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REVIEW

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Breaking the medication overuse headache cycle: from nociplastic pain mechanisms to patient-centered interventions — the Junior Editorial Board vision

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Abstract

Background Medication-overuse headache (MOH) is a prevalent and disabling secondary headache disorder that arises in individuals with a pre-existing primary headache as a consequence of regular overuse of acute medications. Increasing evidence suggests that MOH shares fundamental pathophysiological and behavioural features with nociplastic pain conditions, supporting the view that it cannot be explained solely as a pharmacological complication. Rather, MOH appears to reflect complex interactions between neurobiological vulnerability, maladaptive neuroplasticity, and behavioural factors. In this review, we reappraise MOH through the lens of nociplastic pain to provide a unifying framework for its pathophysiology and management.

Main body Evidence from neuroimaging, neurophysiological, genetic, and experimental studies consistently indicates that MOH is associated with central sensitization, impaired descending pain modulation, and dysfunction of reward and cognitive control networks, particularly involving fronto-striatal and brainstem circuits. These alterations closely resemble those observed in other nociplastic pain conditions and appear largely reversible following successful withdrawal and preventive treatment. Behavioural features such as craving, impulsivity, catastrophizing, and cephalalgiophobia play a pivotal role in maintaining medication overuse and predicting poor outcomes, reinforcing the conceptualization of MOH as a biobehavioural syndrome. Management strategies have evolved from detoxification-centered approaches toward integrated, patient-centered care. While withdrawal remains a cornerstone of treatment, growing evidence supports flexible strategies in which preventive therapies, especially CGRP-targeting monoclonal antibodies and gepants, can be initiated before or alongside withdrawal, reducing headache burden and facilitating disengagement from acute medication overuse. Behavioural and psychological interventions, including cognitive behavioural therapy and mindfulness-based approaches, are essential to address emotional drivers, enhance adherence, and modulate nociplastic mechanisms. Current guidelines increasingly endorse multimodal and multidisciplinary management, although evidence quality remains heterogeneous.

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Conclusion Reframing MOH within a nociplastic pain framework supports a shift from rigid detoxification models toward personalized, mechanism-based, and multidisciplinary care. Future research integrating clinical, imaging, neurobiological, and behavioural markers, potentially supported by artificial intelligence–based predictive models, may further refine patient stratification and optimize long-term outcomes in MOH.

Keywords Medication-overuse headache, Nociplastic pain, Central sensitization, CGRP-targeting therapies, Behavioural interventions, Withdrawal, Personalized medicine

Introduction

Medication-overuse headache (MOH) is a disabling secondary headache disorder occurring in individuals with a pre-existing primary headache due to regular overuse of acute medications for more than three months. It should be distinguished from medication overuse, which refers to excessive intake of acute medications that may occur without headache chronification, whereas MOH is characterized by chronic headache attributed to such overuse [1].

MOH affects approximately 1–2% of the general population, disproportionately impacts women in their most productive years, and represents a frequent cause of referral to tertiary headache centres [2]. It is associated with substantial disability, impaired quality of life, and a significant socioeconomic burden [3]. Migraine is the most common underlying disorder, followed by tension-type headache, often associated with non-steroidal anti-inflammatory drugs (NSAIDs) overuse, while cluster headache represents a less frequent but clinically relevant substrate [4, 5]. Triptans, NSAIDs, opioids, and combination analgesics differ in their propensity to induce MOH and clinical course: triptans are linked to faster onset but quicker resolution after withdrawal, NSAIDs contribute substantially to MOH, particularly in tension-type headache, opioids are associated with more severe and refractory disease, and combination analgesics carry a high risk of dependence-like behaviours [6].

Nociplastic pain, introduced by the International Association for the Study of Pain (IASP), provides a useful framework to reinterpret MOH. Nociplastic pain arises from altered nociceptive processing in the absence of clear evidence of tissue damage or disease or lesion of the somatosensory system [7]. Although different primary headache disorders have distinct pathophysiological mechanisms, central sensitization, maladaptive neuroplasticity, and impaired descending pain modulation, hallmarks of nociplastic pain, are consistently observed in alla type of primary headache disorders and MOH [8]. Nociplastic pain is typically characterized by spontaneous pain without a clear peripheral driver, whereas MOH is associated with a well-defined trigger, namely repeated exposure to acute medications. In this context, MOH may be conceptualized as a condition with nociplastic features, regardless of the underlying primary headache type, in which sustained medication overuse contributes to maladaptive plasticity and promotes a shift toward altered pain processing. This evidence supports the view of nociplastic pain as a unifying pathophysiological framework across headache disorders [9]. Epidemiological data further support this overlap, as chronic migraine (CM), chronic tension-type headache, and MOH frequently co-occur with other nociplastic pain conditions, including fibromyalgia and irritable bowel syndrome [4, 10, 11]. This reconceptualization suggests that MOH management should extend beyond medication withdrawal to include preventive pharmacological therapies, behavioural and psychological interventions, and lifestyle modifications targeting central pain dysregulation. Accordingly, this review re-evaluates MOH pathophysiology through the lens of nociplastic pain and proposes a personalized, multidimensional management framework.

Pathophysiology and neurobiology

Although MOH is a well-recognized clinical entity, its pathophysiology remains incompletely understood. Available evidence indicates maladaptive neuroplastic changes affecting both ascending nociceptive transmission and descending modulatory pathways at cortical and brainstem levels. These alterations include central sensitization, characterized by increased responsiveness to nociceptive and non-nociceptive inputs, together with impaired pain control mechanisms. According to the IASP, central sensitization is defined as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [12]. Chronic exposure to acute headache medications also induces peripheral sensitization, driven by activation of trigeminovascular afferents and neurogenic inflammation. Repeated peripheral nociceptive input may promote a shift toward predominant central sensitization and nociplastic pain features, leading to sustained hyperexcitability within central pain pathways [2].

While both peripheral and central sensitization contribute to MOH pathophysiology, central sensitization appears to predominate, likely reflecting maladaptive plasticity, increased central pain network activity, and impaired descending pain modulation. In addition, genetic susceptibility and inflammatory mechanisms, including alterations of the gut–brain axis, may

contribute to the underlying biological vulnerability observed in MOH [2, 4].

