopulations of patients, at around the third or fourth decades (33.8 ± 12.3 for female patients; 37.8 ± 10.4 for male patients), headache frequency increases, along with the loss of typical characteristics of the primary headache disorder was observed (4,17).

Subtypes of MOH (ICHD-3) (3)

Headache ≥15 days/month in a patient with a pre-existing primary headache due to:

- **Ergotamine-overuse headache**: Regular intake of ergotamine on ≥10 days/month for >3 months. It usually, but not invariably, resolves after the overuse is stopped
- **Triptan-overuse headache**: intake of one or more triptans on ≥10 days/month for >3 months. Symptoms usually remit after discontinuation.
- **Non-opioid analgesic overuse headache**: Regular intake of non-opioid analgesics (excluding acetaminophen, NSAIDs, and aspirin) on ≥15 days/month for >3 months.
- **Opioid-overuse headache**: Regular use of one or more opioids for more than 10 days/month for >3 months.
- **Combination-analgesic overuse headache**: Regular intake of one or more combination analgesics on ≥10 days/month for >3 months.

Pathophysiology

The pathophysiology of migraine chronification remains difficult to elucidate fully. Proposed mechanisms include

dysfunction of descending pain modulatory networks, alterations in the trigeminal–cranial autonomic system function, thalamic contributions to central sensitization, and medication-associated central sensitization (14,15,18). Figure 1 summarizes the most frequently proposed mechanisms.

MOH pathophysiology is still far from being completely elucidated, but there have been recent advances in the field that give us some light on what is happening. It is well known that MOH is not reported in the absence of an underlying headache disorder, so it is best studied developing from migraine (19). Three proposed mechanisms are described as follows:

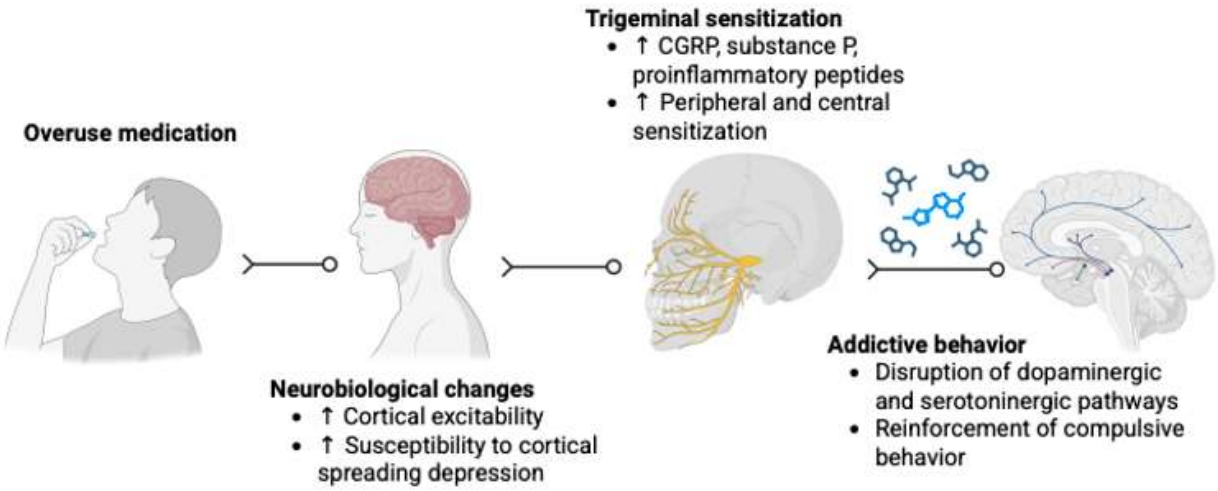

Figure 1. Proposed pathophysiological mechanisms of medication-overuse headache.

Reward-Seeking Disorder

Common risk factors for the overuse of pain-relieving medication and substance addiction include genetic predisposition and psychiatric disorders, primarily depression and anxiety (20,21). MOH shares behavioral, genetic polymorphisms, and neural pathways with drug addiction (20, 21). Dopamine and the mesocorticolimbic system play a critical role in both substance addiction and central pain sensitization in the chronicity of migraine (20–22).

