MEDICATION OVERUSE HEADACHE

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Abstract
Medication overuse headache (MOH) is a secondary headache type caused by the overuse of acute headache medications, occurring only on a pre-existing headache. The current definition has removed the two main causative factors included in previous classifications: a substantial increase in frequency and/or intensity of pain, and the reversal of the deteriorated headache after medication withdrawal. This change makes diagnosing MOH at the individual level challenging, and the concept remains a matter of debate. However, there is compelling evidence for the harmful effects of medication overuse in both human and animal studies. A susceptible brain is a necessary prerequisite for medications to exert their deleterious effects. Genetic polymorphisms, neurophysiologic and imaging alterations, comorbidities, environmental or lifestyle factors, and even demographic and socioeconomic factors may affect the brain's susceptibility in headache sufferers. Some of these factors might result from MOH after its establishment. The management of MOH is multidimensional. The first important step is prevention. Following diagnosis, management begins with educational advice and extends to outpatient or inpatient withdrawal of the overused drugs, whether abrupt or gradual. This process may include the use of adjunctive pharmacotherapy for withdrawal symptoms, the addition of preventative treatment, and, if needed, non-pharmacological interventions. All these topics are discussed in the current review, in line with the recent guidelines of the European Academy of Neurology.

Keywords: headache, migraine, medication overuse, analgesics, withdrawal

ΚΕΦΑΛΑΛΓΙΑ ΑΠΟ ΚΑΤΑΧΡΗΣΗ ΦΑΡΜΑΚΩΝ

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Περίληψη
Η κεφαλαλγία από κατάχρηση φαρμάκων (ΚΚΦ) είναι μια δευτερογενής κεφαλαλγία, που προκαλείται από την κατάχρηση φαρμάκων για την αντιμετώπιση της οξείας κεφαλαλγίας και εμφανίζεται μόνο σε έδαφος προϋπάρχουσας κεφαλαλγίας. Ο τρέχων ορισμός της αφαίρεσε τους δύο κύριους αιτιολογικούς παράγοντες, οι οποίοι περιλαμβάνονταν στις προηγούμενες ταξινομήσεις: σημαντική αύξηση στη συχνότητα ή/και την ένταση του πόνου και την αποκατάσταση της επιδεινωθείσας κεφαλαλγίας μετά τη διακοπή των φαρμάκων. Αυτό καθιστά δύσκολη τη διάγνωση της ΚΚΦ σε ατομικό επίπεδο και η έννοια στο σύνολό της παραμένει επί του παρόντος θέμα αντιπαράθεσης. Ωστόσο, υπάρχουν αδιάσειστα στοιχεία για τις βλαβερές συνέπειες της υπερβολικής χρήσης φαρμάκων, τόσο σε μελέτες σε ανθρώπους όσο και σε πειραματόζωα. Ένας επιδεκτικός στην ΚΚΦ εγκέφαλος είναι η απαραίτητη προϋπόθεση για να ασκήσουν τα φάρμακα τα αρνητικά αποτελέσματά τους. Γενετικοί πολυμορφισμοί, νευροφυσιολογικές και απεικονιστικές αλλοιώσεις, συννοσηρότητες, περιβαλλοντικοί παράγοντες ή παράγοντες του τρόπου ζωής ή ακόμη και δημογραφικοί και κοινωνικοοικονομικοί παράγοντες, μπορεί να επηρεάσουν την επιδεκτικότητα του εγκεφάλου του κεφαλαλγικού ασθενούς. Κάποια από τα παραπάνω μπορεί να είναι αποτέλεσμα της ΚΚΦ, μετά την εγκατάστασή της. Η διαχείριση της ΚΚΦ είναι πολυδιάστατη. Το πρώτο σημαντικό βήμα είναι η πρόληψη. Το επόμενο βήμα, μετά τη διάγνωση, ξεκινά με εκπαιδευτικές συμβουλές και επεκτείνεται στην εξωνοσοκομειακή ή ενδονοσοκομειακή απόσυρση των φαρμάκων κατάχρησης, είτε απότομη είτε σταδιακή, με χρήση ή όχι συμπληρωματικής φαρμακοθεραπείας για τα συμπτώματα στέρησης, με προσθήκη προφυλακτικής αγωγής και εάν χρειάζεται, μη φαρμακολογικές παρεμβάσεις. Όλα αυτά τα θέματα συζητούνται στην τρέχουσα ανασκόπηση, σύμφωνα με τις πρόσφατες οδηγίες της Ευρωπαϊκής Ακαδημίας Νευρολογίας.