Sensitization of pain networks

Evidence from animal models

Basic research studies support a close link between MOH and central sensitization, showing that repeated administration of acute headache medications, including triptans, NSAIDs, and paracetamol, induces persistent neuroplastic changes within pain networks. In a triptan-induced MOH model, six injections of sumatriptan administered every other day produced time-dependent and generalized allodynia in both cephalic and extracephalic regions [13]. Notably, even 14 days after drug discontinuation, animals displayed exaggerated behavioral responses to a nitric oxide (NO) donor, which induced delayed and prolonged cutaneous allodynia resembling NO-triggered migraine attacks, indicating sustained peripheral and central sensitization [13]. This latent pronociceptive state was accompanied by increased and persistent expression of calcitonin gene-related peptide (CGRP) and substance P in the trigeminal ganglia [13]. Consistently, prolonged exposure to eletriptan or indomethacin for 30 days resulted in upregulation of multiple genes involved in migraine pathophysiology, including CGRP, pituitary adenylate cyclase-activating protein (PACAP), vasoactive intestinal polypeptide (VIP), somatostatin, transient receptor potential vanilloid 1 (TRPV1) channel, and cyclooxygenases (COX-1 and COX-2) [14].

Alterations at the network level have also been demonstrated. Repeated rizatriptan administration induced mechanical allodynia in response to bright light stress, and in a glyceryl trinitrate–induced CM model, mice exhibited increased activation of bright-light–responsive neurons in the spinal trigeminal nucleus caudalis, indicating long-lasting neuroplastic changes in trigeminal nociceptive processing [15]. In a rizatriptan model, network analyses identified the spinal trigeminal nucleus caudalis and prelimbic cortex as key hub regions, with altered connectivity between the prelimbic cortex, insula, and spinal trigeminal nucleus implicated in MOH development [16]. Finally, animal studies have shown that repeated and long-term administration of acute headache medications increases susceptibility to cortical spreading depression (CSD) [17–19]. Chronic exposure is associated with altered serotonin signalling, including increased CSD-evoked 5-HT_{2A} receptor expression and c-Fos activation in the cortex and trigeminal nucleus caudalis [19–21], as well as dysregulation of serotonin receptors and transporters in the frontal cortex following prolonged paracetamol administration [22].

Evidence from neurophysiological studies

Neurophysiological findings also support the presence of cortical and subcortical hyperexcitability in MOH patients. An early study using pain-related evoked potentials demonstrated facilitation of trigeminal and somatic cortical responses with preserved brainstem reflexes, indicating a predominant supraspinal sensitization that normalized after withdrawal [23]. Nociceptive withdrawal reflex paradigms further showed a reduced temporal summation threshold and deficient diffuse noxious inhibitory control, both of which improved following detoxification, reflecting reversible spinal and supraspinal disinhibition [24, 25]. Laser-evoked potential recordings confirmed that habituation deficits of the N2/P2 complex recovered only in clinically improved patients [26]. Subsequent work using somatosensory evoked potentials (SSEPs) demonstrated increased thalamocortical activation and enhanced lateral cortical inhibition, suggesting hyperresponsiveness of both ascending and modulatory systems [27, 28]. SSEP analyses, including high-frequency oscillation, revealed that hyperexcitability of the thalamocortical drive and impaired habituation normalized after medication withdrawal [29]. Complementary repetitive transcranial magnetic stimulation (rTMS) studies showed reduced cortical inhibition in triptan overusers and abnormal short-term potentiation that reverted after detoxification [30, 31]. More recently, a visual evoked potential study reported excessive suppression of cortical responses to repeated stimuli, suggesting overactivation of parieto-occipital inhibitory networks as a possible adaptive shift following chronic overuse [32]. Quantitative sensory testing (QST) is a valuable tool to characterize altered pain processing. In nociplastic pain conditions, it consistently demonstrates widespread pain hypersensitivity, including hyperalgesia and allodynia extending beyond the primary site of symptoms, supporting a predominant central dysfunction. Dynamic measures further reveal increased temporal summation, reflecting enhanced facilitatory mechanisms, and reduced conditioned pain modulation, indicating impaired descending inhibitory control [8]. Similarly, studies in MOH have shown widespread pain hypersensitivity, increased temporal summation, and reduced conditioned pain modulation, consistent with enhanced central facilitation and impaired inhibitory control [24, 33]. Notably, these alterations appear at least partially reversible following medication withdrawal, supporting a model of maladaptive yet dynamic central pain processing [24]. These findings align MOH with other nociplastic pain disorders characterized by hyperexcitability, defective habituation, and impaired descending inhibitory control, highlighting its reversible yet state-dependent neurophysiological dysfunction [7].

Evidence from neuroimaging studies

Neuroimaging evidence indicates that MOH, similarly to other chronic pain syndromes, is characterized by alterations of central nociceptive networks. Structural magnetic resonance imaging (MRI) studies have identified gray matter volume changes in brain regions involved in pain processing and modulation, including the periaqueductal gray, thalamus, anterior cingulate cortex (ACC), insula, and orbitofrontal cortex (OFC) [34]. Importantly, longitudinal investigations have shown partial or complete normalization of these alterations following medication withdrawal, supporting maladaptive but reversible neuroplastic changes rather than irreversible damage [34, 35]. Functional neuroimaging findings further support the dynamic nature of MOH-related brain alterations. Functional MRI studies report reduced activation within nociceptive networks, including the primary somatosensory cortex and parietal regions, with recovery of normal activation patterns within months after withdrawal [36]. In parallel, enhanced responsiveness of the trigeminothalamic system has been described, resembling findings observed in other central sensitization conditions [37]. Comparative studies revealed both shared and condition-specific patterns of dysfunction: MOH showed altered activity of the periaqueductal gray, orbitofrontal cortex, and mesocorticolimbic structures, particularly the nucleus accumbens and frontal regions, partly overlapping with CM and irritable bowel syndrome, but differing from fibromyalgia, which is characterized by more widespread sensory amplification and default mode network alterations, with less involvement of reward-related circuits [38–43].

Beyond nociceptive networks, converging molecular and functional MRI evidence highlights a prominent involvement of reward-related circuits in MOH. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) studies demonstrated hypometabolism in the thalamus, ACC, insula, and OFC, with persistent OFC hypometabolism after withdrawal, suggesting maladaptive reward processing and vulnerability to relapse [39]. Consistently, dysfunction of mesocorticolimbic dopaminergic pathways and altered functional connectivity within motivational and default mode networks have been reported [38, 39, 44]. Overall, MOH combines central sensitization with a distinctive dysregulation of reward-related networks, distinguishing it from other chronic pain conditions.

Genetic factors

Clinical and epidemiological evidence suggests that MOH has a genetic component. The disorder predominantly occurs in individuals with pre-existing primary headache disorders, particularly migraine, and is more frequent among those with a family history of MOH or substance use, suggesting a heritable vulnerability [45–47]. Candidate gene studies indicate that genetic factors may influence not only susceptibility but also disease expression and clinical course. The ACE insertion/deletion polymorphism has been associated with chronic daily headache with medication overuse and with altered cortical sensory processing in MOH, implicating vascular regulation and mechanisms of headache chronification [48]. Although the BDNF Val66Met variant does not appear to confer a direct risk for MOH, Val66Met allele carriers within medication overuse cohorts showed higher drug intake and longer disease duration, consistent with its role in synaptic plasticity and central sensitization [49]. Similarly, variants in COMT (rs4680, rs6269 and related haplotypes) and in the serotonin transporter gene SLC6A4 (5-HTTLPR and STin2) have been linked to pain sensitivity, headache burden, and relapse after withdrawal, suggesting modulation of disease severity and treatment outcome rather than baseline susceptibility [50, 51].