Patients with MO may develop behaviors similar to those seen in substance addiction, such as ritualized drug use, psychological attachment to medications, and withdrawal symptoms, all of which suggest a correlation with drug addiction (21–23). Regular and frequent use of medications to treat headaches can facilitate the acquisition of Pavlovian learning. Additionally, this refers to how environmental stimuli that initially do not elicit a response become associated with the drug or the act of consuming it. Eventually, these stimuli alone can trigger the craving response or substance-seeking behavior, in this case, the painkiller, leading to the formation of habits and compulsive behaviors (20,22–24).

MOH is related to alterations in the brain reward system, with its primary neuroanatomical substrate being the mesocorticolimbic system. This dopaminergic circuit combines the mesocortical and mesolimbic pathways, both originating in the ventral tegmental area (VTA) of the midbrain, which is the origin of the dopaminergic pathways (20–22). Both pathways originate in the VTA but differ in their projections: the mesocortical pathway goes to the ventromedial and dorsomedial prefrontal cortex and is related to cognitive and emotional functions, while the mesolimbic pathway projects to the ventral striatum, mainly to the nucleus accumbens, and is related to motivation and reward (20–22).

Neuroimaging studies suggest similarities between MO and drug addiction (20–22). Structural MRI of the brain with morphometric measurements demonstrates that patients with migraine and MOH, compared with healthy controls, have a larger volume of gray matter in the ventral striatum, an area implicated in reward behaviors and addiction (20–23).

Regarding functional studies with brain magnetic resonance imaging, it was evident that the representation of the subjective value of a larger but long-term reward in key brain regions, such as the dorsomedial prefrontal cortex, ventral striatum, and ventromedial prefrontal cortex was weaker in patients with MOH (20–23). Furthermore, the results of functional studies were characterized by altered processing and disconnection in the brain's reward system during choices between intertemporal alternatives and in the resting state (20–23). As a result, CM with MOH is associated with a dysregulated reward system. The intake frequency of acute abortive medication and impulsive choice behavior play important roles in this dysregulation (18–22).

Trigeminovascular Complex and pain processing

The trigeminal system is the principal pathway for

processing the nociceptive information arising from cranial structures (25). It has ascending nociceptive pathways all the way to the cortex and of course the descending modulatory ones. Current hypotheses focus on hyperexcitability of neurons in either the trigeminal system or the cortex, but most likely in both (25).

In migraine, it is well known that activation of first-order neurons (trigeminal and occipital) through the release of inflammatory mediators and neuropeptides leads to peripheral sensitization. If not stopped, Central sensitization occurs, meaning that second and third-order neurons are now capable of generating pain without needing first-order neurons activation (26). Because migraineurs are most vulnerable to developing MOH, migraine and MOH likely share some neural mechanisms (27).

Preclinically, chronic exposure to analgesics has been shown to induce an up-regulation of mediators (28). Exposure to opioids or triptans in rats led to a sensitized state of pronociceptive transmission. After 7 days of infusion, the stimulus required to elicit a withdrawal reflex was shown to decrease gradually, and after discontinuing the infusion, it showed a time-dependent reversal (27). These observations show us that somehow the trigeminal system can be modulated when exposed to analgesics, but it should be noted that this can only happen in the context of a patient with a previous headache disorder.

Altered cortical excitability and maladaptive neuroplasticity

Evidence exists supporting that medication induces changes in cortical excitability, too. Preclinical studies have shown that exposure to paracetamol or sumatriptan increases the frequency of cortical spreading depression (CSD) events and decreases the threshold for electrically induced CSD, respectively (27).

The expression of c-fos protein in neurons is usually considered an indicator of neuronal excitation. Chronic administration of paracetamol increased CSD-evoked c-fos expression in superficial layers of the trigeminal nucleus caudalis, which suggests an increase in activation in the nociceptive pathway (28).