Λέξεις κλειδιά: κεφαλαλγία, ημικρανία, αναλγητικά, κατάχρηση φαρμάκων, απόσυρση

Introduction

Many drugs prescribed for various medical conditions may cause headaches as an adverse drug reaction. This can occur under the ordinary use of the prescribed drugs, meaning within the range of dosages and duration of treatment as instructed by the patients' doctors. For several drugs, this adverse reaction is frequent, and the same is true for other non-medicinal substances like alcohol, carbon monoxide, or nitric oxide.

Under the current diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3),[1] all these headache-provoking drugs and substances are grouped under the heading "headache attributed to a substance or its withdrawal" (coded as 8). People susceptible to this headache type may or may not have a pre-existing headache disorder. In the latter group, the phenomenology of their headache may resemble the pre-existing one.

Given that headache is a common symptom, how can we diagnose whether a headache is caused by the drug or substance used rather than merely occurring by chance? According to the current criteria of the International Headache Society (IHS),[1] the following rules should be fulfilled:

- The usage or withdrawal of a substance known to cause the observed type of headache.
- The causation between headache and substance use is decided by at least two of the following:
  - Close temporal relation between the exposure to or withdrawal from the substance and the subsequent headache.
  - Cessation of the usage or exposure to the substance results in a close temporal sequence of either pain freedom or pain relief, or the same occurs within a defined period in the case of headache after substance withdrawal.
- The characteristics of the headache are typical for withdrawal from or exposure to the substance.
- There is evidence of some other type of causation.
- There is no better explanation from any other ICHD-3 diagnosis.

A subcategory of this general category, "headache attributed to a substance or its withdrawal," is medication overuse headache (MOH), coded 8.2. The distinguishing characteristic of MOH from the rest of this category (code 8) is that the substances causing the headache are medications used by patients for the acute treatment of their headaches. MOH occurs only if these medications are overused, which is defined as usage above a cutoff of days per month (d/m), determined separately for each class of medications. It is surprising that MOH has been described almost exclusively in headache patients and not in other medical disorders, despite the overuse of analgesic medications for these disorders. A question raised about the concept of MOH is how a clinician can determine the causation between medication overuse (MO) and MOH. Are the current diagnostic criteria sufficient to guarantee MO as the causative factor for the resulting headache, namely MOH?

The concept of MOH through the history of ICHD revisions

The first clinical observation of a new headache type provoked by the excessive use of ergotamine preparations was published in 1951 by Peters and Horton.[2] In the following years, these initial clinical observations were verified and expanded. Eventually, this headache type was included as a distinct category of secondary headache disorder in ICHD-1, under the heading "Headache induced by chronic substance use or exposure".[3]

In each subsequent revision of ICHD-1, several amendments have been made concerning the diagnostic criteria of MOH (see Table 1). The result of these successive modifications are the current criteria, summarized as follows[1]:

- The patient has a pre-existing headache disorder (not only a primary headache disorder) occurring on ≥ 15 d/m.
- Usage of common analgesics and NSAIDs on ≥ 15 d/m, and the rest (triptans, opioids, combinations of substances in one preparation, and combined overuse of different drug classes and preparations, but not each individual drug class) on ≥ 10 d/m. The duration of overuse should be more than 3 months, in a roughly regular manner, e.g. 3 or 4 times per week.
- No other ICHD-3 diagnosis may better explain the headache.

Table 1. Diagnostic criteria of MOH through ICHD revisions

MOH	ICHD-1 1988[3]	ICHD-2 2004[4]	ICHD-2R 2005[5,6]	ICHD-3b 2013[7,8]	ICHD-3 2018[1]
Occurs in patients with a pre-existing headache disorder	Included in all ICHD versions, either in the main body of the diagnostic criteria or in the following notes or comments				
Frequency of headache	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m
Headache developed or markedly worsened	Included as criterion	Included as criterion	Included as criterion	*Removed*	*Removed*
Pain freedom or notable relief after discontinuation	Within 1 month	Within 2 months	Within 2 months	*Removed*	*Removed*
Clinical characteristics	Described for ergotamine overuse (diffuse, pulsating)	Described as variable with peculiar shifting pattern	Removed	*Removed*	*Removed*
Definition of medication overuse	Dosages per month (e.g. >50 gr aspirin or >100 combined analgesics tablets)	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m
Probable/Definite headache definition	Not included	Introduced	Remained	Removed	Removed
Not explained by another ICHD diagnosis	Not mentioned explicitly	Not mentioned explicitly	Not mentioned explicitly	Stated explicitly	Stated explicitly

Obviously, the two major factors establishing causation between MO and MOH, are absent from the current criteria. These factors, written in italicized in Table 1, are:

The development of a new type of headache or the marked worsening of a pre-existing one.

