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Primer

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Medication overuse headache

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Abstract

Medication overuse headache (MOH) is a secondary headache disorder attributed to overuse of acute headache medications by a person with an underlying headache disorder, usually migraine or tension-type headache. MOH is common among individuals with 15 or more headache days per month. Although MOH is associated with substantial disability and reductions in quality of life, this condition is often under-recognized. As MOH is both preventable and treatable, it warrants greater attention and awareness. The diagnosis of MOH is based on the history and an unremarkable neurological examination, and is made according to the diagnostic criteria of the International Classification of Headache Disorders third edition (ICHD-3). Pathophysiological mechanisms of MOH include altered descending pain modulation, central sensitization and biobehavioural factors. Treatment of MOH includes the use of headache preventive therapies, but essential to success is eliminating the cause, by reducing the frequency of use of acute headache medication, and perhaps withdrawing the overused medication altogether. Appropriate treatment is usually highly effective, leading to reduced headache burden and acute medication consumption.

Sections

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Introduction

Medication overuse headache (MOH) was first described by Peters and Horton in 1951 (ref. [1]). This condition has been termed rebound headaches, drug overuse headaches, drug-induced headache (ICD-10), medication misuse headache or medication adaptation headache[2]. In 1988, the *International Classification of Headache Disorders*, first edition (ICHD-1), codified MOH as a secondary headache disorder[3]. To meet the diagnostic criteria for MOH in the most recent ICHD edition (ICHD-3), patients must have headache on ≥15 days per month together with overuse of acute treatments for a pre-existing (usually primary) headache disorder (overuse being defined by thresholds that vary with medication class), both persisting for >3 months[4] (Box 1). These criteria are widely but not universally accepted. Diagnosis of MOH implies that the overused medication is the cause of the frequent headache. By contrast, the term medication overuse (MO) implies only the use of acute medications that exceed the specified thresholds, not any causal relationship with headache or increased headache frequency[5].

Up to 90% patients with MOH have a history of either episodic migraine and/or tension-type headache (TTH) as the pre-existing headache disorder[5–9]. Increases in attack frequency are usually associated with increasing acute medication intake. MOH may exacerbate other headache disorders including post-traumatic headache and idiopathic intracranial hypertension[10]. Of note, MOH is not reported in people without a pre-existing headache disorder taking acute analgesics for other pain indications[11]. Analgesic overuse has been associated with chronic headache in people with low-back pain and neck pain in some reports, but the association was stronger for migraine[11].

MOH is preventable and treatable. Many cases are the result of misguided self-treatment, but some cases, especially those involving triptans, barbiturates or opioids (such as codeine) are due to incorrect prescribing, with many clinicians unaware of the risks of MOH and of the strategies to prevent and manage it. Some in the advocacy community argue that the term MOH is inappropriate because it seems to blame the patient for a condition that is driven by the pre-existing headache and is often caused or exacerbated by excessive prescribing and/or poor medical management and advice[12]. Although we agree, MOH is the term in current use, and it is used in this Primer in the absence of an accepted better term.

This Primer provides an overview of the epidemiology, pathophysiology, clinical presentation and diagnosis of MOH. Moreover, it discusses effective management strategies in clinical practice and outlines the overall prognosis for MOH once treated.

Box 1

Diagnostic criteria for medication overuse headache according to ICHD-3

- Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[a]
- Not better accounted for by another ICHD-3 diagnosis

ICHD-3, International Classification of Headache Disorders, third edition[4].
[a]Regular overuse is classified as: ≥10 days per month for triptans, ergots, opioids, combination analgesics; ≥15 days per month for simple analgesics (such as paracetamol or NSAIDs); and ≥10 days per month for combinations of multiple drug classes.

Epidemiology

Epidemiological studies can show association but, generally, cannot produce evidence of causation, and identified cases of MOH should, therefore, be considered only as probable MOH (pMOH). This term is not defined in ICHD-3, and most articles we reviewed use the term MOH without making this distinction. Therefore, we use MOH rather than pMOH. More is said about this later (see 'Limitations of population-based studies').

Incidence

The incidence of MOH has been studied in only one longitudinal population study[9]. The Nord-Trøndelag Health Survey (HUNT), a Norwegian longitudinal population-based cohort study, reported 11-year follow-up of 26,197 responders (63% of 41,766 eligible)[9]. This study found an incidence of 0.72 cases of MOH per 1,000 person-years. However, this study did not take into account cases that might have resolved during the 11 years.

Prevalence

The Global Burden of Disease (GBD) study collates all published data (and some unpublished data), applying modelling to interpolate results for countries for which data are lacking[13]. The GBD study in 2015 was the last iteration to include MOH as a separate entity (subsequently, MOH was regarded as a sequela of migraine or TTH), and it estimated that around 59 million people globally had MOH[14]. Moreover, a systematic literature search found 27 reports of 24 datasets from 16 countries, with an adult prevalence in the general population of 1–2% in most cases[2]. With a world population of approximately 7 billion in 2015, of whom about 68% were adults[15], the number of adults living with MOH is likely to be within the range 48–95 million. With a world population now of 8 billion, of whom about two-thirds are adults[15], the number of adults living with MOH is probably within the range 50–100 million. Although findings in the GBD study and the systematic literature search are reasonably aligned, individual study estimates varied from <1% to >7% in the review[2]. The differences in estimates may reflect true differences in prevalence, as MO is expected to be influenced by geography, environment, ethnicity and culture, and by quality and availability of medical care. Indeed, comparison of results across regions[16–25] (Table 1) demonstrates an average prevalence of 3.4% (median 2.6%), with a range of 0.6–7.1% with methodological variables largely eliminated, suggesting that high variability among countries is real.

The causes of widely ranging prevalence estimates despite methodological standardization may be found in association analyses. MOH is more common among women than men and boys, which is expected as migraine prevalence is two- to threefold higher among women[26]. The prevalence of MOH increases with age, at least until middle age, as, empirically, MOH in most cases develops many years after the onset of the underlying headache disorder, while the prevalence curves of both migraine and tension-type headache rise towards middle age then decline. Other factors may also be involved. Data from adolescents and children are limited. Six completed Global Campaign schools-based studies, in Benin (T. J. Steiner, unpublished work), Ethiopia[27], Iran[28],

Table 1 | Point prevalence estimates of probable medication overuse headache in adult studies using standardized methodology and questionnaire

Country	World Bank income level[b]	Year of study	*n*	Reported prevalence (%)	Reported associations
WHO Africa region					
Benin[a]	Lower-middle	2019	2,400	2.2	Not yet available
Cameroon[a]	Lower-middle	2019	3,100	6.2	F:M ratio 2.6:1
Ethiopia[25]	Low	2014	2,385	0.7	F:M ratio 1.8:1
					Age-related, peaking at 1.5% in 46–55-year age group
					Urban dwelling (OR 6.1)
Zambia[24]	Lower-middle	2012	1,085	7.1	F:M ratio 1.6:1 maximum in 50–65-year age group
					Urban dwelling (OR 8.6)
					Higher income (OR 6.0)
WHO Americas region					
Perú[a]	Upper-middle	2019	2,149	2.6	Not yet available
WHO Eastern Mediterranean region					
Morocco[a]	Lower-middle	2015	2,558	5.9	F:M ratio 2.4:1
Pakistan[23]	Lower-middle	2012	4,223	0.8	F:M ratio 1.3:1
					Increasing with age to maximum in 60–65-year age group (OR 3.3) vs 18–25 years
					Urban dwelling (OR 1.9)
Saudi Arabia[22]	High	2012	2,316	1.8	Female sex (OR 4.7)
					Maximum (7.8%) in 46–55-year age group
WHO European region					
Lithuania[21]	High	2010	573	3.2	Female sex (OR 2.9)
					Maximum (6.0%) in 46–55-year age group
Russia[20]	Upper-middle	2008	2,025	7.1	Not reported
WHO South East Asia region					
India (Karnataka)[19]	Lower-middle	2009	2,329	1.2	Female sex (AOR 5.9)
					Maximum (2.6%) in 56–65-year age group
India (Delhi and National Capital Territory Region)[a]	Lower-middle	2019	2,067	3.4	F:M ratio 5:1
					Maximum (7.8%) in 46–55-year age group
Nepal[18]	Lower-middle	2013	2,100	2.1	Female sex (AOR 2.6)
					Maximum (3.7%) in 56–65-year age group
WHO Western Pacific region					
China[17]	Upper-middle	2009	5,041	0.6	F:M ratio 3:1
Mongolia[16]	Lower-middle	2018	2,043	5.7	F:M ratio 1.4:1
					Maximum (9.0%) in 35–54-year age group
					Rural dwelling (OR 2.4)
					Obesity (OR 1.8)

AOR, adjusted odds ratio; F:M, female to male; OR, odds ratio. [a]In analysis, but not yet published. [b]World Bank Country and Lending Groups.

Lithuania[29], Mongolia[30] and Zambia[31] using standardized methodology[32] demonstrated increasing prevalence from childhood (mean 0.4%) to adolescence (mean 1.2%). The estimates in Table 1 show no influence of world region, but these are large heterogeneous groupings. A low prevalence of both migraine and TTH in China (9.3% and 10.8%, respectively)[17] explains its low prevalence of MOH. This is not true of Ethiopia (MOH prevalence of 0.7% despite migraine prevalence of 17.7%), a highly ruralized low-income country with limited access to both medications and health care[25]. The high prevalence of MOH in Zambia was speculatively attributed to four coincident factors: highly prevalent migraine (22.9%), poor access to health care, absent public health education and, in urban areas, easy access to over-the-counter medication[24]. The high prevalence of MOH in Russia was attributed, with some evidential support, to poor health care[20], but all four factors

may have a role. Although Table 1 suggests no influence of income level on the prevalence of MOH, deficient health care is an evident factor. In countries with good health care, higher relative frequency of MOH is observed among groups who, because of socioeconomic disadvantage, including low education level, are less likely to secure its benefits[33–35]. By contrast, access to medication, which is distinct from health care, is a prerequisite for MO.

Associated factors and risk factors

In cross-sectional studies[33,35,36], MOH was associated with female sex, adulthood, a low level of education and low household income. In a large US population survey, MO occurred in 15% of respondents with migraine, and the odds of MO increased with age, being married, smoking, presence of psychological symptoms, ictal cutaneous allodynia, greater migraine symptom severity and higher headache pain intensity[5]. The most frequently overused drugs were triptans, followed by opioids and barbiturates, whereas MO was observed less frequently in people who use NSAIDs[5]. Of note, cross-sectional data cannot determine whether MO is a cause or consequence of these headache features.