Beyond monoaminergic pathways, glutamatergic mechanisms may contribute to cortical sensitization in MOH. The GRIA3 rs3761555 variant has been shown to influence somatosensory evoked potential amplitudes in MOH patients, supporting a role for glutamate-driven plasticity within pain networks [52]. Pharmacogenomic influences have also been described: while the WFS1 His611Arg polymorphism does not differ in frequency between MOH patients, episodic migraine, and controls, the R/R genotype has been associated with markedly higher consumption of symptomatic medications, particularly combination analgesics, within the MOH group [53]. Together, these findings suggest that genetic factors in MOH preferentially modulate medication use behaviour, impulsivity, and relapse risk, aligning with the overlap of this disorder with addiction-related pathways. In line with this view, recent genome-wide association studies of chronic overlapping pain conditions have demonstrated that nociplastic pain is a polygenic and heritable trait, with enrichment of headache- and migraine-related gene sets, supporting shared genetic vulnerability between migraine and MOH [54]. Finally, epigenetic mechanisms may further shape MOH susceptibility. A case–control study reported altered DNA methylation patterns in MOH patients, including hypermethylation of CORIN, CCKBR, and CLDN9 in innate immune cells, alongside increased neutrophil-to-lymphocyte ratios that improved with headache frequency reduction, suggesting an interaction between epigenetic regulation, immune activation, and disease expression [55].

Inflammation

A growing body of clinical and preclinical evidence supports a role for systemic inflammation and gut

Table 1 Withdrawal strategies and clinical outcomes across randomized controlled trials in medication overuse headache

Study (first author, year)	Country	Sample size (*n*, % female)	Setting	Withdrawal timing	Withdrawal intensity	Rescue medication	Duration of withdrawal / total follow-up period	Bridging/Preventive treatment	Main results
Rossi, 2006 (90)	Italy	120 (84%)	Inpatient vs. Outpatient	Abrupt (advice alone vs. structured detoxification)	Complete	Indomethacin, naproxen, or eletriptan (≤ 2 days/week)	8 days (inpatient) / 2 months	Prednisone (not in advice-only group) / Concurrent preventives	Simple strong advice alone was as effective as structured pharmacological detoxification.
Bøe, 2007 (96)	Norway	100 (74%)	Inpatient (3-day)	Abrupt	Complete	Only hypnotics or antiemetics	4 weeks / 4 weeks	Prednisone vs. placebo (6-day) / Preventives tapered off	Prednisone did not shorten or reduce withdrawal headache compared with placebo.
Pageler, 2008 (98)	Germany	20 (94%)	Inpatient	Abrupt	Complete	IV lysine acetylsalicyclic acid	5 days / 5 days	Prednisone vs. placebo	Prednisone significantly reduced duration and severity of withdrawal headache compared with placebo.
Hagen, 2009 (81)	Norway	56 (60%)	Outpatient	Abrupt	Complete	Diclofenac, naproxen, or metoclopramide (≤ 2 days/week)	3 months / 12 months	Arm-specific	Preventive treatment alone was more effective than withdrawal alone.
Créac'h, 2011 (93)	France	82 (78%)	Inpatient vs. Outpatient	Abrupt	Complete	Cryotherapy, TENS or NSAIDS (≤ 2 days/week)	8 days / 2 years	Bridging: Amitriptyline / Concurrent preventives	In-patient supervision offered no benefit over out-patient withdrawal in efficacy or comfort.
Sandrini, 2011 (99)	Italy	68 (80%)	Inpatient or day-hospital	Abrupt	Complete	IM ketoprofen	8 ± 2 days / 12 weeks	Botulinum toxin type-A (BTA) vs. placebo	BTA did not reduced headache days, however, did reduce days with acute med use, compared to placebo.
Rossi, 2013 (94)	Italy	137 (80%)	Inpatient vs. Outpatient	Abrupt (advice alone vs. structured detoxification)	Complete	Acetaminophen, indomethacin, naproxen, or triptans (≤ 2 days/week)	10 days (inpatient) / 2 months	Prednisone (not in advice-only group) / Concurrent preventives	For patients with complicated MOH, inpatient withdrawal was significantly more effective than advice alone or an outpatient withdrawal setting.
Rabe, 2013 (87)	Germany	96 (84%)	Mixed (Inpatient or Outpatient)	Abrupt	Complete	Allowed; Type not standardized	5 days / 14 days	Prednisone vs. placebo / Concurrent preventives	Prednisone did not shorten or attenuate withdrawal headache, bur reduced rescue med use.
Sarchielli, 2014 (88)	Italy	88 (78%)	Inpatient	Abrupt	Complete	Allowed; Type not standardized	6 days / 24 weeks	Valproate vs. placebo (12 weeks)	Valproate group showed reduction in headache days in 12 weeks, but not in 24 weeks, compared to placebo. was higher in the sodium valproate (45.0%) than in the placebo arm (23.8%)
Kristoffersen, 2015 (86)	Norway	60 (87%)	Outpatient	Gradual (advice-based)	Reduced intake (advice)	Allowed; Type not standardized	3 months	About 16–20% used preventives (No difference between arms)	A single brief consultation significantly reduced both medication and headache days.
Taghdiri, 2015 (89)	Iran	80 (89%)	Outpatient	Abrupt	Complete	Allowed; Type not standardized	8 weeks / 8 weeks	Bridging: Prednisone or celecoxib / Preventive: topiramate	Both celecoxib and prednisone equally reduced headache frequency and rescue med use.
Rausa, 2016 (145)	Italy	27 (85%)	Outpatient	Advice only	Reduced intake (advice)	Allowed; Type not standardized	4 months	Concurrent preventives (with or without 9 weekly sessions of EMG biofeedback)	Biofeedback + pharmacotherapy showed higher rate of episodic conversion and reduced analgesic intake, compared to pharmacotherapy only.