Activation of the trigeminovascular system, extending from the trigeminal ganglion to the cortex, is mediated by inflammatory mediators and several neuropeptides and is known to cause headaches. Analgesics and triptans have been shown to reduce the threshold at which the trigeminovascular system can be activated and increase the frequency of CSD in the cortex (an event that is thought to initiate a headache, at least in migraine with aura). All of these suggest that analgesics and triptans can modulate peripheral and central structures related to the generation of pain in headache, facilitating it. Hyperexcitability of peripheral and central structures through a decrease in the threshold to generate pain in the headache brain through modulation of analgesics and/or triptans may lead to a state in which it is easier to trigger a headache or worsen one (27–29).

However, several issues remain unanswered. First, preclinical studies using rodent models have provided valuable insights; nevertheless, evidence from animal studies is limited by potential differences between the species. Second, CSD is not found in migraine without aura. Thirdly, everything mentioned above explains what we believe is happening in MOH, but not how or why. Further research is needed to fully understand the pathophysiology of this complex headache disorder.

Reliable animal models are crucial for developing preventive strategies that could halt the progression from episodic to CM. These models also provide platforms for testing the efficacy of potentially useful pharmacological agents (18).

Influence of overused medication type

The pathophysiological mechanisms underlying MOH may differ by specific drug class. Current evidence is limited, but suggests that:

- **Opioids**: Overuse may induce hyperalgesia through recurrent activation of nociceptive pathways, glial activation, and pro-inflammatory states (29). In animal studies, opioids elicit cutaneous allodynia and latent sensitization. Chronic exposure to opioids induces CGRP overexpression in dorsal root ganglion neurons (19).
- **Triptans**: Prolonged exposure increases circulating levels of calcitonin gene–related peptide (CGRP) (28). Overuse induces latent sensitization, with pronociceptive adaptations in dural afferents and heightened trigger susceptibility (30). Triptans are now the most common cause of MOH in high-income countries (12) and appear to precipitate MOH faster and at lower doses than other drugs, after only 1.7 years of use versus 4.8 years with analgesics (17,31).
- **Acetaminophen** (Paracetamol): Overuse may alter cortical excitability, increase cortical spreading depression susceptibility and enhance trigeminal nociception (32).
- **Dipyrone**: a study in rats has suggested that prolonged treatment with dipyrone (metamizole) can cause sensitization of the trigeminal system and potentially induce MOH, with females being more vulnerable (33).
- **Barbiturates**: Previously leading global MOH inducers, they have been withdrawn in Europe but remain available in the United States (34).
- **Ergotamine**: Headache caused by ergotamine abuse is primarily explained by rebound vasodilation following chronic vasoconstriction

Diagnosis and clinical features

In migraineurs, episodic headaches become daily or near

daily, occurring in ≥15 days per month, and may present features of diffuse or holocranial pain, pressure-type or dull, moderate in severity. The duration of pain varies according to medication intake. The associated symptoms of photophobia, osmophobia, and phonophobia, as well as the gastrointestinal symptoms of nausea and vomiting, are not present on most days, and the patients frequently complain about being awakened in the middle of the night, requiring more headache medications (35,36). These new features of a migraineur who developed MOH and the loss of the typical migraine characteristics may confound clinicians by suggesting the presence of another primary headache, such as the tension-type headache. Effort should be directed towards identifying individuals whose condition began as episodic migraine (EM) (35–37). The diagnostic criteria and the headache characteristics are described in Table 2.

Table 2. Diagnostic criteria for medication-overuse headache according to the International Classification of Headache Disorders, 3rd edition

Criterion	Description
Headache frequency	Headache occurring ≥15 days per month in a patient with a pre-existing headache disorder.
Medication overuse	Regular overuse for >3 months of one or more drugs that can be taken for acute or symptomatic treatment of headache.
Threshold for overuse	Depends on drug class: Triptans, ergotamine's, opioids, combination analgesics: ≥10 days/month Simple analgesics (NSAIDs, acetaminophen): ≥15 days/month
Exclusion	Headache not better accounted for by another ICHD-3 diagnosis.
Association	Headache typically develops or worsens during medication overuse and may improve after discontinuation of the overused drug(s).

Other migraine characteristics, such as menstrual aggravation and identifiable migraine triggers, may be present. Most patients also may present a clear family history of migraine and have intermittent full-blown migraine attacks with variable frequency but achieve at least eight days per month (35–37).