A longitudinal study[9] confirmed female sex and low educational level as risk factors for incident MOH (odds ratio (OR) 1.9), but demonstrated that pre-existing headache type (migraine versus no migraine: OR 8.1; any headache versus no headache: OR 5.9) and medicating behaviour at baseline (daily tranquilizers: OR 5.2; analgesics: OR 3.0; sleep-inducing medications: OR 2.5) were stronger risk factors. A range of conditions associated with two-fold risk (whiplash, chronic musculoskeletal disorders, Hospital Anxiety and Depression Scale scores ≥11) were likely to encourage medication use, although there may be other explanations.

Comorbidities

Psychiatric comorbidities including depression and anxiety are associated with MOH[9,37–44]. In addition, depression and anxiety are strong independent risk factors of headache chronification and MO, are associated with negative effects and disability related to MOH, and are predictors of a poorer therapeutic outcome for MOH[45–49]. Risk of suicidality has been reported in individuals with primary headaches including migraine[44]. Interestingly, in a sample of adolescent patients with chronic daily headache, MO was not correlated with suicidal behaviour[50]. However, in a large cross-sectional study from a tertiary headache centre, the presence of MOH in adult patients with migraine was associated with the risks of both suicidal ideation (OR 1.75) and of prior suicide attempt (OR 1.88), after controlling for demographics, headache profile, disabilities, symptoms of anxiety and depression, and sleep quality[42]. It can be hypothesized that untreated psychological factors aggravate or at least maintain the processes that lead to headache chronicity.

MOH is also associated with medical and non-psychiatric comorbidities. A limited number of studies have demonstrated that patients with MOH are more likely to have chronic musculoskeletal complaints, insomnia, hypothyroidism, gastrointestinal problems (bleeding and/or ulcers, irritable bowel syndrome), metabolic syndrome, hypertension and smoking compared with the general population[9,51–54]. MOH has also been associated with stress in one population-based study[55].

Of note, in patients with MOH and other diseases, distinguishing whether the other disease is a comorbidity or an MOH risk factor may be difficult. Moreover, adverse events and toxicities from overused acute headache medications need to be considered, which can include gastritis or gastric ulcer, hepatic and renal impairment.

Burden

The GBD study multiplies the prevalence of a disorder by a disability weight allocated to each health state arising from that disorder[56] and by mean proportion of time spent by people in each health state[13]. The sum of these products yields the total population-level burden, which is expressed as years lived with disability (YLDs). Despite the terminology, disability weights and YLDs are measures of lost health burden, rather than measures of disability[57,58]. YLDs can be used to compare diseases[56]. MOH was ranked eighteenth among all causes of global YLDs in the 2013 GBD; migraine was ranked sixth and TTH was not in the top 20 (ref. [59]).

Lost health results in disability and lost productivity. The Eurolight study, using data from eight European countries, estimated a total annual cost of MOH to the European Union in 2011 of €37 billion, 92% of which was attributed to lost productivity[60]. As MOH is prevalent, highly burdensome, avoidable to the extent that it is iatrogenic and associated with risk factors that may be remediable, it is a clear target for health policy seeking low-cost health gains, whatever the country income level.

Limitations of population-based studies

Population-based studies of MOH, particularly those estimating prevalence, have two intractable problems[61,62]. First, the definition of MOH varies among studies and has changed in succeeding editions of ICHD[3,4,63–65]. Some proposed definitions have tended to conflate MOH with chronic migraine[66]. One systematic review noted that the studies "adopted diagnostic criteria reflecting the changing consensus of their times"[2]. In addition, ICD-10 codes "drug-induced headache", a much broader term that potentially includes headache as an acute or subacute adverse event due to medication used for any purpose. This makes analysis of medical claims and electronic health records very challenging[67]. Second, case ascertainment is difficult as people may not accurately recall the names or quantities of the medications they take, and pharmacy and electronic data can quantify possession but not intake of medication. Days of medication use are crucial to the correct diagnosis of MOH. A patient who takes four opioid analgesic tablets per day on 6 days per month will not meet criteria for MOH. However, if the patient distributes those 24 tablets over 12 days (two per day on average), the overuse criterion for MOH will be met. In other words, persistent and regular overuse is diagnostically important[4], but this is often difficult to establish. Diagnostic instruments in clinical practice — detailed enquiry, physical examination and diary-assisted follow-up — are not possible in cross-sectional population-based studies, which can neither establish causation nor exclude all other possible diagnoses[61,62] as ICHD demands[4]. Furthermore, published estimates of headache prevalence are influenced by methodological differences among studies[26]. The series of population-based studies conducted by the Global Campaign against Headache[68] used standardized methods[69] and questionnaires[70] to minimize these uncertainties while explicitly recognizing that diagnoses of MOH could be no more than pMOH[62,69,70].

Mechanisms/pathophysiology

MOH is well described as a clinical entity, and the link between frequent acute medication intake and increasing headache occurrence is well established, but its pathophysiology is incompletely understood[6,71,72]. MOH is hypothesized to influence the neural pathways of the underlying headache disorder. This phenomenon is best studied for MOH developing from migraine. MOH is not reported in the absence of underlying headache, suggesting a fundamental state of vulnerability especially in

people with migraine[73,74]. Possible neuroanatomical circuits and cellular mechanisms involved in the pathophysiology of MOH are depicted in Figs. 1 and 2, respectively.

Moreover, MOH is a complex headache disorder: multiple genetic, environmental and biopsychosocial factors may have a role in its pathophysiology. Genetic predisposition may interact with other biological, behavioural, psychological and environmental factors to determine the development, mechanism and course of MOH[75,76].

Genetic factors

Although large systematic genome-wide association studies (GWAS) have been performed to compare people with migraine and migraine-free controls, such studies are not available for MOH except for some small non-replicated association studies[77]. The available studies are generally modest in size, evaluate candidate genes and have rarely been replicated. These studies suggest that insertion or deletion polymorphisms in *ACE* (encoding angiotensin-converting enzyme (ACE)), the Val66Met mutation in *BDNF* (encoding brain-derived neurotrophic factor) and polymorphisms in *COMT* (encoding catechol-*O*-methyltransferase) and *SLC6A4* (encoding a serotonin transporter) might have a role in MOH, but the evidence is tenuous[78–81]. These genetic risk factors are associated with abnormalities in metabolic pathways, serotonergic and dopaminergic transmission and drug dependence[77]. ACE is a key enzyme in the renin–angiotensin system and has a role in regulating neural plasticity in the brain[82]. *ACE* polymorphisms interact with monoaminergic synaptic transmission, influencing sensitization and habituation, which may contribute to dependence behaviour (see 'Behavioural and psychological factors', below) in individuals with MOH[47,71,78,83]. In animals, renin increases dopamine and decreases noradrenaline turnover, and angiotensin II affects 5-hydroxytryptamine (5-HT; also known as serotonin) synthesis in the brain in a dose-dependent manner: low angiotensin II concentrations decrease and high concentrations increase the rate of 5-HT synthesis[78,84,85]. Excessive angiotensinergic activity due to polymorphisms in particular genes increases sensitization as a result of MO and determines the lack of habituation, which is proportional to the duration of MO[78]. Combining GWAS findings in migraine with those of depression, major depressive disorders or anxiety may be meaningful, as depressive and anxiety symptoms are important risk factors for MOH and there is strong molecular genetic support for shared genetically determined biological mechanisms underlying migraine and depression[86,87].

Behavioural and psychological factors

Frequent medication taking may be linked to the development of MOH by behavioural and psychological factors and in some patients, substance use disorder[83,88–95]. Both MOH and addiction have overlapping psychiatric comorbidities, personality traits, maladaptive reward system, as well as reversible morphological and functional brain changes related to the mesocorticolimbic reward circuitry[83]. The behavioural sensitization mediated by cortical, striatal and other subcortical structures may contribute to development of MOH (Fig. 1). Individuals with MOH have an increased familial risk of drug dependence and a genetic association with dopaminergic and drug-dependence molecular pathways[83,96]. A case–control study has demonstrated that the presence of a 19 bp insertion/deletion polymorphism (rs72393728/rs141116007) in the dopamine β-hydroxylase gene correlated with the development of MO in patients with chronic migraine[97]. Ritualized drug intake and psychological drug attachment are associated with poor response to acute medication, fear of missing important professional or private events and migraine worsening when the intake of acute medication is paused or terminated[83]. Patients with MOH may also overuse other medications such as eye drops, nasal decongestants, laxatives and sleeping medication[98]. Substance use disorder is primarily associated with opioids and barbiturates[6,99]. These patients take medication more frequently and increase the dose and show craving behaviour[88]. A possible genetic predisposition can have a role in both addictive behaviour and substance abuse[100]. Other risk factors for dependency include low education, sensitization with allodynia, psychiatric comorbidities and drug-seeking behaviours. Maladaptive cognitive patterns, such as pain catastrophizing, anticipatory anxiety and obsessional drug-taking behaviours have also been considered important aspects of MOH[75,76,95]. These factors could alter the control of substance intake and may result in compulsive drug-taking, thus leading to MO[75,76]. In addition, the presence of psychiatric comorbidities in individuals with migraine such as cluster B personality disorders, including borderline or narcissistic personality disorders, may cause behaviours around pain control and treatment control that may result in MO[75,76].

Cephalalgiaphobia, a phobia of a headache attack during a pain-free state or a phobia of pain worsening during mild headache episodes, is a possible form of anxiety disorder and has been described in patients with migraine[101]. It has been linked to progression of episodic migraine to the chronic form and to MOH. Patients with cephalalgiaphobia may develop pain avoidance behaviour and overuse acute headache medications despite being aware that they are using more analgesics than necessary because of the fear of having another migraine attack or a headache exacerbation[101]. By decreasing the threshold for initiating the acute headache medication consumption behaviour and leading to acute MO, this could be one of the underlying mechanisms for development of MOH[101].