Table 1 (continued)

Study (first author, year)	Country	Sample size (*n*, % female)	Setting	Withdrawal timing	Withdrawal intensity	Rescue medication	Duration of withdrawal / total follow-up period	Bridging/Preventive treatment	Main results
Cevoli, 2017 (101)	Italy	57 (88%)	Inpatient	Abrupt	Complete	Only hypnotics or antiemetics	5 days / 3 months	Concurrent preventives	No significant difference between methylprednisolone IV, paracetamol IV, and placebo on headache outcomes.
Carlsen, 2018 (83)	Denmark	72 (79%)	Outpatient	Abrupt	Complete vs. Restriction (≤ 2 days/week)	levomepromazine or promethazine + (For reduced intake group) usual med	2 months / 12 months	Subsequent preventives	Complete withdrawal showed higher efficacy in reduced headache days and episodic conversion, compared to reduced intake.
Pijpers, 2019 (100)	Netherlands	179 (76%)	Outpatient	Abrupt	Complete	No allowance	12 weeks / 48 weeks	BTA vs. placebo / Other preventives tapered off	BTA did not afford any additional benefit over acute withdrawal alone.
Carlsen, 2020 (85)	Denmark	120 (77%)	Outpatient	Abrupt	Complete vs. No restriction	Only hypnotics or antiemetics (withdrawal period). Short-term medications ≤ 9 days/month (follow-up period).	8 weeks / 32 weeks	Concurrent preventives vs. None	Withdrawal combined with prevention was superior to withdrawal only or prevention only.
Schwedt, 2022 (91)	USA	720 (88%)	Outpatient	No formal withdrawal	Restriction (≤ 2 days/week) vs. No restriction	(Switching arm) To other class of acute med. (Non-switching) Usual med without restriction	12 weeks	Concurrent preventives	Non-switching was noninferior to switching for reduction of moderate-severe headache days.
Grazzi, 2023 (97)	Italy	177 (89%)	Inpatient or day-hospital	Abrupt	Complete	IV metoclopramide or indomethacin	5–8 days / 12 months	IV steroids and ademetionine, followed by oral steroids and benzodiazepines (during withdrawal) / Mindfulness program (during follow up)	Additional mindfulness program showed additive effect in reduction of headache frequency, disability and impact.

barrier dysfunction in MOH. In rodent models of NSAID-induced MOH, elevated circulating levels of lipopolysaccharide binding protein, VE-cadherin, and occludin have been demonstrated, consistent with disruption of intestinal and vascular barriers and the translocation of bacterial endotoxin. These changes were paralleled by increases in IL-6, IL-17, HMGB1, and CGRP, all of which are implicated in trigeminovascular sensitisation and maintenance of chronic pain [56]. Human studies have provided converging evidence. In a clinical cohort of patients with CM and MOH, serum levels of LPS, HMGB1, HIF-1α, IL-6, CGRP, and VE-cadherin were significantly elevated compared to episodic migraine and healthy controls, and these elevations correlated with headache frequency, disability, and measures of anxiety and depression. Importantly, nearly half of MOH patients also reported irritable bowel syndrome, and those individuals showed higher VE-cadherin levels, underscoring gut–brain interactions [57]. Another animal study has shown that immune regulation contributes to MOH pathophysiology. In a sumatriptan-overuse model, CCL2–CCR2 chemokine signalling was not required for the induction of behavioural sensitisation but was essential for the therapeutic effect of low-dose interleukin-2, which reverses sensitisation through expansion and infiltration of regulatory T cells into the dura and trigeminal ganglion [58]. These findings highlight the role of neuroimmune interactions in MOH resolution and suggest that immune-targeted therapies may represent a new pathway. Similar patterns have also been reported in fibromyalgia, irritable bowel syndrome, and other nociplastic pain conditions, suggesting shared biological mechanisms [57, 59].

Psychological dimensions

MOH is increasingly recognized as a disorder with substantial psychological and behavioural implications [60]. Key psychological dimensions include craving, impulsivity, and maladaptive coping mechanisms, which sustain medication overuse and predict poorer outcomes after withdrawal [61]. Up to 65–70% of patients show behavioural features consistent with psychological dependence on acute medications, even without dose escalation typical of substance use disorders [62]. Craving, affecting more than half of patients, is often associated with anticipatory anxiety and fear of headache recurrence, creating a self-reinforcing loop in which emotional dysregulation drives medication intake beyond pain intensity [63, 64]. Impulsivity, particularly in the urgency and lack of premeditation domains, is elevated in MOH [65, 66]. Neuroimaging studies support these findings, demonstrating functional alterations in fronto-striatal circuits, including reduced activation of the dorsolateral prefrontal cortex and ACC, key regions for inhibitory control and decision-making [67]. Psychiatric comorbidities further complicate clinical management. Depression and anxiety are reported in up to 35–50% of patients, often at subthreshold levels that increase disability and relapse risk [61, 68–70]. Additionally, pain catastrophizing, marked by magnification of pain threat and helplessness, is observed in several cases and correlates with higher medication consumption and worse outcomes [71]. Cephalalgiophobia, an excessive fear of headache recurrence, promotes anticipatory medication use, avoidance behaviours, and hypervigilance, and is present in more than 50% of MOH patients [72, 73]. High cephalalgiophobia scores are associated with anxiety, medication misuse, and reduced withdrawal success. Overall, these findings support the view of MOH as a biobehavioural syndrome rather than a purely pharmacological complication. Assessment of craving, impulsivity, and cephalalgiophobia may improve risk stratification, treatment personalization, and long-term outcomes.

These psychological features overlap with those observed in other nociplastic pain conditions, commonly associated with depression, anxiety, and catastrophizing [74]. Catastrophizing is linked to increased opioid use and exaggerated negative cognitive–affective responses to pain, and similarly contributes to medication overuse in MOH [75, 76]. Craving for medications in nociplastic pain correlates with catastrophizing, suggesting a complex interaction between psychological aspects often present also in MOH [77]. Nociplastic pain can be conceptualized as a learned process of threat, fear, and maladaptive coping that perpetuates chronic pain and medication overuse [78]. These shared features support considering MOH within a nociplastic pain framework to improve understanding and promote multidisciplinary management.

Withdrawal strategies: therapeutic approaches, outcomes and limitations

Withdrawal of the overused medication remains the cornerstone of management for MOH. Early clinical studies in the 1980s and 1990s demonstrated that medication withdrawal leads to long-term reductions in headache frequency and intensity [79, 80]. Later, a multicenter randomized controlled trial (RCT) confirmed that abrupt withdrawal significantly decreased both the duration of headache and the number of days with acute medication use compared with continued treatment [81]. The primary rationale is not merely to stop the offending agent but to restore the balance of the pain-modulating system and reverse central sensitization [24, 82]. Nevertheless, the optimal withdrawal approach remains debated. Table 1 summarizes withdrawal strategies applied across RCTs in MOH, which vary in timing (abrupt vs. gradual),

intensity (complete cessation vs. reduced intake), setting (inpatient vs. outpatient), and duration.