The resolution of MOH after medication withdrawal.

Both factors were included in the diagnostic criteria of ICHD-1 and ICHD-2 but were removed in ICHD-3 (both beta and final versions). Nevertheless, these causation factors remain in the general diagnostic criteria for the category coded 8 ("Headache attributed to a substance or its withdrawal") , indicating that while they do not apply to each headache disorder in this category, they serve as a guideline for most.

Thus, with the removal of the previously recognized causation factors, we might envision the following scenario:

a migraineur fulfilling the diagnostic criteria for chronic migraine, without MO, begins overusing triptans (> 10 days/month) for the last 6 months. There is no change in the frequency or the intensity of her headaches-only the overuse of triptans. Does such a patient fulfill the current MOH criteria?

The answer is clearly yes, based purely on the criteria. Thus, a new headache type, MOH, is diagnosed without any change from the pre-existing one. In this and many similar cases diagnosed as MOH, the headache may develop in the future, making it a probable headache (pMOH).[9] However, a diagnosis of probable MOH is not defined in the ICHD-3 diagnostic criteria. The comments section of ICHD-3 acknowledges that the term pMOH is reasonable, especially in epidemiological research.[1]

These conceptual modifications of the MOH definition make its nosological entity highly controversial.[10] Additionally, a review of six observational clinical trials published between 2006-2016, which examined the proportion of MOH patients whose headaches improved solely after the withdrawal of overused medications, found that only about 30% showed improvement on average.[11] Such findings cast further doubt on the existence of MOH, even when applying the causation criterion of headache resolution after medication withdrawal.

An argument presented by Jes Olesen,[8] supporting his proposed modifications of MOH in ICHD-2, was that a notable group of chronic migraineurs with MO, despite being unresponsive to prophylactic treatment, became responsive just after withdrawing the overused medications. This clinical observation was based on his personal unpublished data. However, this observation suggests the broad spectrum of harmful effects of MO but does not support the addition of a new headache type to a pre-existing one, namely MOH.

Epidemiology, Risk Factors, Comorbidities

The worldwide median prevalence of MOH is estimated at 1-2%, with studies from different countries ranging between 0.5% and 7.2%, and a female-to-male ratio of 4:1.[12-13] Peak prevalence occurs in the sixth decade of life and is more frequent in lower socioeconomic statuses.[12]

In Greece, the prevalence is estimated at 0.7% (95% CI: 0.5-0.9), with a female-to-male ratio of 4:1, peak prevalence in the 35-54 age group, and higher prevalence in the C2 socioeconomic class, corresponding to skilled manual labor.[14] The prevalence of MO alone without MOH is 2.0% (95% CI: 1.75–2.30).

The incidence of MOH was estimated in a longitudinal population-based cohort study in Norway with 26,197 participants.[15] The incidence was 0.72 per 1000 person-years (95% CI: 0.62–0.81). Risk factors identified by multivariate analysis in this study are illustrated in Table 2. A separate clinic-based study with 142 female migraineurs found the odds ratio of metabolic syndrome as a risk factor for MOH to be 5.3[16] (Table 2).

Most of these risk factors are psychiatric disorders, which are common comorbidities of MOH. The Eurolight project, a cross-sectional survey of 10 European Union countries, reported that depression was five times more prevalent in patients with probable MOH than in healthy subjects (OR: 5.5 for both males and females), and anxiety was ten times more prevalent in males (OR: 10.4) and seven times in females (OR: 7.1).[17] Similarly, 57.7% of MOH patients were reported to suffer from anxiety and 40% from depression in the COMOESTAS cohort, a multicenter study with six months follow-up.[18] A more detailed investigation of psychiatric comorbidities has been reported by Radat et al.[19] (Table 3).