In addition, MOH sufferers evolving from EM may frequently reveal psychological and/or sleep disturbances, which contribute to the transformation or perpetuation into the CM and MO presentation (35–38). The overuse of symptomatic medications becomes more consistent over time and is anticipated with increased refractoriness and subsequent escalation of the number of headache days (35,36,39). Since this clinical presentation may overlap with CM, except for the frequency of using headache medications for longer than three months, a thorough medical history must be taken, and red flags for other secondary conditions leading to more frequent headaches and more medication consumption must be identified. Moreover, health professionals need to be aware of the oscillating nature of migraine and pitfalls that may occur in those who do not present a progressive clinical picture or start to take more medications as a consequence of a new onset headache (35,36,39).

Therefore, the diagnosis of MOH is essentially clinical, with the demonstration of a previous primary headache that evolved gradually into a daily or near-daily headache associated with the use of headache medications over a minimum of three months. The identifiable features of primary headache, as well as the absence of neurological signs or symptoms that may suggest other secondary causes, must be emphasized, along with the need for a reliable neurological evaluation (39).

Risk factors

Comorbidities

Numerous studies have identified a wide range of demographic, clinical, and psychiatric factors that increase the risk of developing MOH. A significant body of research stems from large, population-based studies, providing robust data on these associations.

Demographic and lifestyle factors, for instance, are commonly implicated. Data from the MAST (Migraine in America Symptoms and Treatment) highlighted the relevance of specific clinical features, such as the presence of cutaneous allodynia, higher body mass index, psychological disorders, and smoking. The baseline frequency of headaches was also a powerful predictor of overuse, reinforcing the idea that more severe or frequent headache patterns are a key risk factor for developing MOH (40). MOH patients exhibit psychiatric comorbidity rates similar to those of other chronic headache populations (41–43). Given the parallels between MOH and addictive disorders (44), as well as dependence-related behaviors (45,46), personality traits may further complicate the clinical course.

The CaMEO (Chronic Migraine Epidemiology and Outcomes) study found strong associations between MO and several medical and psychiatric conditions. Relevant comorbidities included hypercholesterolemia, arrhythmia, hypothyroidism, irritable bowel syndrome, and chronic musculoskeletal pain syndromes like chronic lower back pain and osteoarthritis. The study also underscored the strong link between MOH and psychological disorders, specifically depression, panic attacks, and insomnia (47).

Based on the European HUNT Study, a baseline headache frequency of 7-14 days, age <50 years, migraine history, low education, musculoskeletal pain, gastrointestinal disorders, depression, anxiety, insomnia, smoking, sedentarism and use of sedatives were associated with a higher risk of MOH (48).

Other independent studies and meta-analyses support and expand on these findings, consistently identifying a history of migraine, baseline headache frequency, lower socioeconomic status, and the presence of depression or anxiety as the most common risk factors for the development of MOH (46,49,50).

Sociodemographic and lifestyle factors

Data from the MAST study revealed that female sex, older age, marital status, lower socioeconomic status, and education were all associated with an increased risk of acute MO in individuals with migraine (40), therefore those with MOH are more likely to be women, have a lower education level, be married or unemployed, experience migraine remission during pregnancy, and after menopause. Constipation and lack of oral contraceptive use are also more frequent, as is polypharmacy, particularly with sedative–hypnotics and antihypertensive agents (51). In comparative analyses, unemployment ($p < 0.01$), cigarette smoking ($p < 0.05$), and daily benzodiazepine use ($p < 0.001$) were significantly more frequent among persistent or relapsed overusers (52).

Dependence patterns

Current opioid users with probable dependence have Migraine Disability Assessment (MIDAS) scores more than twice as high as occasional users, with higher rates of emergency care utilization compared with non-users (53).

Genetic factors and susceptibility.

Beyond the demographic and clinical factors, the search for genetic markers for MOH is an emerging area of research (see Table 3). While less studied than the genetics of primary headaches like migraine, a systematic review found a potential role for polymorphisms within the dopaminergic gene system. These genetic variants, along with other genes related to drug-dependence pathways, may serve as susceptibility factors for the development of the disorder or influence the amount of medication consumed monthly (54).