Withdrawal timing and intensity

Withdrawal timing refers to the speed of discontinuation, distinguishing abrupt (immediate) from gradual (stepwise) withdrawal, whereas intensity indicates whether the overused medication is completely discontinued or merely reduced in frequency. In clinical practice, these constructs often overlap: abrupt withdrawal is typically complete, whereas gradual strategies generally involve restricted use rather than complete cessation. Evidence from RCTs suggests that both the speed and extent of withdrawal critically influence outcomes. In a Danish RCT, Carlsen et al. randomized 72 patients with MOH to either complete withdrawal or reduced intake (≤ 2 days/week) for 8 weeks and followed them for 12 months. Both approaches were effective, but complete withdrawal achieved greater reductions in monthly headache days (-46% vs. -22%, $p = 0.005$) and higher conversion rates to episodic migraine (50% vs. 42%, $p = 0.04$) [83]. In terms of feasibility, only 9% of patients in the complete-withdrawal group reported that it was "very difficult or impossible" to stop overusing medication, compared with 68% in the reduced-intake group ($p < 0.001$) [84]. Both groups were treated on an outpatient basis, with only one dropout (in the complete-withdrawal arm) and no adherence difference between strategies. A subsequent three-arm RCT by the same group compared complete withdrawal plus preventive medication versus preventive medication alone or withdrawal only. Although the groups showed no difference in migraine days or headache intensity, the combination group achieved the highest rate of MOH resolution (96.8% vs. 74.3% vs. 88.9%, respectively, $p = 0.03$) [85].

Rescue medication policy during the withdrawal phase is another key determinant. Several studies provided withdrawal instructions without specifying restrictions on rescue medication [86–89], whereas others allowed only predefined agents, such as levomepromazine, metoclopramide, indomethacin, or triptans [81, 83, 85, 90]. From a clinical perspective, the choice of rescue medication is likely to depend on the type of overused drug, the desired intensity of withdrawal and the treatment setting (inpatient vs. outpatient). Recently, the MOTS trial, a large multicenter pragmatic randomized controlled trial conducted in the United States, randomized patients with CM and MOH to either switch to a different class of acute medication with restricted intake (≤ 2 days/week) or continue their current overused medication without intake limitations [91]. All participants received concurrent preventive therapy, and all interventions were performed in the outpatient setting. After 12 weeks, the non-switching group was noninferior to the switching group in reducing moderate-to-severe headache days (-9.1 vs. -9.3 days, $p = 0.75$).

Setting and duration of withdrawal

Inpatient programs allow strict supervision and faster detoxification, typically over 3–10 days, which coincides with the expected period of transient withdrawal headache, often accompanied by nausea, sleep disturbances, and irritability [92]. While inpatient withdrawal ensures close monitoring and early control of acute symptoms, it is resource-intensive and less accessible. In contrast, structured outpatient protocols employ longer but more flexible schedules, often spanning several weeks, with comparable long-term outcomes. In a French RCT including 71 patients with MOH, complete withdrawal performed in inpatient versus outpatient settings yielded no significant difference in monthly headache-day reduction (41% vs. 51%, $p = 0.140$ at two months; 53% vs. 55%, $p = 0.964$ at two years) or reversion to episodic headache (51% vs. 61%, $p = 0.477$ at two months; 46% vs. 53%, $p = 0.638$ at two years) [93]. Similarly, in an Italian RCT of 120 MOH patients without major medical or psychiatric comorbidities, inpatient withdrawal (including prednisone, fluid replacement, and antiemetics) and intensive outpatient advice achieved similar rates of conversion to episodic migraine after two months (76.9% vs. 77.5%, $p > 0.05$) [90]. However, a subsequent RCT by the same group focusing on complicated MOH, including patients with comorbid medical illness or psychiatric disorders, found that inpatient withdrawal achieved superior outcomes (88.8% vs. 60.1%, $p < 0.01$) [94]. Likewise, the COMOESTAS study, a large multicenter open-label trial conducted from seven different countries, compared inpatient and outpatient withdrawal in 376 MOH patients and found no significant difference in the proportion reverting to episodic headache (54.7% vs. 50.0%, $p > 0.05$) after 6 months [95]. Notably, none of these studies included patients overusing opioids or barbiturates.

Regarding withdrawal duration, protocols vary widely, and currently there is no existing consensus. Inpatient programs generally employ absolute withdrawal over 3–10 days [90, 94, 96–99], whereas outpatient regimens extend from four weeks to three months [81, 83, 91, 100], reflecting flexibility in managing adherence and rebound symptoms.

Bridge therapies to manage rebound symptoms

The abrupt or gradual discontinuation of overused medications frequently leads to a transient worsening of headache frequency and intensity [101]. This withdrawal phase is commonly associated with additional rebound symptoms, such as nausea, vomiting, sleep disturbances, anxiety, and restlessness, that typically last 2 to 10 days [101, 102]. This constellation of symptoms constitutes a

withdrawal syndrome that can severely burden patients with MOH and often undermines adherence to discontinuation. To improve tolerability and facilitate successful detoxification, expert consensus recommends the use of pharmacological bridging therapies, including corticosteroids and antiemetics [102].

Corticosteroids are the most extensively studied agents for bridging therapy. Initial enthusiasm stemmed from positive findings in a large case series, which led expert consensus to support their use [103, 104]. A subsequent small retrospective study further suggested that combined intravenous prednisone and diazepam could reduce both headache frequency and withdrawal symptoms compared with untreated discontinuation [87, 96, 101, 105]. However, RCTs evaluating corticosteroids during MOH withdrawal failed to demonstrate superiority of prednisone or prednisolone over placebo [104]. Although additional evidence is needed to draw firm conclusions, current data increasingly suggest limited efficacy of corticosteroids as bridging agents, leading to a trend away from their routine use.

Antiemetics, such as prochlorperazine and metoclopramide, have also been proposed as potential bridging options, though supporting data remain scarce. While these agents are effective in alleviating migraine-associated nausea and vomiting, robust RCTs specifically addressing their role in MOH withdrawal are lacking [103]. Nevertheless, expert consensus continues to endorse their use, either as monotherapy or in combination with corticosteroids, particularly for patients with moderate to severe withdrawal symptoms in whom nausea and vomiting are prominent features.

Clinical implications and limitations

Across randomized and observational studies, medication withdrawal alone leads to substantial improvement in most patients with MOH. Approximately 50–70% experience at least a 50% reduction in headache frequency or reversion to an episodic pattern within three to six months after discontinuation [81, 85, 95, 100]. Short-term outcomes are generally favorable, but relapse occurs in 10–45% of patients within 6–12 months, highlighting the importance of ongoing follow-up and preventive strategies after detoxification [92, 95]. Despite strong evidence supporting medication withdrawal as the foundation of MOH management, several methodological and practical challenges persist. Existing RCTs exhibit marked heterogeneity in withdrawal protocols, including differences in inclusion criteria, treatment setting, duration, and definitions of success. Blinding and placebo control are inherently challenging in withdrawal trials, introducing expectation bias and variability in adherence reporting. High dropout rates (up to 30%), often driven by early symptom worsening or anxiety about pain recurrence, further complicate interpretation of efficacy data [95]. Furthermore, from a clinical standpoint, the greatest limitation lies in poor tolerability and low adherence, which are influenced not only by the withdrawal protocol but also by the patient–physician relationship and degree of counseling. Taken together, these methodological and contextual disparities highlight the need for individualized, patient-centered approaches that balance efficacy, tolerability, and feasibility. Current evidence suggests that for most patients with MOH, outpatient-based withdrawal, whether through standardized protocols or intensive education, can achieve meaningful clinical benefit. If a patient refuses abrupt complete withdrawal, it may still be reasonable to maintain preventive treatment while switching the overused drug and restricting its intake, or even allowing continued acute medication. Conversely, inpatient withdrawal may be preferable in patients with medical or psychiatric comorbidities, opioid or barbiturate overuse, or prior failure of outpatient detoxification, where close monitoring can improve safety and success rates.