Substance abuse involving substances other than those defined in MO, such as nicotine or caffeine, has been reported repeatedly.[15,19] Could the overused medications for headaches not only be overused but also abused? If they are abused, might a diagnosis of dependence disorder also apply to the patient? This line of thinking is reinforced by the ICHD-3 recommendation to use the Severity of Dependence Scale

Table 2. Risk factors for MOH[15]

Risk factors	Odds Ratio
Headache 7-14 d/m	19.4
Migrainous headache	8.1
Any headache	5.9
Metabolic syndrome	5.3[16]
Use of tranquilizers	5.2
Non-migrainous headache	4.9

Combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Hospital Anxiety and Depression Scale score ≥ 11	4.7
Use of analgesics (for any condition)	3.0
Physical inactivity	2.7
Use of sleep-inducing medication	2.5
Hospital Anxiety and Depression Scale/ Depression (≥11)	2.6
Sick leave (>2 weeks previous year vs no)	2.5
Self-reported whiplash	2.2
Hospital Anxiety and Depression Scale/ Anxiety (≥11)	2.0
Insomnia	1.9
Chronic musculoskeletal complaints	1.9
Female gender	1.9
Low education	1.9
Age >50 y.o.	1.8
Smoking	1.8
Gastrointestinal complaints	1.6
Daily caffeine (≥540mg)	1.4

(SDS) in MOH patients [1]. Is MOH ultimately an addiction disorder? Applying the DSM-IV diagnostic criteria [20-21], a cluster randomized pragmatic, double-blind trial [22] classified 50% of MOH patients as substance dependent. Another multicenter, cross-sectional study found that 66.8% of MOH patients met the same DSM-IV criteria for substance dependence [23-24]. However, the DSM-V diagnostic criteria, published in 2013, introduced the term "substance use disorder" (SUD), combining the previously separate diagnoses of substance abuse and dependence . A conceptual analysis of the symptoms and behavioral changes of patients with SUD, according to DSM-V, concluded that they do not apply to the diagnosis of MOH [26]. Thus, the issue of addiction in MOH patients remains controversial.

Other medical conditions reported to be comorbid with MOH include musculoskeletal and gastrointestinal disorders,[15] as well as metabolic syndrome. [16] However, there is no robust evidence for other specific disorders that may be comorbid with MOH.

Pathophysiology

MOH results from the action of MO on a brain susceptible to developing it, rather than solely from the drug action (MO).[9,12] This susceptibility occurs only in the brains of headache patients, which is why MOH does not present in other medical disorders. However, the duration of MO leading to the presentation of MOH varies depending on the specific overused drug (Table 4).[27] Despite the shorter duration for MOH presentation after triptan overuse, the percentage of MO patients developing MOH may be smaller compared to those overusing analgesics and opioids.[28]

Table 3. Psychiatric comorbidities with MOH, compared to migraine (according to ICHD-2, 2004)

Psychiatric disorder	Odds Ratio
Major depression	21.8
Panic disorder	12.1
Substance abuse	7.6
Generalized anxiety disorder	6.0
All mood disorders	4.5
Social phobia	4.3
All anxiety disorders	3.5

Table 4. Mean duration (years) of MO for the development of MO per used drug class and drug[27]

Analgesics		4.8
	Common analgesics	5.2
	Analgesics + Caffeine	5.4
	Analgesics + Codeine	5.5
	Opioids	2.2
Triptans		1.7
	Sumatriptan	2.4
	Zolmitriptan	1.7
	Naratriptan	0.7
	Rizatriptan	0.3
Ergots		2.7

Genetic susceptibility

A large systematic review analyzed 17 gene polymorphism association studies in MOH, encompassing an overall analysis of 50 polymorphisms in 33 genes.[29] The genes identified with a potential relation to MOH included polymorphic variants of dopaminergic genes (SLC6A3, DRD2, DRD4), which affect susceptibility to MOH, and genes associated

with drug dependence (ACE, BDNF, HDAC3, WSF1), which affect the frequency (in days/month) of drug use. Specifically, the ACE D/D polymorphism severely decreased habituation after somatosensory stimulation, while the ACE I/D genotype exhibited a milder decrease.[9] Similarly, the common single-nucleotide polymorphism 196G>A of BDNF results in decreased activity through Val66Met substitution, ultimately reinforcing substance abuse behavior.[9] However, the lack of replication studies and various methodological issues in the published studies make these results inconclusive.[29]