Sex-specific factors

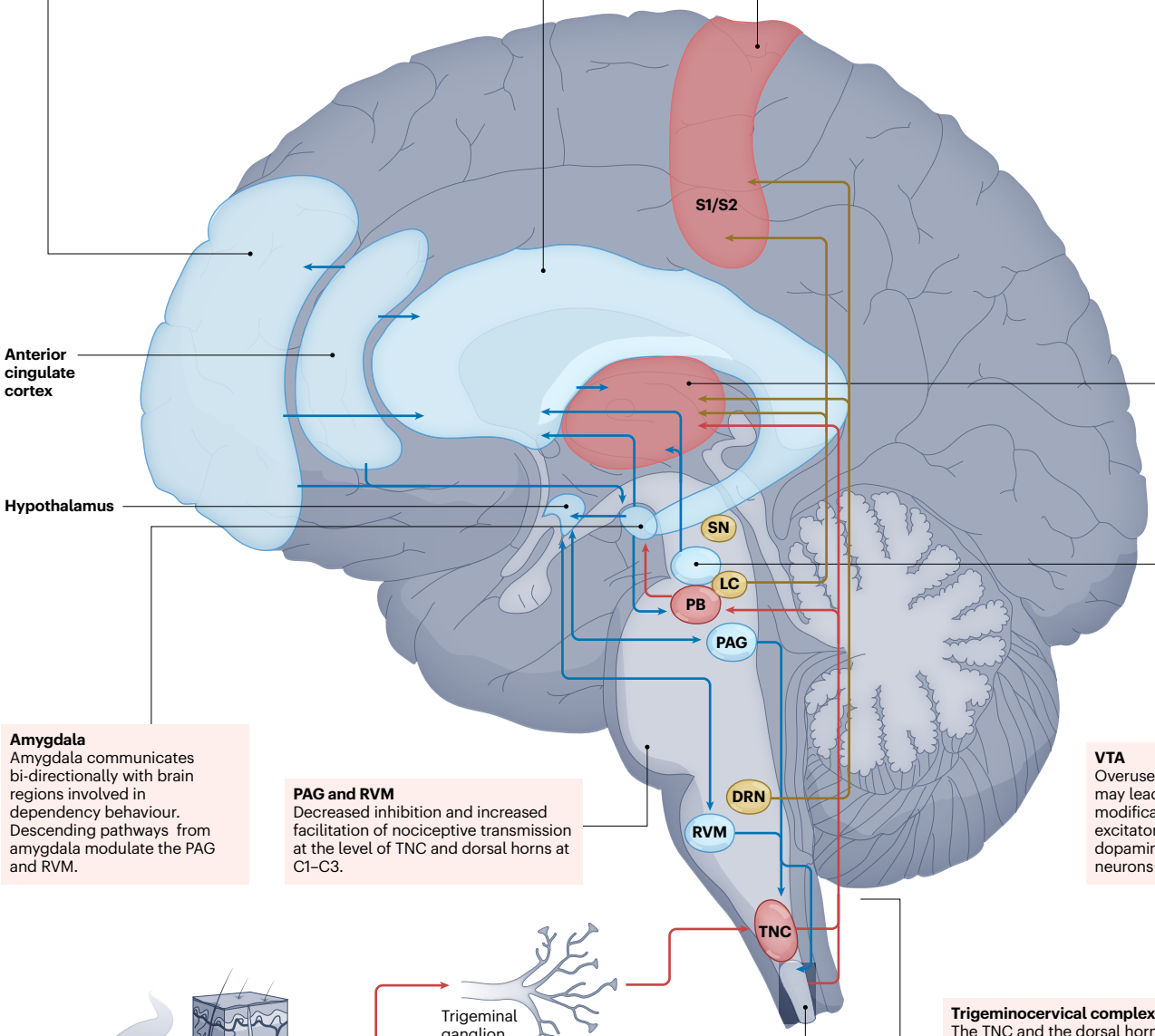
Sex-specific factors, including the role of female sex hormones, may be implicated in MOH. The most frequently reported trigger of migraine in women is menstruation (78%): menstruation-associated migraine is usually attributed to the cyclical fall in oestrogens[102,103]. Oestrogens have a role in the production and uptake of 5-HT[104] and enhance the sensitivity of certain 5-HT receptors; therefore, falls in oestrogen levels decrease serotonergic tone, which may lead to headache[104]. Oestrogen also increases the production of prolactin, a neurohormone that produces female-selective nociceptor sensitization and enhanced release of calcitonin gene-related peptide (CGRP), thus increasing risk of migraine pain attacks[105,106]. Perimenstrual migraine attacks are associated with longer duration, higher headache intensity, less pain coping and more pronounced photophobia and phonophobia than non-perimenstrual attacks[107]. Triptans are less effective (more recurrences of headache) during perimenstrual migraine attacks and, therefore, more triptans are needed for perimenstrual attacks, which makes women more vulnerable to MO and MOH[107,108]. Most importantly, the longer duration of perimenstrual migraine attacks is associated with higher recurrence risk and increased triptan use[108]. The menopausal transition phase is an important risk factor for worsening of pre-existing migraine[109]. Perimenopause is defined as the period before menopause, when the menstrual cycle length becomes irregular, up to 1 year after the last menstrual period (menopause). Most likely, this perimenopausal worsening is partly explained by the shorter cycle length, resulting in more perimenstrual migraine attacks. From menopause onwards, migraine improves in about two-thirds of women with migraine without aura[109]. The sex-hormonal influence on the increased risk of MO in

Prefrontal cortex
Medial prefrontal cortex receives dopaminergic input from VTA and is involved in central sensitization.

Basal ganglia
Ventral striatum (nucleus accumbens, olfactory tubercle) receives dopaminergic input from the VTA and is involved in medication-induced central sensitization. Dorsal striatum (caudate nucleus, putamen) receives dopaminergic input from the SN and maintains habit to overuse medications.

Somatosensory cortex
Ascending input from thalamo-cortical projections increases cortical excitability. Noradrenergic inputs from the DRN and serotonergic inputs from the LC to the cortex are involved in sensory integration and central sensitization.

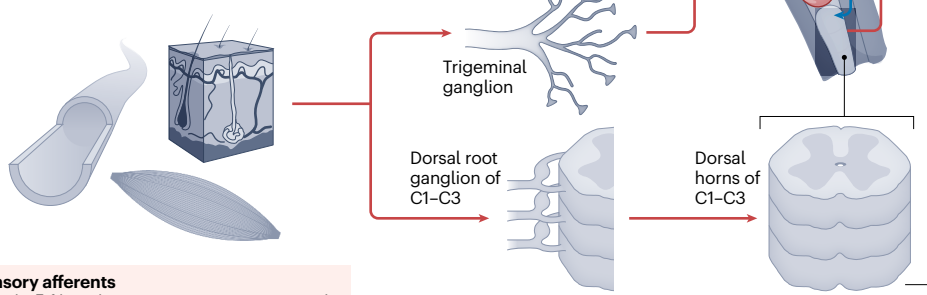
Thalamus
Ascending inputs from TNC and dorsal horns at C1–C3 levels lead to central sensitization of third-order neurons in thalamus. Noradrenergic inputs from the DRN and serotonergic inputs from the LC to the thalamus are involved in sensory integration and central sensitization.



Amygdala
Amygdala communicates bi-directionally with brain regions involved in dependency behaviour. Descending pathways from amygdala modulate the PAG and RVM.

PAG and RVM
Decreased inhibition and increased facilitation of nociceptive transmission at the level of TNC and dorsal horns at C1–C3.

VTA
Overused medication may lead to modification of excitatory synapses in dopamine-containing neurons in the VTA.



Trigeminocervical complex
The TNC and the dorsal horns of C1–C3 make up the TCC. Increased nociceptive transmission leads to central sensitization at these second-order neurons.

Sensory afferents
C and Aδ fibres become pro-nociceptive and transmit peripheral input from head and neck structures (for example, skin, muscle, intracranial blood vessels) to the trigeminal and C1–C3 dorsal root ganglions.

Medulla and upper cervical spinal cord
Nociceptive input is transmitted through trigeminal ganglion and dorsal root ganglions to second-order neurons at the brainstem level.

Fig. 1 | Proposed neuroanatomical circuits relevant to pathophysiology of medication overuse headache and medication overuse. The possible pathophysiological mechanisms of medication overuse headache (MOH) involve potential genetic factors, peripheral mechanisms and central mechanisms, including descending pain modulation. Overuse of acute headache medication alters the function of the central 5-hydroxytryptamine (5-HT)-dependent descending modulating system, which can result in increased neuronal excitability in peripheral and central nervous system structures that result in headache, hyperalgesia and/or allodynia. Increased cortical excitability lowers the threshold for the development of cortical spreading depression. Upregulation of pathways that involve calcitonin gene-related peptide (CGRP) might contribute to chronicity of headache. Pathophysiology of MOH may involve possible behavioural sensitization mediated by cortical, striatal and other subcortical structures. With activation of trigeminal neurons, the stimulus also propagates in several brainstem nuclei, including the dorsal raphe nucleus (DRN), the locus coeruleus (LC) and the periaqueductal grey (PAG). These project noradrenergic and serotonergic inputs to thalamus and cortex for sensory and nociceptive integration. The central sensitization may be enhanced by dopaminergic input from the ventral tegmental area (VTA) to both cortical (prefrontal and limbic areas) and subcortical (ventral striatum) structures. Maintenance of the drug overuse habit may be sustained by the increased dopaminergic input to the dorsal striatum from neurons of the substantia nigra (SN). The GABAergic inputs from the striatum integrate with other sensory inputs in the thalamus and possibly contribute to central sensitization in MOH. PB, parabrachial nucleus; RVM, rostral ventromedial medulla; TCC, trigeminocervical complex; TNC, trigeminal nucleus caudalis.

women with migraine emphasizes the need to develop female-specific (presumably hormonal) prophylactic treatment. However, only small underpowered studies have been performed and no clear proof to provide sex-hormonal therapy has been provided so far.

Structural and functional brain changes

Neuroimaging studies have demonstrated differences in brain structure, function and metabolism associated with MOH compared with those who have primary headaches without MOH and/or healthy controls. Differences have been demonstrated in multiple brain regions, including the hippocampus, periaqueductal grey (PAG), posterior cingulate cortex, thalamus, cerebellum, orbitofrontal cortex (OFC) and the mesocorticolimbic reward system[110–113]. Moreover, one brain voxel-based morphometry study found larger grey matter volume in pain-associated regions including the PAG, thalamus and ventral striatum in patients with MOH compared with healthy controls, suggesting alteration in pain modulating and processing regions in patients with MOH[112].

Alterations in metabolism have also been observed in various brain structures associated with MOH, such as regions of the thalamus, OFC, anterior cingulate cortex and ventral striatum, compared with healthy controls[114]. For example, a recent PET study demonstrated decreased dopamine transporter availability in the medial OFC of those with MOH compared with healthy controls, further implicating the mesocorticolimbic dopamine system in the pathophysiology of MOH[115]. Interestingly, some of these alterations are normalized after withdrawal of acute headache medication[114]. However, one PET scan study found persistent glucose hypometabolism in the orbitofrontal area after withdrawal of medication[114]. This area may be involved in drug dependence and may be a risk factor for subsequent relapse of MO and recurrent or persistent MOH. Functional MRI studies demonstrated reduced responses to painful stimulation in patients with MOH compared with healthy controls, which normalized after discontinuation of the overused medication[113,116,117].