Preventive treatments

Timing of preventive treatment initiation: pre-withdrawal, concurrent, or post-withdrawal

In contrast to bridge therapies, which primarily address short-term withdrawal burden, preventive treatments aim to reduce long-term relapse risk by targeting mechanisms underlying headache chronification. When preventive medication is considered in MOH management, the optimal timing of initiation remains a key issue. The choice between bridge therapy alone, preventive treatment, or their combination should be individualized, considering headache severity, comorbidities, prior treatment history, and patient preference [103].

Two main strategies have been described: pre-withdrawal initiation of preventive therapy or initiation concurrent with withdrawal. Pre-withdrawal initiation involves starting preventive treatment while the patient continues overusing acute medication, with the aim of reducing baseline headache frequency and reliance on abortive drugs, potentially mitigating abrupt cessation and withdrawal symptoms [103, 106–110]. Supporting this approach, recent studies indicate that CGRP-targeting therapies can induce MOH remission, with reductions in acute medication use even without prior withdrawal. Notably, a prospective RCT reported no difference in the reduction of moderate-to-severe headache days between patients who modified acute medication intake and those who continued it while receiving preventive therapy [110].

Alternatively, preventive treatment may be initiated concurrently with withdrawal. Evidence suggests that this strategy may improve adherence, increase remission

rates, and facilitate reversion to episodic migraine [85, 111]. In a large RCT comparing withdrawal plus preventive therapy, withdrawal alone, and preventive therapy alone, all approaches reduced headache frequency; however, the combined strategy produced the greatest reductions in headache and migraine days, acute medication use, and pain intensity, as well as the highest likelihood of stopping overuse and reverting to an episodic pattern [85]. A subsequent analysis showed that this approach also most effectively reduced dependence-like behaviours, a key predictor of relapse [111]. Consistently, the COMOESTAS study demonstrated significant reductions in headache frequency and high rates of reversion to episodic headache when preventive therapy was initiated alongside withdrawal [95].

Overall, while both strategies appear effective, no trials have directly compared pre-withdrawal versus concurrent initiation. Current recommendations favor a stepwise approach, beginning with patient education, followed by bridge therapy in selected cases, and preventive treatment in patients at higher risk of severe withdrawal or relapse, including patients with daily headaches, previous detoxification failures, or frequent use of high-risk medications such as opioids, benzodiazepines, or barbiturates [93, 94, 103, 112, 113].

Pharmacological therapies

For many years, evidence guiding the management of MOH was limited, largely relying on small observational studies or without proper controls. Early RCTs primarily evaluated preventive treatments in CM populations, including subsets of patients with medication overuse. Two placebo-controlled multicenter RCTs assessing topiramate in CM reported inconsistent results in patients with medication overuse, with efficacy observed in the European but not the American trial, possibly reflecting differences in MOH prevalence and study design [114, 115]. Valproate has shown modest efficacy in a randomized study following medication withdrawal, but its use is limited by safety concerns, particularly in women of childbearing potential [88].

Evidence for onabotulinumtoxinA in MOH is mainly derived from subgroup analyses and real-world studies. In the PREEMPT trials, where a substantial proportion of patients had MOH, onabotulinumtoxinA significantly reduced headache frequency and disability compared with placebo, although reductions in overall acute medication use were less consistent [116, 117]. Long-term real-world data suggest greater efficacy with higher dosing (195 vs. 155 U) in patients who failed previous withdrawal and preventive attempts [118]. However, a dedicated RCT evaluating onabotulinumtoxinA as an add-on to acute withdrawal did not demonstrate superiority over withdrawal alone, highlighting the complexity of disentangling withdrawal and preventive effects [100].

Anti-CGRP monoclonal antibodies (mAbs) have emerged as highly effective and well-tolerated preventive treatments for CM, with growing evidence supporting their use in MOH. Post-hoc analyses of phase III RCTs and real-world studies consistently demonstrate that anti-CGRP mAbs reduce headache frequency, acute medication use, disability, and patient-reported outcomes in patients with MOH, even without prior discontinuation of overused medications [119–127]. Importantly, patients with MOH benefited from preventive treatment without prior discontinuation of overused medications, and those who reverted to non-overuse status maintained clinical benefits over 12 months. Consequently, current guidelines endorse anti-CGRP mAbs as preventive therapy for CM with MOH, in combination with education and reduction of acute medication use [119].

Small-molecule CGRP receptor antagonists (gepants) represent another effective preventive option. Post-hoc analyses and real-world data indicate that atogepant significantly reduces monthly headache and migraine days, improves patient-reported outcomes, and decreases acute medication intake in patients with CM and medication overuse, with rapid onset of benefit [127–130]. Like anti-CGRP mAbs, gepants appear effective regardless of immediate withdrawal, offering a pragmatic strategy to interrupt the MOH cycle while targeting migraine chronification mechanisms.

Anti-PACAP monoclonal antibodies represent an emerging preventive approach for migraine; however, their role in MOH remains speculative. While early data supports efficacy in reducing migraine frequency, dedicated studies in MOH populations are lacking, and their impact on medication overuse and relapse prevention has yet to be established [131, 132].

Notably, several preventive treatments used in MOH also show efficacy in comorbid nociplastic pain conditions. OnabotulinumtoxinA and anti-CGRP mAbs have demonstrated benefits in migraine patients with fibromyalgia, temporomandibular disorder, vulvodynia and other chronic pain syndromes, suggesting shared neurobiological mechanisms underlying migraine, MOH, and nociplastic pain [133–137]. In summary, preventive treatment represents a cornerstone of MOH management, particularly when combined with withdrawal strategies. While topiramate and onabotulinumtoxinA have moderate supporting evidence, anti-CGRP mAbs and gepants offer effective, well-tolerated, and withdrawal-independent options that improve headache control, reduce medication overuse, and lower relapse risk. Further RCTs are needed to optimize long-term strategies and clarify their role across overlapping nociplastic pain conditions.