Central sensitization

Common symptoms in migraineurs include increased sensitivity to light (photophobia) and sound (phonophobia), as well as the perception of innocuous stimuli as painful (allodynia). The underlying neurophysiological basis of these symptoms is the well-known phenomenon of sensitization, which involves neural mechanisms such as lowering the depolarization threshold, increased temporal summation, and expansion of receptive fields.[9,12-13] Due to the sensitization process, repeatedly administered sensory stimuli result in long-lasting, high-amplitude evoked potentials, as recorded using neurophysiological techniques, without the reduction observed in normal controls. This phenomenon is known as non-habituation. In MOH patients overusing analgesics and triptans, the sensitization process and the subsequent lack of habituation are further amplified, as shown by somatic and trigeminal pain-related cortical potentials.[30] Similar results have been recorded using different sensory modalities, such as somatosensory evoked potentials,[31] CO2 laser-evoked potentials,[32] and the cold pressor test.[33] The amplification of the sensitization process in MOH has also been confirmed in animal experiments.[34-35] Additionally, animal studies have shown that perturbations in serotoninergic and endocannabinoid metabolism result in increased sensitization.[9]

All these human cortical alterations, observed using clinical neurophysiological methods, were reversed after the complete withdrawal of the overused drugs.[30,36]

Structural, functional and metabolic imaging alterations

Since MOH is defined as a chronic (≥15 days/month) headache occurring on a pre-existing one, any structural alteration compared to healthy controls might be attributed to the pre-existing headache type rather than MOH itself. Similarly, if the control group comprises episodic rather than chronic headache sufferers, any structural imaging differences may result from the chronicity of the pre-existing headache, which is part of the concept of MOH, rather than medication overuse. Therefore, methodologically, the most valid comparison should be between the MOH group and the chronic type of pre-existing headache. However, several studies on MOH have been performed in comparison to healthy controls[37-38] or episodic migraineurs.[39-40] A voxel-based morphometry study (VBM)[41] compared a group of 66 chronic migraineurs, 33 of whom had MOH, with the rest being without MOH, and another group of 33 healthy controls. The comparison between the two groups of chronic migraineurs showed a decrease in gray matter volume (GMV) in the rectal gyrus of the orbitofrontal cortex bilaterally, as well as a decrease in GMV in the left middle occipital gyrus. Conversely, an increase in GMV was observed in the left temporal pole/parahippocampus. These GMV alterations accounted for 31.1% variance in the frequency of analgesic use. Additionally, the VBM analysis of both MO and non-MO chronic migraineurs compared to healthy controls revealed decreased GMV in the precuneus, cerebellum, and multiple areas of the frontal, temporal, and occipital lobes.

Structural imaging alterations related to MOH involve:

- The orbitofrontal cortex, a key node of the mesocorticolimbic dopaminergic system (including also nucleus accumbens, striatum and ventral tegmental area)
- The left middle occipital gyrus and left temporal pole/parahippocampus, both parts of the reward system.[42-43]

In contrast to gray matter, white matter lesions have been less studied in MOH. One study with 38 chronic migraineurs, 58 MOH and 45 healthy controls, found significantly fewer periventricular white matter lesions in MOH patients compared to chronic migraineurs without MOH. The authors hypothesized a possible anti-inflammatory role of NSAIDs, commonly used by MOH patients, in the pathogenesis of these lesions.[44-45]

A functional MRI study tested decision-making under risk in four groups: MOH patients, MOH patients six months after detoxification, chronic migraineurs without MOH, and healthy controls.[46] The comparison between MOH patients and chronic migraineurs without MOH demonstrated reduced activity in the substantia nigra/ventral tegmental area complex and increased activity in the ventromedial prefrontal cortex compared to MOH patients at six months after detoxification. Another fMRI study examined brain activity under noxious mechanical stimuli to fingers, comparing MOH patients to healthy controls.[47]

Resting-state fMRI studies have tested functional connectivity (FC)[39] or FC plus diffusion tensor im-

aging.[48] Both compared MOH patients to healthy controls, with one study differentiating the control group as episodic migraineurs and the other as chronic myofascial pain patients.