Altered pain processing

The greatest predictor of headache chronification is the frequency of attacks, suggesting that the attacks themselves may promote nociceptor sensitization[118–120]. Migraine attacks may elicit a priming effect, a form of pain memory, that lowers the threshold for activation of nociceptors, therefore increasing the chances of the next attack[120]. Concomitant with peripheral nociceptor sensitization, adaptive changes occur in central ascending nociceptive transmission circuits that result in a net amplification of afferent input, a process termed central sensitization[121,122].

The perception of pain ultimately results from the modulation of ascending nociceptive input through modulatory circuits that inhibit or facilitate the transmission of nociception[123]. Disruption of these pain modulatory pathways to favour enhanced facilitation over inhibition is likely to also increase vulnerability to pain from normally innocuous stimuli. The efficiency of descending inhibition is assessed in humans with the conditioned pain modulation (CPM) procedure, which is analogous to the diffuse noxious inhibitory controls (DNIC) response in animals[124,125]. Rodent studies have suggested the importance of enhanced descending facilitation following corticotropin-releasing hormone (CRF)-mediated release of dynorphin and activation of κ-opioid receptors (KORs) in the central nucleus of the amygdala[126,127]. Collectively, peripheral and central sensitization and disruption of DNIC or CPM reflect a state of vulnerability termed 'latent sensitization', whereby headache can result from normally innocuous external triggers. These mechanisms of amplification may also promote headache attacks from homeostatic disruptions that can influence neural circuits in the hypothalamus and other brain regions. Such triggers could include hormonal changes linked to the menstrual cycle, sleep disruption, dehydration, odours, foods and missing meals[128,129]. Commonly used acute migraine or headache medications promote adaptive changes in peripheral nociceptors, amplification in central circuits and disruption of descending modulation that increase vulnerability to pain attacks and that likely contribute to MOH[71,130,131] (Fig. 1). Although the underlying molecular mechanisms need to be clarified, preclinical studies have implicated the contribution of prolactin receptor isoforms that promote increased excitability of afferents, which occurred selectively in females[132]. Repeated sumatriptan produces downregulation of expression of the prolactin receptor long isoform (PRLR-L) selectively in the trigeminal ganglion of female mice. Decreased expression of PRLR-L biases prolactin signalling to the prolactin receptor short isoform (PRLR-S), which leads to peripheral nociceptor sensitization and pain responses to ubellulone, a TRPA1 agonist that may promote headache in individuals with underlying primary headache disorders[133]. This mechanism reveals a qualitative sex difference in pain mechanism that may promote increased pain attacks in females[132]. Moreover, patients with MOH have decreased pain thresholds and increased pain response for supra-threshold pain stimulation compared with healthy controls, reflecting central sensitization[134–138]. The pain sensitivity to mechanical stimulation was increased further in cephalic than in extracephalic regions in patients with MOH[134]. However, the extracephalic pressure pain thresholds were also decreased in patients with MOH compared with healthy controls, indicating the involvement of central sensitization in MOH[134]. Enhanced temporal summation of pain, a marker

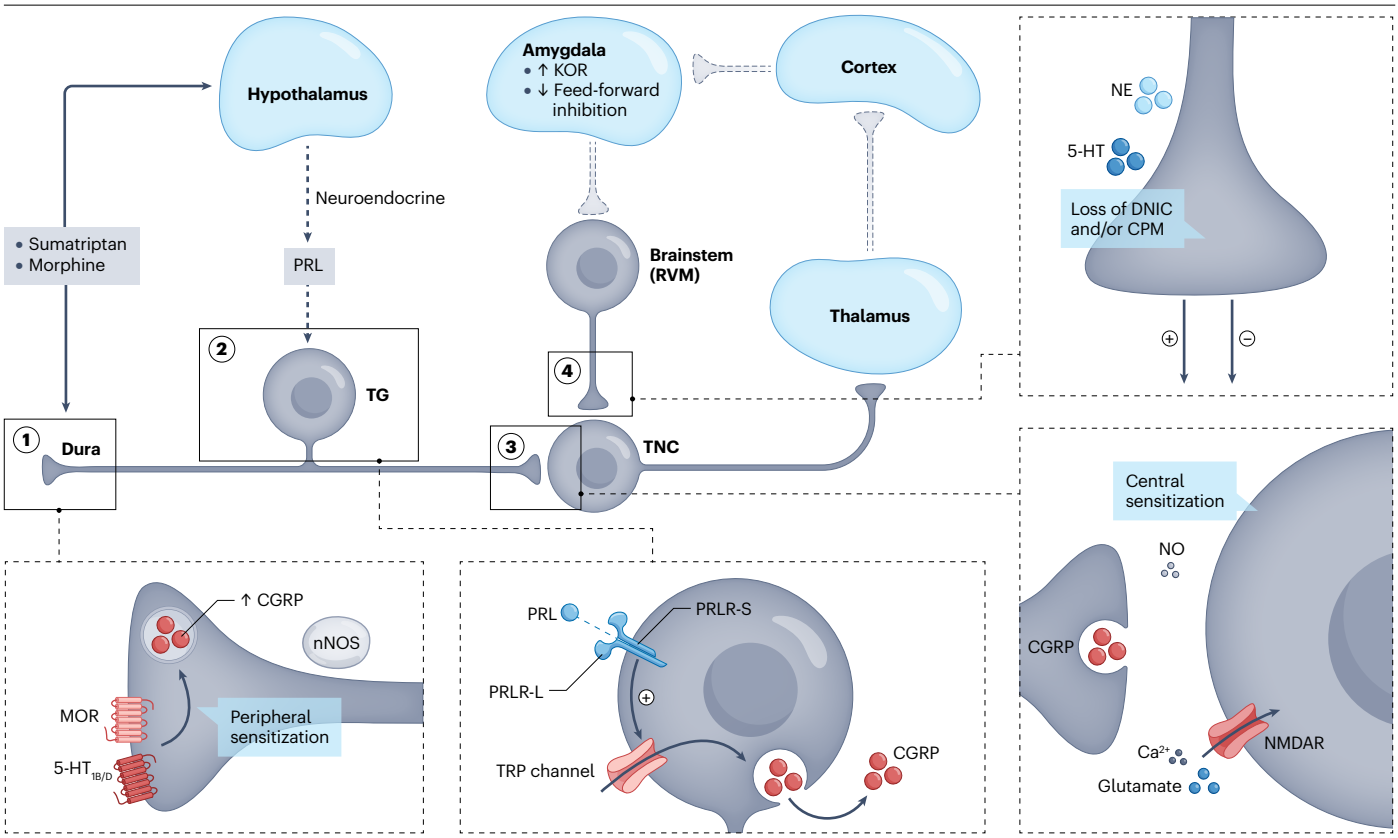


Fig. 2 | Putative cellular and molecular mechanisms of medication overuse headache. Amplification of pain processing involves peripheral sensitization of trigeminal dural afferents, central sensitization at the level of secondary neurons in the trigeminal nucleus caudalis (TNC) and in brain regions including the thalamus, cortex, amygdala, hypothalamus and descending pain modulatory centres in the brainstem, as well as neuroendocrine (NE) mechanisms. (1) Triptans and opioids sensitize trigeminal ganglion (TG) neurons, which results in increased expression of calcitonin gene-related peptide (CGRP) and neuronal nitric oxide synthase (nNOS). (2) Neuroendocrine mechanisms involving modulation of hypothalamic–pituitary–adrenal axes and increased secretion of prolactin (PRL) and corticotropin-releasing factor could contribute to pain sensitization. In mouse models of medication overuse headache (MOH), PRL selectively sensitizes female TG neurons in a female-specific manner by downregulating prolactin receptor long isoform (PRLR-L) and increasing signalling via the prolactin receptor short isoform (PRLR-S). (3) Increased neurotransmission from TG neurons ultimately promotes sensitization of secondary neurons in the TNC likely via mechanisms that involve long-term potentiation and *N*-methyl-D-aspartate (NMDA) receptor (NMDAR). (4) Medication overuse promotes adaptations in the descending pain modulatory pathways, likely involving serotonergic and noradrenergic signalling, that favour pain facilitation and diminish pain inhibition. Changes in descending pain modulation are revealed by the loss of conditioned pain modulation (CPM) observed in patients with migraine and by κ-opioid receptor (KOR)-mediated loss of diffuse noxious inhibitory controls (DNIC) in rodent models of MOH. 5-HT, 5-hydroxytryptamine; MOR, μ-opioid receptor; RVM, rostral ventromedial medulla.

of central sensitization, was also reported in patients with MOH and with migraine as the primary headache[137,138]. Furthermore, possible loss of CPM in patients with chronic daily headache and MO has been demonstrated[138].

CGRP has an important role in human nociceptive processing including trigeminal nociception[139,140] and is involved in the pathophysiology of migraine[119]. Moreover, CGRP has been suggested to be important for the development of MOH. In animals, prolonged exposure to analgesics upregulates CGRP in dorsal root ganglia, indicated by increased *CGRP* mRNA and protein expression[72,141–143]. For example, chronic exposure to opioids induces CGRP overexpression in dorsal root ganglion neurons[141,144], and chronic triptan exposure increases the number of CGRP-positive and neuronal nitric oxide synthase (nNOS)-positive dural afferent neurons in the trigeminal ganglion with long-lasting cutaneous tactile allodynia indicative of central sensitization[131,145,146]. In addition, in animals, 2 weeks of triptan exposure elicits enhanced cutaneous allodynia and increased CGRP levels in the blood following challenge with a nitric oxide donor, sodium nitroprusside[145].

Activation of trigeminal nociceptive pathways may propagate in several brainstem nuclei including the dorsal raphe nucleus, the locus coeruleus and the PAG, which can project noradrenergic and serotonergic inputs to thalamus and cortex for sensory and nociceptive integration[147]. It has been proposed that the central sensitization in MOH may be enhanced by dopaminergic input from the ventral tegmental area to both cortical (prefrontal and limbic areas) and subcortical (ventral striatum) structures, and maintenance of the habit of overusing acute headache medications may be sustained by the increased dopaminergic input to the dorsal striatum from neurons of the substantia nigra[147]. Moreover, the GABAergic inputs from the striatum may integrate with

other sensory and nociceptive inputs in the thalamus and possibly contribute to the central sensitization in MOH[147].