Psychological and behavioural approaches

As MOH is characterized by excessive use of acute medications and impaired impulse control, with a strong biobehavioral component, behavioral interventions play a central role in its management. While withdrawal and pharmacological prophylaxis primarily address the physiological dimension, cognitive and emotional factors often persist and undermine long-term outcomes. Psychological approaches, including psychoeducation, motivational interviewing, cognitive behavioral therapy (CBT), and mindfulness, target these drivers, enhancing adherence, self-efficacy, and sustained recovery.

CBT, integrating cognitive and behavioral techniques, has demonstrated efficacy in promoting healthy lifestyle habits, improving coping strategies, reducing pain catastrophizing, and modifying maladaptive beliefs [138]. Patients with MOH frequently display dependency-related behaviors, such as anxiety over medication availability and perceived loss of control. Multiple studies showed that adding behavioral and educational interventions to standard withdrawal protocols improves outcomes, adherence, and self-management [139, 140]. Behavioral strategies are commonly integrated with withdrawal, with or without pharmacological prophylaxis, and this combined approach is supported by growing evidence. When structured education, headache diaries, and direct communication with healthcare providers are included, relapse risk is significantly reduced [97, 140–144]. Motivational interviewing, particularly when implemented after withdrawal, has been shown to reduce medication intake and improve coping, although its effect on headache frequency appears limited when added to pharmacological prophylaxis alone [139]. Other behavioral approaches, such as biofeedback and progressive muscle relaxation, have demonstrated benefits in long-term relapse prevention, with effects persisting up to three years in some studies [145, 146]. Mindfulness-based interventions have gained increasing attention, aiming to improve pain awareness, emotional regulation, and coping capacity [147–149]. When combined with standard withdrawal strategies, mindfulness has been associated with reductions in headache frequency, medication use, disability, and healthcare costs [97]. Notably, mindfulness-based programs alone have shown comparable long-term efficacy to pharmacological treatments in reducing headache frequency, disability, and depressive symptoms [150].

Behavioral support is particularly important during and after withdrawal. The phase III MIND-CM trial demonstrated that adding a six-session mindfulness program to standard care significantly increased the proportion of patients achieving a ≥ 50% reduction in headache days at 12 months compared with treatment as usual alone [97]. Functional MRI findings from the same cohort showed increased connectivity in salience and sensorimotor networks and cortical thickening in the insula and ACC, consistent with improved pain and emotion regulation [151]. Relapse data further highlight the importance of continued psychological care, with approximately 40% of patients relapsing within one year after withdrawal in the absence of ongoing behavioral support [152]. Behavioral interventions, particularly CBT and mindfulness, may contribute to clinical improvement not only by reducing medication reliance but also by modulating nociplastic mechanisms present in MOH through enhanced top–down inhibitory control and reduced catastrophizing. Emerging evidence suggests associated neuroplastic and neurochemical changes in serotonergic and dopaminergic systems within insular and mesocorticolimbic regions, providing a biological rationale for their integration into long-term MOH management [153]. Overall, these findings support behavioural therapies as integral to MOH management, targeting both psychological and nociplastic mechanisms, and highlight the importance of sustained therapeutic alliance.

Clinical practice guidelines: review and critical appraisal

Clinical practice guidelines provide structured recommendations for the management of MOH. All major guidelines adopt the International Classification of Headache Disorders (ICHD-3) diagnostic criteria [154] and emphasize prevention, with education and counselling as the first and essential step [103, 155, 156]. The European Academy of Neurology (EAN) recommends education alone in uncomplicated cases, noting that even simple informational tools may help prevent MOH [155]. Danish and German guidelines further highlight the role of general practitioners and pharmacists in early detection and prevention [103, 156]. Denmark has also shown that national awareness campaigns can rapidly improve public knowledge of MOH [157]. Similarly, French recommendations acknowledge that counselling alone may reduce acute medication intake below diagnostic thresholds [158, 159]. While there is broad agreement on the importance of withdrawal, recommended strategies vary. The EAN supports withdrawal to restore an episodic headache pattern and improve quality of life and healthcare costs, allowing rescue or bridging therapies in selected cases. The guideline endorses topiramate, onabotulinumtoxinA, and CGRP-targeting therapies for CM with medication overuse, while other agents (e.g., beta-blockers, flunarizine, and amitriptyline) are widely used despite limited RCT evidence [155]. The Danish guideline recommends complete cessation of acute medications for two months, favouring this over restricted use, with short-term bridging or inpatient tapering reserved for high-risk cases. Bridging therapy may include low-dose

neuroleptics or antiemetics, while inpatient methadone tapering is advised for opioid or barbiturate overuse. Preventive therapy should be initiated concurrently with withdrawal, with agent selection based on the underlying headache disorder [156]. French and German guidelines similarly favor withdrawal combined with education and early preventive treatment, reserving inpatient management for complicated cases. Both guidelines support the use of topiramate, onabotulinumtoxinA, and anti-CGRP mAbs [85, 103, 158]. The Japanese and Brazilian guidelines support outpatient withdrawal with counselling, reserving hospitalization for severe or refractory cases. The Brazilian consensus recommends initiating preventive therapy at withdrawal, with topiramate and onabotulinumtoxinA as first-line options, while other agents are considered second-line due to lower evidence. The Japanese guideline similarly emphasizes preventive therapy as central to MOH management [160, 161].

Most guidelines additionally emphasize non-pharmacological and multimodal approaches, including education, headache diaries, CBT, mindfulness, relaxation techniques, and multidisciplinary care, which may help reduce relapses despite limited high-quality evidence [103, 156, 158, 160, 161]. Overall, although guidelines represent important progress, quality evidence remains low, and uncertainties persist regarding optimal withdrawal strategies, bridging therapies, and timing of preventive treatment.

Toward personalized withdrawal: future directions

Several predictors of MOH outcomes have been investigated, including clinical characteristics, medication overuse patterns, psychiatric comorbidities, and cognitive-behavioural traits. Among clinical predictors, high headache frequency and elevated disability scores are consistently associated with unfavourable outcomes [111, 162–164]. Other factors linked to relapse include smoking, alcohol consumption, persistent high migraine frequency after withdrawal, multiple prior preventive failures, poor sleep quality, high bodily pain, and use of codeine-containing medications [165–167]. Conversely, daily caffeine intake above 200 mg and higher self-rated health have been associated with lower risk of chronic headache at one-year follow-up [111].

Conflicting results have been reported regarding the role of primary headache type, pain intensity, and attack duration. While some studies identified migraine as a predictor of better long-term outcomes and lower relapse rates, others found no significant effect of headache subtype [152, 162–164, 166].

The class of overused medication is a reliable predictor of outcome. Triptan overuse is associated with more favourable responses to withdrawal, lower relapse rates, and greater reductions in headache days compared with other drug classes [152, 162, 168, 169].