An 18 FDG PET study[49] compared 68 healthy controls to 16 chronic migraineurs with MOH and found marked hypometabolism in several brain regions: orbitofrontal cortex, bilateral thalamus, anterior cingulate gyrus, ventral striatum, insula and right inferior parietal lobule. Notably, after detoxification, hypometabolism reverted in all areas except the orbitofrontal cortex, suggesting a possible causative relationship to MOH.[45,50-51]

A single magnetic resonance spectroscopy study[52] did not demonstrate any significant biochemical (N-acetylaspartate/creatine ratio) neuroimaging difference in chronic migraineurs between those with MOH and those without.

Treatment

"Prevention is always better than cure."

Many of the drugs defined by specific cut-off points for MO are readily accessible due to their availability over-the-counter (OTC). Consequently, the likelihood of a primary care physician offering advice on avoiding MO, and thereby preventing MOH in the future, is minimal. A feasible preventive measure would be to include a warning on the packaging of OTC analgesics, stating that overuse of the drug may worsen headaches or increase resistance to prophylactic treatment if used excessively. Such warnings should be mandated by authorities such as the EMA and FDA.

Similarly, nationwide campaigns could raise awareness about MOH resulting from MO. A study conducted in Denmark[53] targeted the general population and specific groups such as pharmacists and general practitioners (GPs). The two main stakeholders in this campaign were the National Headache Center and the Association of Danish Pharmacists, with the Migraine and Headache Patient Organization joining in later stages. This campaign succeeded in raising awareness from 31% to 38%, although the implementation percentage remains unknown.

Nevertheless, prevention is the best way to ensure the avoidance of future development of MOH.

Treatment strategies after the diagnosis of MOH

The main options of management of established MOH are[54]:

- Educational counselling, meaning brief advice alone.
- Withdrawal of overused medications, either abrupt or gradual, with or without supportive medications during the withdrawal phase.
- Preventive treatment initiation, either pharmacological or not.
- Combinations of two or all three of the above.

-Advice alone

The first treatment strategy was investigated by an Italian open-label trial,[55] which studied 120 MOH patients (according to ICHD-2 criteria) without psychiatric comorbidities, previous detoxification failures, or overuse of barbiturates, benzodiazepines, or opioids (non-complicated MOH). The patients were randomized into three detoxification treatment groups:

A) advice alone

B) advice + preventive treatment + steroids

C) advice + preventive treatment + steroids + fluid replacement and antiemetics

After 2 months, 75.4% of patients succeeded in detoxification, defined as a reversion to an episodic headache type from the chronic one (MOH represents a chronic type of headache) or use of symptomatic medications for fewer than 10 days/month. There was no significant difference between the three groups.

A few years later, the same researchers conducted a similar study with 137 MOH patients who had psychiatric comorbidities, previous detoxification failures, various environmental and socioeconomic problems, and nearly daily medication overuse, including barbiturates, benzodiazepines, or opioids (complicated MOH).[56] In this study, group C (pharmacological intervention) reverted chronic headaches to episodic ones or reduced medication overuse to simple use in 89% of patients, compared to 60% in groups A and B.

A Norwegian cluster-randomized trial, the BIMOH trial,[57-60] recruited GPs in primary care and randomized them into two groups:

-The brief intervention group (BI), where GPs provided educated advice to MOH patients (according to ICHD-2R criteria).

-The business-as-usual (BAU) group, where GPs continued their usual practice

Subsets of the study were blinded (during the first 6 months), open-label (after the first 6 months), or used a cross-over design (for those initially randomized to the BAU group). The open-label part of the trial started after the first 6 months and continued up to the end of the 16-month follow-up period. Despite the large sample of the general population screened, only 259 MOH patients were diagnosed (1.02%),[60] and 60 patients completed the study. At the end of the 16-month follow-up, both the BI and BAU groups demonstrated significant decreases in monthly headache days and monthly medication days. The BI group (both early and late) experienced a decrease in headache days

per month by 8.7 (6.4–10.9) and medication days per month by 13.9 (11.2–16.7), representing nearly a 70% improvement compared to 26% in the BAU group. Additionally, 50% of the BI group reverted from chronic to episodic headaches, compared to only 6% in the BAU group.