Alteration of cortical excitability

Animal studies have demonstrated that repetitive and chronic administration of analgesics and sumatriptan may lead to long-lasting increased susceptibility to evoked cortical spreading depression (CSD)[72,148–150]. The occurrence of cortical hyperexcitability in MOH is also supported by clinical evidence. Patients with MOH demonstrated larger amplitude of pain-related cortical potentials evoked by electrical sensory stimulus on the forehead or a limb compared with controls. Withdrawal from overuse drugs reduces the facilitation of pain-related cortical potentials in the trigeminal region[151]. In addition, patients with MOH showed abnormal cortical responses to somatosensory stimulation and lacked the habituation phenomenon[152].

In animals, chronic exposure to acute headache medications might increase the frequency of CSD, CSD-evoked 5-HT2A receptor expression, and FOS immunoreactivity in the cerebral cortex and trigeminal nucleus caudalis (TNC)[72,148,150]. 5-HT is an important neurotransmitter in pain modulation in humans and has a role in the pathophysiology of primary headache including migraine and TTH[153,154]. Chronic use of acute headache medications has been suggested to alter the function of the central serotonin-dependent modulating system[72,130]. For example, a 15-day treatment with paracetamol in animals led to downregulation of the 5-HT2A receptor, upregulation of the 5-HT transporter in the frontal cortex and increased 5-HT levels in platelets[155]. Moreover, acute administration of paracetamol increases 5-HT levels in the cortex and pons, probably via an indirect mechanism, as this drug does not have affinity for 5-HT receptors[156,157]. The persistent exposure to increased levels of 5-HT downregulates the receptors and upregulates the 5-HT transporter[158]. The change in platelet 5-HT level may reflect the similar change in 5-HT level in the central nervous system. The changes in the serotonergic neuromodulatory system, upregulation of vasoactive and pro-inflammatory mediators may increase susceptibility to CSD, central sensitization and an increase in nociceptive sensory fields[155]. Furthermore, in animal models, sex-hormonal levels modulate the vulnerability to CSD, making female mice more prone to CSD[159].

Mechanisms of MOH treatments

Numerous clinical studies have shown that withdrawal from analgesics and overused antimigraine drugs is associated with clinical improvement, including decreased frequency and intensity of headache, in a high percentage of patients[160–164]. This improvement is associated with changes in the endocannabinoid system such as reversion of the functional activity of the endocannabinoid system, which may therefore be implicated in the mechanism of MOH[137]. Pain perception studies have demonstrated a decrease in central sensitization after withdrawal treatment[137,138,165]. The response to supra-threshold pain stimulation decreased to a normal level several months after withdrawal of medication[134]. The reversal of enhanced temporal summation after withdrawal treatment may indicate a normalization in the *N*-methyl-D-aspartate (NMDA) receptor channel by its blockage with magnesium (normal resting membrane potential) with subsequent reduction in central sensitization in patients with MOH[134,137,138,166]. The reduction in central sensitization could possibly be due to either the decrease in medication use or the decrease in headache frequency[134]. In addition, improvement of DNIC or CPM dysfunction after withdrawal treatment has been reported[138].

More recently, CGRP-targeting monoclonal antibodies have proved effective in reducing the number of migraine days in people with migraine who overused acute medications, suggesting that CGRP may mediate the process of peripheral and/or central sensitization in these patients[72,167–170]. Interestingly, data from preclinical models suggest that small-molecule CGRP receptor antagonists (gepants) are unlikely to cause MOH. In animal studies, ubrogepant (a CGRP antagonist) did not elicit cutaneous allodynia and latent sensitization (as a surrogate marker of MOH) in contrast to agonist drugs such as triptans, ditans or opioids[171]. Recently, rimegepant, known for its efficacy in the acute treatment of migraine, also had a preventive effect in patients with migraine[172]. Data from clinical trials suggest that use of gepants, CGRP receptor antagonists, do not seem to lead to MOH[173]. On the basis of these findings, the American Headache Society[174] provided a commentary on the potential benefits of gepants for MOH avoidance.

Diagnosis, screening and prevention

Diagnostic criteria

As previously mentioned, diagnostic criteria for MOH are found in ICHD-3 (ref. [4]) (Box 1). Individuals receive an MOH diagnosis along with the pre-existing headache diagnosis, the latter of which is often migraine or TTH. How overuse of medication is defined in diagnostic criteria varies with the class of medication, either as ≥10 headache days per month or ≥15 headache days per month. Medication use counts regardless of whether the medication was taken to treat headache or for another reason.

MOH diagnostic criteria have notable limitations. Determining the direction of the relationship between MO and worsening of a pre-existing headache or emergence of a new type of headache is often challenging in individual patients. In some situations, it is likely that frequent use of medications leads to new or worsening headaches, whereas at other times increasing headache frequency may lead to increasing use of acute headache medications. Headache improvement after discontinuation of the overused medication provides evidence for MOH but is not required for diagnosis according to ICHD-3 criteria. Furthermore, the thresholds for defining MO, although empirically based, are not absolute[175]. For example, using opioids and barbiturates for less than 10 days per month may increase the risk of developing more frequent headaches and may cause MOH[6,176]. ICHD-3 criteria do not consider the medication dosage per day, which may affect the risk of MOH. Moreover, MOH can develop as an apparent complication of other secondary headaches, such as post-traumatic headache, hydrocephalus and idiopathic intracranial hypertension, which is not fully elucidated in the ICHD-3 criteria[10,177–179]. However, of note, patients with secondary headaches may have undetected pre-existing migraine or TTH.

Clinical presentation

As mentioned, most patients with MOH have underlying migraine, TTH or both[175,180]. The clinical features of MOH are highly variable. By definition, headache is present on more days than not[4], but its characteristics and duration each day are influenced in many cases by the type of underlying headache and in all cases by the nature of the medication being overused. In a prospective study, patients with migraine, TTH or combination of these headaches with analgesic overuse were more likely to develop a diffuse holocranial dull-pressing headache, often without accompanying migrainous symptoms[175]. By contrast, triptans produced a daily migraine-like headache that occurred in the morning, disappeared rapidly after triptan use but that reappeared after a few

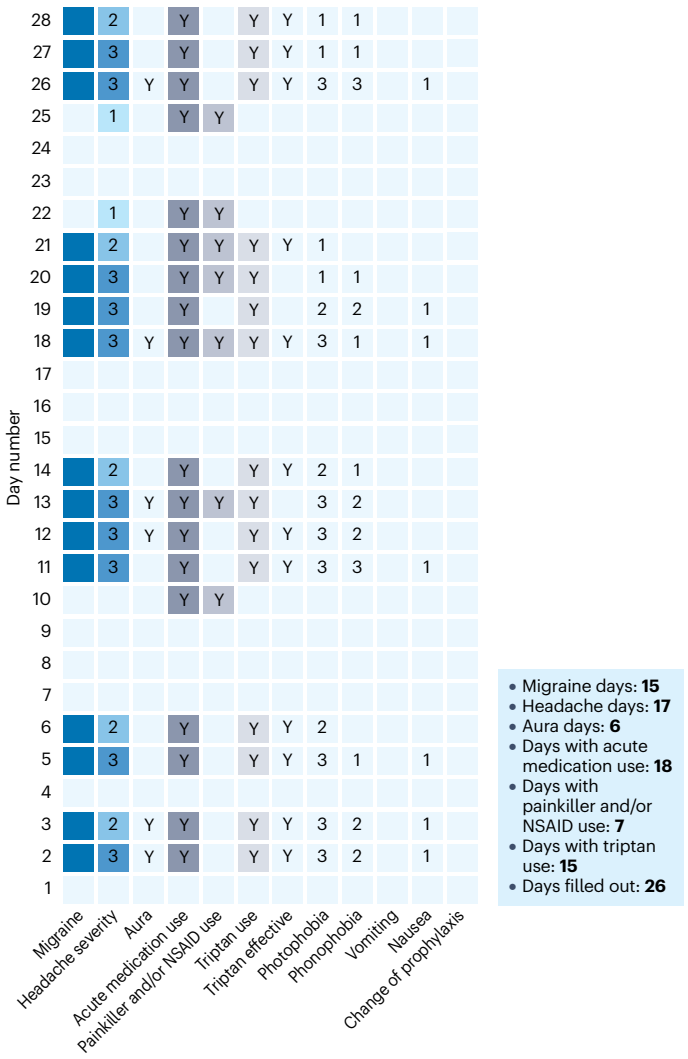


Fig. 3 | Example of an electronic headache diary of a patient with chronic migraine and medication overuse headache. Subjects received a daily alert at 8 a.m. and reported on headache and migraine symptoms of the previous day (from midnight to midnight). Questions included the presence or absence of headache, aura symptoms, use of (migraine-specific and non-migraine-specific) acute medication and, if applicable, additional questions on the duration of the headache and associated symptoms (unilateral location, pulsating quality, pain intensity, increase with routine physical activities, nausea, vomiting, photophobia and phonophobia). Questions on preventive medication use and general well-being were also asked each day. Participants received a reminder at 6 p.m. if the electronic headache diary (E-diary) was not yet completed that day. After completion the response could not be altered, and if the E-diary was not completed within 48 h it was locked[186]. A cycle is defined as 4 weeks (28 days). A validated algorithm calculates whether a day is a headache and/or migraine day. Headache severity is indicated by a score of 1 to 3. Intake of acute headache medications (analgesics/NSAIDs and/or triptans) is shown in the figure. Whether a triptan is effective is also shown. Only associated symptoms such as nausea/vomiting/photo- and phonophobia are shown. Other details are not shown in this view. Change of prophylaxis can be shown if applicable. The patient in the figure has chronic migraine and medication overuse headache with 17 headache days per month (28 days) of which 15 are migrainous, and in total 18 days of acute medication use (15 days with triptan and 7 days with analgesic/NSAID). In this cycle, 26 of 28 days were filled out.

hours or the next day[175]. Patients who overused multiple drug classes reported more frequent use of acute medications and fewer crystal-clear days (that is, days without headache and having minimal or no migraine symptoms) than those who overused triptans[181]. On average, at the time of medical presentation of MOH, patients have had any headache disorder for 20 years with MO for ~6 years, which is clear evidence of lack of awareness of MOH[71,182,183].