Psychiatric comorbidities and specific psychological profiles consistently emerge as negative predictors. Depression predicts chronic headache persistence, relapse, and repeated detoxification, while obsessive–compulsive traits and substance-dependence behaviours are linked to early relapse and poor discontinuation rates [111, 164, 170–172]. This is further supported by evidence that genetic variants linked to addiction and dopaminergic and serotonergic pathways (DRD2, COMT, SLC6A4 genes) predict unsuccessful detoxification, suggesting a polygenic influence on response to medication withdrawal [50, 169].

Several negative outcome predictors are shared with nociplastic disorders, such as fibromyalgia, where, as in MOH, depression and high perceived pain predict poor treatment response [173]. This overlap supports the need for individualized, multidisciplinary, and non-pharmacological approaches targeting patient-specific comorbidities [174].

Despite promising findings, substantial heterogeneity exists across studies, reflecting variability in withdrawal strategies and outcome definitions, including headache reduction, withdrawal success, and relapse rates. Large prospective studies with standardized methodologies are needed to identify reliable outcome predictors and enable patient stratification for personalized withdrawal strategies. Non-pharmacological, individualized approaches targeting nociplastic mechanisms represent a promising research direction. In this context, the advancement of artificial intelligence-based algorithms applied to the headache field may play a crucial role in the near future, with the potential to offer new algorithms for modelling personalized treatments [175]. Indeed, one study using a machine learning approach trained on clinical and biochemical features, drug exposure, and lifestyle information has shown to help predict the risk of medication overuse in subjects with migraine, revealing potential in the context of predictive medicine [176].

Conclusions

MOH represents a condition in which biological vulnerability, maladaptive neuroplasticity, and behavioral factors interact. The evidence reviewed supports reframing MOH within a nociplastic pain framework, characterized by central sensitization, impaired descending modulation, and dysfunction of reward- and control-related networks, rather than as a purely pharmacological consequence of medication excess (Figure 1). Importantly, these alterations appear largely reversible, highlighting the potential for recovery with appropriate, mechanism-based interventions. Medication withdrawal remains a cornerstone of management, but long-term success

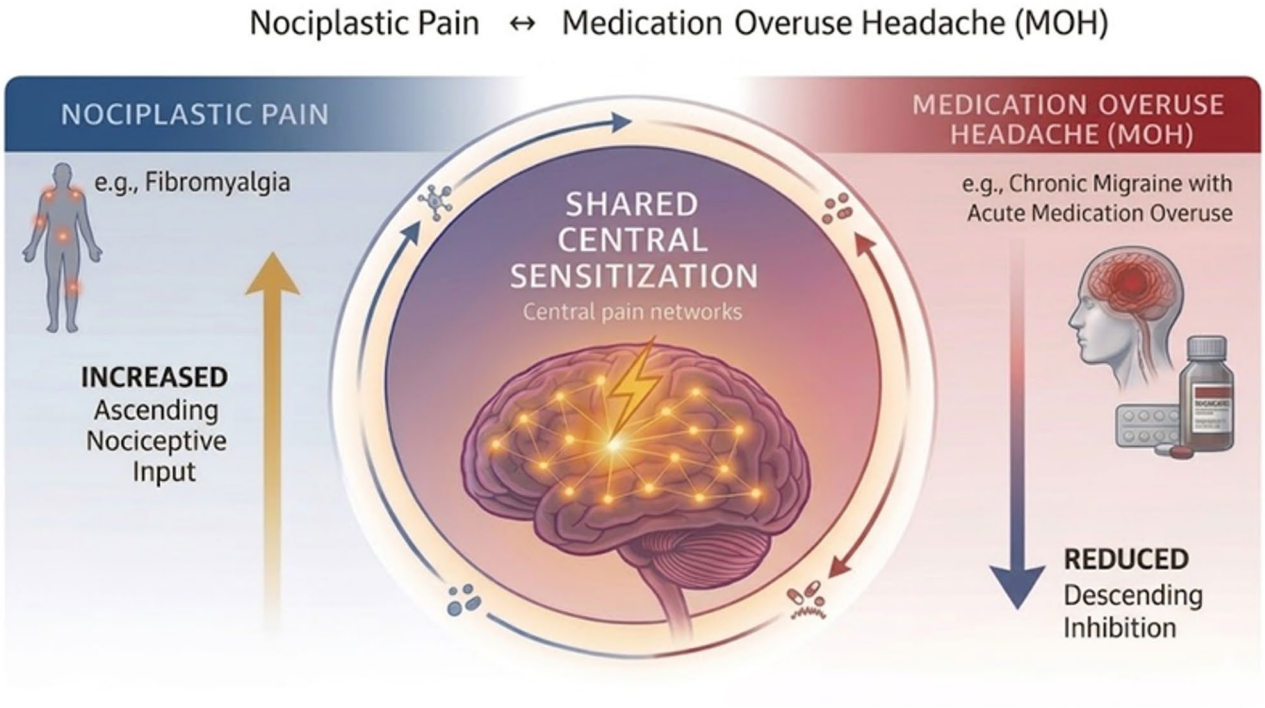

Fig. 1 Nociplastic framework of medication overuse headache. Schematic representation of the proposed mechanisms underlying medication overuse headache within a nociplastic pain model, including increased ascending nociceptive input, reduced descending inhibitory control, and central sensitization

depends on its integration with preventive and behavioral strategies. Increasing evidence supports patient-centered approaches in which preventive treatments, particularly CGRP-targeting therapies, may be initiated before or alongside withdrawal, reducing headache burden and facilitating disengagement from acute medication overuse. Recognizing MOH as a biobehavioral syndrome is essential, as craving, impulsivity, catastrophizing, and cephalalgiophobia strongly influence outcomes and relapse risk. Behavioral interventions, including CBT and mindfulness-based approaches, target both psychological drivers and nociplastic mechanisms by enhancing top–down pain modulation and adherence. Future research integrating clinical, neurobiological, and behavioral markers, potentially supported by artificial intelligence–based predictive models, may enable personalized, multidisciplinary care and more effective long-term management of MOH.

Author contributions

R. Messina planned the study, organized the manuscript structure, collected the entire body of the manuscript, and drafted the Introduction and Conclusion sections. P. Martelletti planned the study and supervised the whole manuscript. The remaining authors drafted sections of the manuscript, in detail: M. Castaldo and A. Onofri (Psychological dimensions, and Psychological and behavioural approaches); WS Ha and W. Wells-Gatnik (Withdrawal strategies); D. Vuralli, S. Merve Yener, WS Ha and W. Wells-Gatnik (Pathophysiology and neurobiology); A. Labastida-Ramirez and E Rubio-Beltran (Preventive treatments); S. Merve Yener (Clinical practice guidelines); G. Sebastianelli (Toward personalized withdrawal).

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