The Akershus study, another Norwegian study on the effect of brief information in treating MOH, was uncontrolled. The results showed a 76% decrease in medication overuse, and the number of headache days per month decreased from 22 to 6.[61]

The conclusion, supported by the EAN committee recommendation, is to first try advice for MO avoidance in all MOH patients, except for those with complicated MOH as defined above.[54]

-Preventive treatment

All the approved drugs for migraine conducted pivotal clinical trials for the episodic and chronic types only. Clinical trial especially designed for MOH are very rare. For the vast majority of the approved drugs, the evidence supporting the efficacy of the drug on MOH is based on the post hoc analyses of their pivotal clinical trials for chronic migraine. Thus, there is no robust evidence for any of the new or old drugs regarding MOH.

Nevertheless, a recent randomized pragmatic trial, the MOTS trial, warrants that the use of preventive treatment in MOH is efficacious, using whatever drug is approved and marketed in the USA at the present time.[62] This trial enrolled 720 MOH participants randomized into 2 groups and every group initiated the preventative treatment. The difference between them was that the one group continued the overused drug, while the other reverted the overused drug into simple use, that is ≤2 days per week. The baseline headache d/m were 22.5 and 21.4 d/m the medications overuse. The two groups demonstrated very similar reduction of headache d/m: 9.3±7.2 the group with reversal of medications overuse and 9.1±6.8 the other group. The conclusion from this study is that even the switching of the overused drug to simple use is not necessary if the preventive treatment is initiated. However, a third arm with complete withdrawal might be necessary for more definite conclusions. The publication of the MOTS trial was not available at the time of preparation of the EAN guidelines and thus is not included in the review.[54]

Sodium Valproate is one the preventive treatments with a randomized trial designed especially for the study of MOH, the SAMOHA trial.[63] In this 3-month study randomized 88 MOH patients to 800mg of Sodium Valproate or placebo, along with outpatient detoxification and 3 months follow-up. The 50% responder rate for Sodium Valproate was 45.0% versus 23.8% for placebo.

Topiramate conducted 2 clinical trials for chronic migraine, a European trial[64] and a second trial conducted in the USA.[65] Both performed post hoc analysis to extract the subset of MOH patients and analyze their data. The European study was too small (recruited only 59 chronic migraineurs and the MOH subset included 46). The mean migraine d/m reduced by 3.5 d/m in the topiramate group versus 0.8 d/m increase in placebo. The USA study, with 306 patients, did not find any significant difference in comparison to placebo.

All four monoclonal antibodies (mAbs) published post hoc analyses of their chronic migraine pivotal clinical trials, and all of the comparisons favored the mAb versus placebo, except from Eptinezumab. Also, in all cases of mAbs the overused drugs did not withdraw. More specifically, the post hoc analysis of Fremanezumab decreased the migraine d/m in the MOH patients by 4.7 with the monthly injection and 5.2 with quarterly versus 2.5 d/m in the placebo group.[66] The Erenumab trial for chronic migraine demonstrated a decrease of 6.6 d/m for both 70mg and 140mg dose in MOH patients versus 3.5 d/m in placebo.[67] The 50% responder rate was 36% for 70mg, 35% for 140mg and 18% for placebo. The REGAIN trial for chronic migraine of Galcanezumab[68] showed a decrease of migraine d/m, in the MOH subset of patients, by 4.8 d/m in 120mg dose, by 4.5 d/m in 240mg and by 2.3 d/m in the placebo group. Finally, the SUNLIGHT trial of Eptinezumab for chronic migraine was analyzed post hoc and extracted the patients fulfilling the diagnostic criteria of MOH.[69] The difference of MOH group from placebo in mean migraine d/m was 1.2 d/m (p=0.1484) and the mean difference of migraine d/m with acute headache medication was 1.3 (p=0.1363).

OnabotulinumtoxinA also performed a post hoc analysis of the two PREEMPT (1 & 2) phase 3 studies for chronic migraine.[70] The headache and migraine days of MOH patients decreased by 8.2 days per month and 8.1 days per month for OnabotulinumtoxinA, and by 6.2 days per month and 6.0 days per month for placebo. However, the acute headache medication intake did not show any significant difference from placebo, except from triptans. Recently, published a new randomized, double-blind, placebo-controlled clinical trial conducted in the Netherlands.[71] This trial compared OnabotulinumtoxinA to placebo after the abrupt withdrawal of overused medications. The design of this trial differed from the PREEMPT protocol in the placebo arm by injecting normal saline in every extracranial site, as defined by the protocol, except for the 7 frontal injection sites, where they injected 2.5 units of OnabotulinumtoxinA in each site, totaling 17.5 units. The authors justified this approach to maximize double-blinding. The