Diagnosis

The diagnosis of MOH requires a careful history and examination, including a search for 'red flags' to rule out other secondary headaches[184]. Red flags may include systemic symptoms or illness (fever, weight loss), secondary risk factors (HIV, cancer, anticoagulation, pregnancy), neurological symptoms or abnormal signs, sudden onset of headache, onset of headache after age 50, and new, different or progressive headache[184,185]. In the presence of red flags, targeted diagnostic evaluation with blood tests, neuroimaging and/or cerebrospinal fluid testing may be required.

Headache diaries are essential for MOH diagnosis and to measure treatment effects (Fig. 3). These diaries can be used to monitor the frequency and severity of headache, medication use and other features of headache, such as accompanying symptoms. Some studies have demonstrated discrepancies in the numbers of reported migraine days, headache days and days with acute medication use when measured via headache diaries against patient self-report via retrospective recall. The numbers of diary-based monthly migraine days and days with acute medication use are underestimated when fewer than 8 days per month are estimated by patients compared with their E-diary and overestimated when more than 8 days per month were reported[186].

Prevention

As there is a general lack of awareness about MOH, clinicians, pharmacists and individuals with headache need to be educated about the importance of MOH avoidance[187–189]. Patients with frequent headaches who lack education about MOH might think it counterintuitive that taking acute headache medications to treat individual headaches could worsen headache patterns. Educational interventions that target patients and the general public have been made to increase knowledge about MOH[188,190]. Large-scale and nationwide awareness campaigns can harness various communications technologies such as social media, newspapers, radio, television, online videos, online news, academic or professional journal articles, PowerPoint presentations and printed materials and can collaborate with health professional networks, pharmacies and patient organizations. Warnings about MOH are now required by the FDA in the drug facts labels for many over-the-counter pain medications and prescription medications used to treat migraine[191].

It is difficult to predict how fast patients who develop high-frequency headaches progress from lower frequency to higher frequency patterns[8,192–194]. Another key aspect to preventing MOH is to intervene with effective preventive therapies that reduce headache frequency and severity before individuals transition to a high-frequency state. Doing so reduces the need for frequent acute headache medications and therefore reduces the risk of MOH.

Management

Management of MOH has several aspects: patient education, discontinuation or withdrawal of the overused medication, behavioural intervention and preventive treatment that targets MOH as well as

underlying primary headaches. Follow-up and monitoring of patients are also important components of management as MOH can relapse in both the short and long term. Before we discuss each component in detail, it should be noted that we cannot evaluate the quality of treatment studies because no guidelines exist on the design of MOH trials — which includes patient selection, optimal primary end points and follow-up duration. From this point of view, many MOH trials have methodological issues and heterogeneity of nature[195]. Moreover, the concept of MOH and the need for medication discontinuation are often questioned owing to lack of strong biological association and lack of high-quality epidemiological studies[196]. Therefore, the selection of each therapy cannot be prioritized by the absolute strength of evidence but by patient characteristics, including psychiatric and medical comorbidities[197]. With these views in mind, we introduce each therapy in the following sections.

Patient centricity and education

Patient centricity and education are the first steps in MOH management[198]. The concept of MOH and its treatment has always been an uncomfortable one for clinicians and their patients, as the advice to minimize or discontinue medications that provide acute relief from headache seems to contradict the aim of minimizing pain. In addition, headache may transiently worsen when acute medication is reduced or terminated. Thus, clinicians should educate the patient about the concept of MOH, how the frequent use of acute medications can lead to more frequent headaches and that the overused medication should be restricted for the treatment of MOH (see 'Pausing medication or withdrawal', below). Education and patient engagement are important to promote awareness of MOH and for motivation for treatment, as both prevention and treatment of MOH have behavioural aspects. The effectiveness of a consultation was reported in a randomized controlled trial in a primary care setting, which found that advice alone yielded similar treatment outcomes to medical treatment in patients with uncomplicated MOH (defined as triptan or simple analgesic overuse and no major psychiatric comorbidities)[199,200].

Pausing medication or withdrawal

Overused medications should be discontinued, or their frequency of use limited, for treatment of MOH, although the timing of discontinuation or limitation is debated. The benefit of discontinuation was proved in comparison with 'no treatment' controls in a multicentre randomized trial[201]. Various strategies can be used for stopping or limiting the overused medication: early discontinuation of the overused medication without preventive treatment (see 'Preventive treatment', below); early discontinuation of the overused medication plus preventive treatment; preventive treatment with restricted use of the overused medication; and preventive medication without early discontinuation or restrictions on the overused medication. One systematic review compared the first two strategies and revealed that early discontinuation plus preventive medication was superior to early discontinuation alone[202]. This finding was subsequently tested in a randomized controlled study, which found that discontinuation plus preventive medication was superior to discontinuation alone and preventive medication without discontinuation, in terms of conversion transformation to episodic migraine and reversal of MOH[164]. However, the concept of 'early' discontinuation is challenged by studies that did not implement drug discontinuation or withdrawal but showed promising results[167,168,170,203]. Thus, we propose an algorithm that includes both early drug discontinuation with or without preventive medication and early preventive medication with stepwise application of drug discontinuation (Fig. 4).

With regard to the mode of discontinuation, complete discontinuation of acute medications is more effective and feasible than restricted use[204,205]. In terms of speed, abrupt discontinuation of triptans, ergots, simple analgesics, NSAIDs and combination analgesics is recommended and generally safe and well tolerated in most patients, whereas opioids or barbiturates should be gradually tapered to avoid withdrawal symptoms. Patients who discontinue the overused medication may initially be provided with an acute headache treatment from a different medication class to treat breakthrough headaches during the withdrawal period. When the MOH is treated, the previously overused medication can be introduced again but with a reduced frequency of use.

Discontinuation of triptans, ergot and simple analgesics or NSAIDs can be performed in outpatient settings in patients with uncomplicated MOH. However, discontinuation of opioids or barbiturates should be carried out in the inpatient setting if there is concern for physical withdrawal unless gradual tapering is feasible. Other factors, such as severe psychiatric comorbidities, overuse of medications from several classes and prior failed outpatient-based medication pause or withdrawal, are also indications for inpatient treatment when available. In a study in which a high success rate of 71% after an inpatient detoxification programme was reported, earlier life traumas and stressful events were associated with negative outcomes[206]. There is as yet no consensus recommendation regarding duration of withdrawal. The duration of withdrawal from overused medications varies among studies and regions: for example, 7 days for uncomplicated MOH in the COMOESTAS (Continuous Monitoring of Medication Overuse Headache in Europe and Latin America: development and Standardization of an Alert and Decision Support System) protocol[207], 8–10 days for complicated MOH in another study[160], 2 months in the Danish guideline on the diagnosis and treatment of headache disorders[208] and 3 months in the Netherlands[163].

During the acute phase of drug discontinuation, withdrawal headaches of variable intensity can develop and may challenge the discontinuation. Systemic steroids have been widely used to reduce withdrawal headache. However, four randomized controlled trials designed to prove the efficacy of systemic steroids failed to meet the primary end point[209–212]. Nevertheless, secondary end points and clinical observations still showed potential benefits of steroids[209,211,212]. Other strategies to reduce withdrawal headache include regular use of celecoxib[213], intravenous paracetamol and other drugs used for the treatment of status migrainosus, a complication of migraine characterized by a debilitating migraine attack lasting for more than 72 h.

Preventive treatments: pharmacological

The use of preventive medication is recommended from the initial phase of treatment of MOH. Preventive medications can be offered before, at the time of, during or after medication discontinuation. Preventive medication alone was found to be superior to no treatment in a multicentre randomized controlled study[201]. A randomized clinical study in Denmark compared discontinuation only, preventive medication only and combined discontinuation and preventive medication use, and found no difference in reduction of migraine days, acute medication use or headache intensity[164]. However, secondary outcome analysis showed higher rates of transformation to episodic migraine and reversal of MOH in the early discontinuation and preventive medication from the start of withdrawal group compared with the