Table 3. Risk factors associated with medication-overuse headache and their associations show a comparison between European and Latin American patients

Category	Risk Factors	Associations
Demographic	Female sex	Women are at higher risk, especially during reproductive years.
	Age <50 years	Younger and middle-aged adults are more commonly affected.
	Lower education level / low socioeconomic status	Associated with increased risk of overuse and poor access to preventive care.
Clinical	High baseline headache frequency	≥7–14 headache days/month strongly predict MOH development.
	Migraine (vs. other primary headaches)	Migraineurs, particularly chronic migraine patients, are more prone to MOH.
	Comorbid pain syndromes	Chronic musculoskeletal pain, lower back pain, fibromyalgia, and irritable bowel syndrome.
	Medical comorbidities	Hypercholesterolemia, arrhythmias, hypothyroidism.
Psychiatric	Depression and anxiety	Strongly associated with medication overuse and chronicity.
	Panic disorder, insomnia	Frequently comorbid, increasing vulnerability.
	Addiction-related traits	Impulsivity, dependence-related behaviors, ritualized drug use.
Lifestyle	Smoking	It has been identified as an independent risk factor in longitudinal studies.
	Sedentary behavior	Lack of physical activity increases the risk of chronicity.
	Constipation	Reported more frequently in MOH compared to episodic migraine.
Medication-related	Opioid overuse	Induces hyperalgesia, increases risk of refractory MOH.
	Triptan overuse	Associated with a rapid onset of MOH (≈1.7 years of use vs. ≈4.8 years with analgesics).
	Ergotamine overuse	Still prevalent in Latin America; associated with toxicity.
	Combination analgesics	High risk, even at lower intake thresholds.
	Benzodiazepines	Daily use is linked to persistence and relapse after detoxification.
Genetic / Biological	Dopaminergic gene polymorphisms (e.g., DRD2, DRD4, SLC6A3)	Associated with susceptibility and medication intake levels.
	Polymorphisms in BDNF, ACE, HDAC3, WFS1	Suggest involvement of neurotransmitter, metabolic, and dependence-related pathways.
	Altered endocannabinoid system (ECS) function	Reduced endocannabinoid levels reported in MOH patients.

Reported genetic associations

Recent studies have highlighted several gene variants and pathways implicated in MOH susceptibility (54,55):

- Dopaminergic pathways: DRD2, DRD4, SLC6A3, COMT
- CGRP pathway: RAMP1
- Substance-dependence mechanisms: ACE, BDNF, WFS1, HDAC3
- Metabolic pathways: CYP1A2, MTHFR
- Inflammatory response: TNF-β G252A

Among the most consistent associations, the following variants have been linked to MOH clinical characteristics:

- WFS1 His611Arg
- BDNF rs6265
- HDAC3 rs2530223
- 5HT2A C516T
- ACE I/D
- Haplotype combinations in SLC6A4 polymorphisms (STin2 VNTR–rs1042173)

CGRP and endocannabinoid pathways

- CGRP signaling. Clinical trials demonstrate that CGRP monoclonal antibodies (mAbs) are effective in CM prevention, even among subgroups with medication overuse (56).
- Endocannabinoid system. Some trial shows a regulation in pain perception, inflammation, and neurotransmission (57–60):
  1. Its main bioactive lipids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), act through CB1 and CB2 receptors.
  2. Enzymes controlling their synthesis and degradation maintain ECS homeostasis.
  3. Reduced endocannabinoid levels have been reported in MOH patients, indicating ECS dysfunction contributes to disease mechanisms.

Epidemiology and burden of disease in Latin America

Disability levels in MOH are markedly elevated, as the MIDAS score is nearly three times higher in MOH patients compared with those suffering from EM, and similar to other forms of chronic daily headache (61). Despite this, the true prevalence of MOH across countries is likely underestimated and has varied over time due to evolving diagnostic criteria and reporting methods (1).

With an urbanized population of approximately 85.5%, Latin America (LA) is estimated to reach around 670 million inhabitants by 2025, representing about 8% of the global population. However, epidemiological studies on MOH in this region remain scarce or are often classified under the broader category of chronic headache disorders (62,63).