PREEMPT trials had been criticized for not adequately masking the disappearance of wrinkles, which occurred only in the OnabotulinumtoxinA arm, making both doctors and patients aware of the substance injected in the forehead and thus unblinding the trial. The surprising result of this meticulously designed randomized controlled trial (RCT) was the absence of any significant difference between OnabotulinumtoxinA and placebo in all outcome measures. This trial challenges the findings from the PREEMPT trials, where OnabotulinumtoxinA showed a significant reduction in headache and migraine days. An expert in OnabotulinumtoxinA criticized the study's methodology for injecting 17.5 units in the frontal area of the patients in the placebo arm, which is 50% of the officially recommended dose.[72] The authors replied that 17.5 units is the lowest ever dose given in humans, not only for headaches but for other diseases as well, citing multiple references.[73] Despite these contradictory results between this RCT and the post hoc analyses of the PREEMPT trials, as well as real-world evidence studies showing significant decreases in headache days after OnabotulinumtoxinA treatment,[74] the robustness of the quality of evidence always favors RCTs. Nevertheless, the EAN guidelines recommend the use of OnabotulinumtoxinA for MOH at present, though the debate regarding the 17.5 units of placebo in the forehead continues.

The EAN guidelines also caution against methods like acupuncture, occipital nerve stimulation, or drugs with small trial sizes, like sodium valproate,[63] pregabalin, beta-blockers, or amitriptyline, that lack well-documented evidence for MOH. However, for some drugs like amitriptyline, it is affordable due to the high prevalence of depression in MOH patients.[54] Additionally, the cost of new and well-documented drugs is high, leading many social security organizations in developed countries to establish prescribing rules that place new drugs as a last resort. Thus, older drugs with poor or absent documentation become an inevitable part of the therapeutic algorithm.

-Withdrawal of Overused Treatment and Predicting Relapse

There is a longstanding belief among headache experts that withdrawing the overused medication can relieve headache pain and improve responsiveness to prophylactic treatment. However, this is not well-documented with high-quality evidence in the literature.[75] For patients, the most affordable approach during the withdrawal stage is the limited use of acute headache medications, with the addition of treatments like antiemetics, antidepressants, or steroids. This approach was applied in the COMOESTAS protocol,[76] achieving a 46% cessation of overuse, conversion to simple use, and reversal of chronic headache to an episodic one. Contrastingly, some researchers, particularly in Northern Europe, advocate for abrupt and complete withdrawal, citing better results.[77] In a small RCT involving 72 MOH patients, 59 completed detoxification. One group was not allowed any acute headache medications, while the other could use them up to two days per week. After detoxification, preventives were initiated if indicated. At six months, the first group saw a 46% reduction in mean migraine days per month, versus 22% in the second group. Additionally, the chronic headache reverted to an episodic one in 70% of the first group versus 42% in the second. However, the number of days of acute medication intake did not show a significant difference between the groups. A slow tapering procedure is recommended for MOH patients overusing drugs such as barbiturates, opioids, or tranquilizers, and inpatient treatment is advised in these cases.[54] Two RCTs investigating the role of steroids as an adjunct treatment during withdrawal found no difference from placebo.[78-79]

Relapse rates vary significantly after detoxification. At six months, relapse rates range from 0% to 41%,[54,58] and at 12 months, they range from 13% to 41%.[54] The longest observational study[80] followed 56 patients for nine years, reporting that 32% met the criteria for MOH at the ninth year. Most of these relapses were in patients who responded poorly to the initial detoxification and had persistent chronic headaches after nine years. The majority of relapses occur within the first year after detoxification.[81] Predictors of relapse include the type of headache and the class of overused drug. The greatest risk of relapse was for patients with a combination of migraine and tension-type headache (TTH), followed by TTH alone, with migraine presenting the lowest risk. Common analgesics posed the greatest relapse risk, while triptans posed the lowest.[81] Other predictors include an increased number of previous preventative treatments, a higher number of headache days per month either before or after withdrawal,[82] a higher score on depression inventories like Beck's, a previous withdrawal attempt within the last three years, and a referral to an emergency department.[83] Combining pharmacotherapy with a short-term psychodynamic psychotherapy program can decrease the relapse rate at six and twelve months,[84] although mindfulness training does not have the same effect.[85]

Conflict of Interest

The author declares no conflict of interest.

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