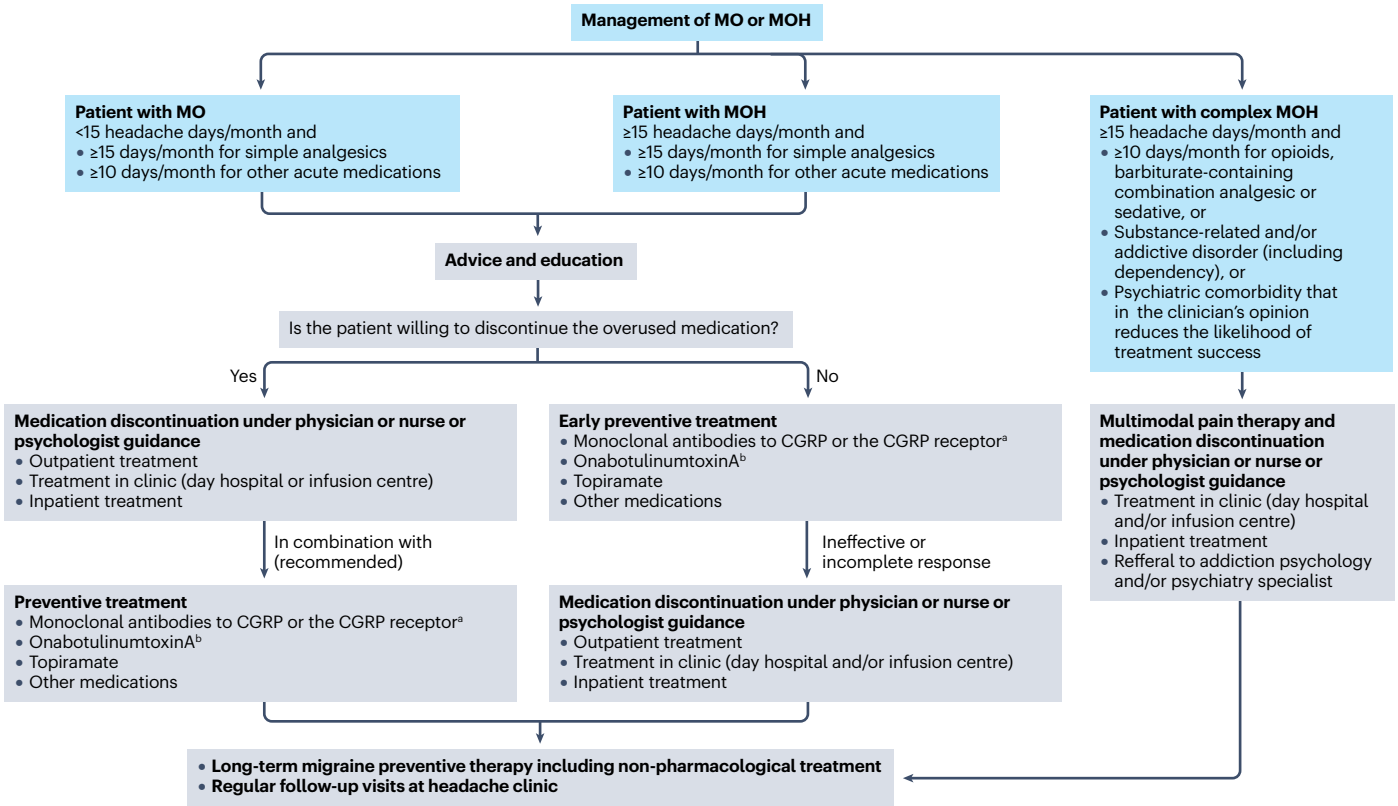


Fig. 4 | Proposed prevention and treatment algorithm of medication overuse headache. Flow chart depicts treatment strategies for medication overuse (MO) and medication overuse headache (MOH) that have proven effectiveness. However, the comparative effectiveness of these strategies is largely unknown. Both approaches for MO and MOH without complications can be effective but the preventive treatment and discontinuation/withdrawal approach is viewed as the more pragmatic approach and the one that is likely easier for patients. The choice of strategy may vary among countries based on local practice guidelines and among patients within the same country. Both treatment approaches share the same goal of having the patient stop the MO. The patient has a role in determining the optimal treatment strategy. If a patient has zero intention of immediately stopping their overused medication, suggesting such an approach will not succeed. By contrast, if the patient is motivated to stop the overused medication, then that is a reasonable approach, as long as they are given rescue treatment or medications to treat severe headaches with a limited frequency. Advice and education include instructing the patient to reduce intake of acute medication to <15 days for simple analgesics or NSAIDs and <10 days per month for all the other acute medications (triptans, ergots or combination analgesics). Medication discontinuation/withdrawal indicates stopping acute headache medication (with the exception of barbiturates or opioids, which would require multimodal therapy). Multimodal pain therapy is a multidisciplinary treatment that comprises pharmacological and non-pharmacological therapies. Many clinicians offer preventive pharmacological treatment from the beginning whereas others attempt withdrawal of the overused medication as the first step. [a]OnabotulinumtoxinA should be used only for prevention in a patient with chronic migraine. [b]Monoclonal antibodies to calcitonin gene-related peptide (CGRP) or the CGRP receptor are indicated for prevention of episodic and chronic migraine.

other two groups[164]. Furthermore, another randomized trial found that migraine preventive treatment without switching or restricting the overused medication is non-inferior to preventive therapy with switching from the overused medication to an alternative medication with a restricted frequency of 2 days or less per week[203]. These two trials suggest an importance of early preventive medication for the treatment of MOH. In the further course of treatment, regular follow-up visits and preventive medical treatment is given to prevent relapse into renewed overuse of acute headache medications.

Several preventive medications that target the primary headache subtype that underlies MOH can be used. Among those, medications with potential efficacy against MOH include topiramate[214], valproic acid[215], onabotulinumtoxinA[216] and monoclonal antibodies to CGRP or the CGRP receptor[167,169,170,214–217] (Table 2). The efficacy of topiramate for MOH was assessed in MO subgroup analyses of two trials on chronic migraine without discontinuation of overused medication; one trial demonstrated a significant reduction in monthly migraine days compared with placebo, whereas the other trial was negative but showed efficacy in the triptan overuse subgroup[218]. Thus, topiramate is likely effective for the treatment of patients with chronic migraine and MO, but use of topiramate can be hampered by adverse effects[214,217]. Valproic acid has demonstrated efficacy (≥50% reduction in monthly headache days) in the treatment of MOH with history of migraine after detoxification[215]. OnabotulinumtoxinA was more effective in reducing headache days than placebo in MO subgroup analyses of two trials in patients with chronic migraine without discontinuation of overused medication[216]. However, one double-blind, placebo-controlled, randomized clinical trial during which all participants with MOH received acute withdrawal therapy failed to show additional benefit of onabotulinumtoxinA over medication discontinuation only

in terms of reducing monthly headache days[163]. All four currently available monoclonal antibodies to CGRP or the CGRP receptor reduced monthly migraine days and acute headache medication use, and provided higher 50% responder rates in subgroups of patients with migraine and MO compared with placebo[167–170] (Table 2). More recently, atogepant, a small-molecule CGRP antagonist, was effective and was associated with a greater reduction in acute medication use days in people with chronic migraine and MO compared with placebo[219]. In a randomized controlled study on preventive treatment of migraine with rimegepant, the subgroup analysis of patients with chronic migraine and MO was not reported[220].

Treatment of MOH with β-blockers, flunarizine, tricyclic antidepressants or candesartan has not been studied in randomized trials although these agents are widely used in clinical practice.

Interventional therapies. In a small, controlled trial, repeated sessions of greater occipital nerve blockade with 1% lidocaine yielded additional benefit in terms of reduction in headache days and headache intensity, and decrease in triptan need over acute medication withdrawal alone in patients with triptan overuse headache[221].

Preventive treatments: non-pharmacological

Behavioural interventions. Reducing headache frequency via appropriate preventive therapies, addressing psychological factors such as pain coping methods, anxiety, depression and suicidality, can be important for the holistic treatment of MOH[162]. From a biopsychosocial perspective of MOH, behavioural treatment can be implemented. Some components of behavioural treatment are introduced in the Patient centricity and education section.

Overuse of pain medication has a strong behavioural component, and withdrawal therapy requires substantial adjustments in behaviour and lifestyle[89,93,222,223]. Accordingly, the addition of a behavioural intervention for MOH is likely beneficial, although this approach has mostly been evaluated in observational trials[223,224]. One innovative concealed, double-blind randomized controlled trial compared the effect of maximal behavioural intervention (comprising a contact schedule of education, motivational interviewing and value-based activity planning during 12 weeks of withdrawal therapy) and minimal behavioural intervention (a short contact only) during withdrawal therapy, and both strategies yielded high withdrawal success rates (93% and 86%)[162]. However, this study found that the maximal behavioural intervention was superior to minimal behavioural intervention at 24 weeks after treatment in terms of the number of days per month with acute medication use, although it was provided only during the first 12-week withdrawal period. These data suggest a modest benefit of behavioural intervention during withdrawal therapy for MOH in reducing acute medication use both during and shortly after intervention; however, extension appears needed for a prolonged effect.

Biofeedback and mindfulness have been investigated in two pilot randomized controlled trials for the treatment of MOH and showed promising results as add-on therapies to pharmacological treatment[225,226]. The behavioural intervention can be an independent

Table 2 | Medications with preventive effect on chronic migraine and medication overuse or medication overuse headache assessed in post-hoc analyses of double-blind randomized placebo-controlled trials

Study	Treatment arms	Dose	Reduction in monthly migraine days	Elimination of medication overuse (%)[a]	Treatment duration	*n*
Diener et al. (2007)[214]	Topiramate	100 mg (daily)	−3.7[b]	–	16 weeks	23
	Placebo	NA	−0.5	–	16 weeks	23
Silberstein et al. (2013)[216]	OnabotulinumtoxinA	155–195 units (quarterly)	−8.2***	43.4**	6 months	445
	Placebo	NA	−6.2	31.8	6 months	459
Tepper et al. (2019)[169]	Erenumab	70 mg (monthly)	−6.6**	36.4**	3 months	77
	Erenumab	140 mg (monthly)	−6.6**	34.6**	3 months	78
	Placebo	NA	−3.5	17.7	3 months	113
Dodick et al. (2021)[167]	Galcanezumab	120 mg (monthly)	−4.8***	47.9[c]	3 months	177
	Galcanezumab	240 mg (monthly)	−4.5***	47.7[c]	3 months	175
	Placebo	NA	−2.3	29.6	3 months	344
Silberstein et al. (2020)[168]	Fremanezumab	225 mg (monthly)	−5.2***	60.6**	3 months	198
	Fremanezumab	675 mg (quarterly)	−4.8***	55.2*	3 months	201
	Placebo	NA	−2.8	46.3	3 months	188
Diener et al. (2021)[170]	Eptinezumab	100 mg (quarterly)	−8.4***	51.1[c]	6 months[d]	139
	Eptinezumab	300 mg (quarterly)	−8.6***	54.4[c]	6 months[d]	147
	Placebo	NA	−5.4	32.4	3 months[d]	145
Goadsby et al. (2022)[219]	Atogepant	60 mg (daily)	−7.5	41.8	3 months	170
	Atogepant	30 mg (daily)	−8.3	44.7	3 months	161
	Placebo	NA	−5.6	24.9	3 months	169

NA, not applicable. ***$P \leq 0.001$, **$P \leq 0.01$, *$P \leq 0.05$. [a]No longer fulfils criteria for medication overuse after 3 or 6 months. [b]Assessment over the last 4 weeks of the treatment; difference did not reach statistical significance ($P = 0.07$). [c]*P* values not presented. [d]Assessment over last 3 months of the treatment period.

treatment modality and can positively affect the outcome of MOH treatment.

Acupuncture. Acupuncture has been tested in comparison with topiramate in patients with chronic migraine, and the efficacy end points were superior in patients who received acupuncture in both the whole study participants (chronic migraine) and the MOH subgroup[227].

Neuromodulation. Neuromodulation is an important alternative to pharmacological treatment of migraine, although supporting evidence for its use in MOH is scarce. One study of occipital nerve stimulation in patients with chronic migraine showed potential benefit for MOH, but another small series showed that patients with MO responded less well to occipital nerve stimulation compared with those without MO[228,229]. Efficacy of anodal or cathodal transcranial direct current stimulation has been tested in a randomized controlled trial in patients with chronic migraine and MOH, showing negative results in terms of reduction in headache days and number of analgesics at 6 and 12 months[230]. In another pilot randomized controlled trial, anodal transcranial direct current stimulation induced a more pronounced reduction in monthly migraine days[231]. Non-invasive neuromodulation techniques, including supra-orbital transcutaneous neurostimulation, single-pulse transcranial magnetic stimulation, non-invasive vagus nerve stimulation and caloric vestibular stimulation, have also demonstrated efficacy for prevention of migraine[232–236]. However, as the preventive efficacy of these devices has been proved mostly for episodic migraine, whether they are effective for MOH is unknown. Single-pulse transcranial magnetic stimulation, supra-orbital transcutaneous neurostimulation, non-invasive vagus nerve stimulation, remote electrical stimulation and a wearable neuromodulation device that targets trigeminal and occipital nerve branches are FDA-approved for acute migraine treatment[235,237,238]. These treatments might reduce acute abortive drug intake in patients with migraine as reported in open-label studies, but larger randomized trials are needed to confirm this effect[239,240].