The COMOESTAS project, which included MOH patients from six headache centers in Europe and LA (Argentina, Chile), found that the most frequent primary headache preceding MOH was migraine without aura (77%), among middle-aged adults in their 40s and 50s, predominantly females, with more than 50% reporting onset of primary headache before age 16 (64).

In the LA population, the mean duration of medication overuse was 3.9 years (range 1–30 years). The most overused drugs were ergotamine, alone or in combination with NSAIDs or caffeine (70%), while only 5% reported triptan overuse. Approximately one-third of patients sought emergency care for headache, consulted a general practitioner, underwent neurological evaluation, or had a cranial CT scan within the previous year (65). Compared with EM patients, those with MOH utilized healthcare resources more frequently (51) and exhibited poorer quality of life, as reflected by General Health Questionnaire-28 scores (66). Table 4 illustrates the contrasting patterns of MO and healthcare-seeking behavior between Latin America and Europe.

Table 4. Comparison of medication overuse patterns and healthcare utilization between Latin America and Europe

Indicator	Latin America	Europe
Most overused drug	Ergotamine's (70%)	Triptans (31%)
Use of NSAIDs	33%	54%
Use of combinations	6.3%	24%
Consultation with a general practitioner	27%	57%
Consultation to a headache specialist	38%	83%

Data from the Global Burden of Disease 2021 project revealed that between 1990 and 2021, LA experienced the greatest global increase in migraine burden, with an estimated annual percentage change (EAPC) of 0.28 for prevalence and 0.26 for disability-adjusted life years (DALYs). The Andean subregion showed EAPCs of 0.23 and 0.21, respectively, while Southern and Tropical LA also demonstrated upward trends—likely reflecting rapid urbanization, lifestyle shifts, suboptimal migraine management, and insufficient preventive strategies (67,68).

A Population-based study showed that patients with probable MOH experience headaches an average of 22 days per month, lasting about 7 hours with moderate intensity. The mean proportion of time spent in the ictal state was 24.9%, with an average health loss of 5.6% (disability weight for MOH = 0.223). Both genders showed impaired participation in daily life, from paid work, household activities, and social or leisure pursuits. Interestingly, males reported greater productivity losses

from paid work compared with females (69).
Treatment interventions for MOH in LA have shown a significant reduction in indirect costs and patient burden. Approximately 50% of patients reduced their medication intake by more than 70%. Productivity loss related to headaches (either due to absenteeism or reduced on-the-job efficiency) was reduced by 28% and 49%, respectively, as measured by the MIDAS questionnaire (70,71). Follow-up studies demonstrated sustained benefits, with around half of patients discontinuing medication overuse and reverting to episodic headache within six months (72).

Research gaps and future perspectives

MOH remains a complex and disabling condition at the intersection of primary headache disorders, neurobiological sensitization, and dependence-related behaviors. As part of the comprehensive treatment of migraine with medication overuse, early clinical recognition and further interventions are recommended to prevent the development of addictive behaviors. However, outcomes are complicated, particularly in cases with opioid overuse, psychiatric comorbidities, or failed detoxification attempts. It is important to highlight the importance of MOH prevention; migraine preventive treatment and education on limiting acute medication use are key strategies to minimize MOH risk (72).

MOH also carries a substantial economic burden, increasing both direct and indirect healthcare costs at the individual and societal levels. Predictive models suggest prevalence will continue to rise through 2050, further straining healthcare systems. In Latin America, ergotamine remains the most commonly overused drug, despite being banned in many European countries due to its high toxicity risk. These disparities highlight critical weaknesses in detection and management across regions, underscoring the need for improved clinician education, enhanced clinical diagnostic accuracy, and targeted public health strategies to mitigate the rising global impact of MOH.

Persistent gaps in knowledge include the precise mechanisms by which different drug classes induce MOH, the neurobiological basis of chronification, and the role of genetic and ECS dysfunction in shaping susceptibility. Future research should prioritize identifying biomarkers to predict risk and treatment response, clarifying the mechanisms of drug-specific sensitization, and developing tailored therapeutic interventions that integrate behavioral, pharmacological, and preventive approaches. Addressing these gaps will be crucial to improving outcomes and mitigating the growing health and socioeconomic burden of MOH worldwide.

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Conflicts of interest: The authors declare no conflict of interest related to this work.
Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.