Follow-up of treatment response

As MOH occurs in patients with pre-existing headache disorders[4], follow-up should focus on both the underlying headache disorder and MOH. Assessing patient compliance with preventive medications, withdrawal of overused drugs and acute medication restriction should occur before evaluation of treatment response. Treatment response can be measured using headache diaries to assess changes in monthly headache days, monthly migraine days, days of acute medication use, headache intensity and the efficacy of acute medication.

Prognosis

The short-term prognosis for patients with MOH is generally good, with 66–100% of patients remaining without MO at 2 months and 60–83% at 1 year after withdrawal therapy especially in combination with preventive medication[202]. However, 10–40% of patients may relapse within 5 years after withdrawal[202]. The first year after withdrawal is considered a crucial time period for predicting long-term success and, therefore, close monitoring of the patient during this time frame, preferably with a daily headache diary, is highly recommended[241,242]. The combination of migraine and TTH, overuse of opioids, longer duration of regular acute medication intake, a high number of acute treatments, no improvement after 2 months of withdrawal, smoking, alcohol consumption, patient-reported poor sleep quality and high body pain are predictive factors for relapse of MOH[242–246].

Management in specific populations

Optimal treatment of MOH in children has limited high-quality evidence. In a large-scale observational study, withdrawal with acute, preventive and biobehavioural therapy yielded only a 44.5% response rate in children and adolescents with chronic migraine and MOH[247]. Proven treatment strategies for adult MOH can be applied to children and adolescents. However, oral migraine preventives can have tolerability issues and onabotulinumtoxinA and CGRP-targeting monoclonal antibodies are not approved for use in children and adolescents in most countries. A short-term course of daily naproxen, greater occipital nerve blockade and single administration of intravenous dihydroergotamine can be alternatives for children and adolescents if conventional approaches fail[248].

Like children and adolescents, elderly patients were generally excluded from controlled trials of oral or injection medications for the treatment of MOH. Treatment of elderly patients follows the same general principles of MOH management as that for younger adults. However, in those for whom comorbidities, concomitant medications or adverse effects limit the use of oral preventive medications, onabotulinumtoxinA or CGRP-targeting monoclonal antibodies may be safer.

Pharmacoeconomics

As MOH is a disabling and expensive disease, effective treatment is of great importance and can lead to a substantial drop in socioeconomic and health-care costs. Indeed, one study from a specialized tertiary headache centre found a reduction of 24% in medication expenses after detoxification of MOH[249]. The per-year reduction in medication expenses was most pronounced in patients with triptan overuse and in those who completed a structured medication withdrawal programme provided by the headache centre[249]. Moreover, in a prospective longitudinal study, direct health-care costs (that is, costs of acute medication, visits to health-care professionals and laboratory investigations) were reduced by 52% for the total study population up to 1 year after medication withdrawal with optional preventive medication[183]. In addition, a reduction of 21% in lost work days and higher productivity at work was reported after treatment[183]. However, one of the limitations of this study was that the costs of preventive treatments before and after the withdrawal treatment were not included, but the overall cost of the available preventives such as β-blockers and amitriptyline was very low as the study was conducted before the introduction of CGRP-targeting treatments[183].

Quality of life

MOH is associated with substantial negative effects on quality of life (QoL) and functioning, although these effects have been assessed in only a few studies of which more are clinical than population-based. Patients with MOH have lower short form-36 (SF-36) scores, or of its abbreviated version (SF-12), than the general population[33,250–253]. Moreover, in a Danish population-based study, MOH was associated with low physical health composite score (PCS-12) and mental health composite score (MCS-12), independently of educational status and income[33]. As expected, worse QoL in patients with MOH is associated with higher rates of comorbidity, such as anxiety, depression and stress, and higher headache frequency[250,251,253]. Treatment of MOH by withdrawal of the overused acute headache medication improves QoL, even 6 months and 4 years after the withdrawal[251,252,254]. In one study of inpatient withdrawal therapy, QoL scores were improved after 6 months but were still impaired compared with healthy persons[251].

Outlook

Epidemiology

Future epidemiological studies should use improved methodology and, as far as is practically possible, ICHD diagnostic criteria[69]. Only a limited number of population-based studies of the incidence, risk factors, QoL and prognosis of MOH have been carried out, and future studies are required. Most epidemiological population-based studies are cross-sectional and cannot address the question of causality or whether MO is a consequence of frequent headaches. Thus, longitudinal observational studies are also warranted. Additionally, more epidemiological studies on MOH in children and adolescents are needed.

Pathophysiology

The pathophysiology of MOH is not fully understood. Basic and clinical research studies are urgently needed to clarify the pathophysiological mechanisms of MOH. The findings of structural, functional and metabolic changes in neuroimaging studies and genetic studies need confirmation in additional studies in patients with well-defined MOH. Moreover, the susceptibility to evoked CSD in animal models of MOH, which is believed to be involved in the pathophysiology of headache, needs to be replicated in patients. CSD has been studied indirectly in humans using functional imaging, and this technique could be used in future studies in patients with MOH. Preclinical studies have demonstrated that dysregulation of glial glutamate transporters may have a role in the development of both morphine tolerance and associated hyperalgesia[255]. The role of glutamate transporter in glia cells in the development of central sensitization needs to be explored in MOH.

Diagnosis

Diagnosis of MOH using current ICHD criteria has several challenges. One is related to demonstrating causality, as improvement after withdrawal of the overused medication is no longer required for diagnosis, owing to a need to diagnose MOH in real time. As previously mentioned, the operational definition of MOH according to ICHD-3 requires two components, having ≥15 monthly headache days for >3 months and taking medications at rates above the values specified for particular pharmacological classes (termed MO). In one US population study of people with either episodic migraine or chronic migraine, 17.7% met the ICHD-3 criteria for MO, of whom 67.9% reported <15 monthly headache days and, therefore, did not meet criteria for MOH[256]. In this study, acute MO was associated with monthly headache day frequency, disability and interictal burden, among other factors[256]. In a separate study using similar methods, 15.4% of persons with episodic migraine or chronic migraine met criteria for MO, which was associated with use of triptans, opioids and barbiturates but not NSAIDs[5]. MO was also associated with higher monthly headache day frequency, more severe migraine symptoms including pain intensity and higher rates of cutaneous allodynia, particularly in men. These data favour consideration of MO in persons with migraine, even if their monthly headache frequency is <15 days, and this needs to be studied further. The concept of MOH and its treatment have been challenged so far. The fact that several trials report a clinically relevant headache improvement in a relevant proportion of patients with MO after pausing or withdrawal of the acute medications suggests a strong need for research on the pathophysiology-driven diagnosis and classification of MOH.

Management

Owing to limited understanding of pathophysiology of MOH, disease-specific pharmacological treatments for MOH do not exist. Withdrawal of the overused medications, especially in combination with preventives, is effective; however, the withdrawal protocol is debated and should be further explored. The potential role of novel migraine therapies such as CGRP-targeting treatments in the management of MOH also needs to be explored. Gepants have been introduced as new medications for the treatment of migraine[220,257–259]. Preclinical studies have suggested that gepants may not elicit animal responses suggestive of MOH, unlike triptans and NSAIDs[171,260]; however, the role of gepants in treatment of MOH needs further clinical study.

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Author contributions

Introduction (S.A., R.B.L. and T. J. Steiner); Epidemiology (S.A., T. J. Steiner and R.B.L.); Mechanisms/pathophysiology (S.A., G.M.T., F.P. and C.T.); Diagnosis, screening and prevention (S.A., G.M.T., T. J. Schwedt and R.H.J.); Management (S.A., M.J.L., R.H.J. and H.-C.D.); Quality of life (S.A., T. J. Steiner, T. J. Schwedt and R.B.L.); Outlook (S.A., F.P., R.H.J., H.-C.D. and R.B.L.); Overview of Primer (S.A.).

Competing interests

S.A. received honoraria for consulting from Allergan/AbbVie, Amgen, Biohaven, Eli Lilly, Impel NeuroPharma, Linpharma, Lundbeck, Novartis, Satsuma, Supernus, Teva, Theranica, Percept. S.A. is an associate editor for *Neurology Reviews*, *Frontiers in Neurology* and *BMC Neurology*, serves on the advisory board for the *Journal of Headache and Pain*, and is a member of the Education Committee of the International Headache Society. G.M.T. reports consultancy support from Novartis, Allergan, Lilly, Teva, Lundbeck, and independent support from the Dutch Organization for Scientific Research, the Dutch Heart and Brain Foundations, IRRF and Dioraphte. M.J.L. received honoraria as a consultant and/or speaker for Eli Lilly, Teva, Sanofi-Aventis, SK Pharma and YuYu Pharma; has been the principal investigator or co-investigator in trials sponsored by Eli Lilly, Novartis, Teva (Otsuka), Allergan, Biohaven, Yuhan Company, Samjin Pharm, and DongA ST; received research support from National Research Foundation of Korea. M.J.L. is an associate editor of *Cephalalgia*. F.P. has served as a consultant or received research funding from Amgen, Acadia, Teva, Eli Lilly, Lundbeck, Allergan, AbbVie, AstraZeneca, Ipsen and PeptideLogic and is a founder of Catalina Pharma and Axon Therapeutics. C.T. has received personal fees from AbbVie, Allergan, Biohaven, Eli Lilly, Lundbeck, Novartis and Teva. C.T. has received research funding from the European Commission, the Italian Ministry of Health and Migraine Research Foundation. T. J. Schwedt has received personal income from AbbVie, Allergan, Biohaven, Click Therapeutics, Eli Lilly, Equinox, Lundbeck, Novartis, Tonix and Weber & Weber. T. J. Schwedt holds stock options in Aural Analytics and Nocira and has received royalties from UpToDate. T. J. Schwedt has received research funding from the American Migraine Foundation, Amgen, Henry Jackson Foundation, NIH, Patient Centered Outcomes Research Institute, SPARK Neuro and the US Department of Defense. R.H.J. has received honoraria for lectures and/or patient leaflets from MSD, Berlin-Chemie Menarini, ATI, Novartis, Teva, Allergan, Lundbeck and Pfizer, and has been principal investigator in studies sponsored by Eli Lilly, Lundbeck and ATI. H.-C.D. received honoraria for participation

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