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PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF HEADACHE AND PAIN (D BUSE, SECTION EDITOR)

Medication Overuse and Medication Overuse Headache: Risk Factors, Comorbidities, Associated Burdens and Nonpharmacologic and Pharmacologic Treatment Approaches

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Abstract

Purpose of Review With a worldwide high disease burden, medication overuse headache (MOH) is an endemic and disabling neurological disorder. Because of the limitations of previous study designs, there are still debates and questions regarding the disease's nature and treatment strategy. This review will discuss the following concepts; (1) recent progress in association between medication overuse (MO) and MOH; (2) the burden, risk factors and comorbidities of MOH; (3) evidence of treatment in patients with MOH.

Recent Findings The causal relationship between MO and MOH has not been identified. Currently, the treatment policy is still mainly based on small clinical observations, some with highly specified patients. In addition to withdrawal and preventive treatment, some studies have provided evidence for nonpharmacological treatments.

Summary Well-designed studies for specific treatment strategies with enough statistical power are warranted to make more relevant, better clinical decisions.

Keywords Chronic daily headache · Medication overuse headache · Chronic migraine · Risk factors · Comorbidities · Treatment

Introduction

Patients with primary headache disorders frequently take abortive medications during their headache attacks. From the first report of ergotamine overuse [1] almost 70 years ago, clinicians have reported that the increasing usage of abortive medications seems to only worsen headache frequency. A medication overuse headache (MOH) has been widely accepted and is classified as one important secondary headache disorder in the International Classification of Headache Disorders, 3rd edition (ICHD-3) [2]. However, the association between medication overuse (MO) and MOH is still debated, that is, whether MO is the cause or consequence of chronic daily headaches. In the current review, we will discuss the risk factors, comorbidities, associated burdens and treatments of MOH, as well as the issue between MO and MOH.

MO and MOH

The prevalence of MOH ranges from 0.5–2.6% worldwide, with an average of 1.0% [3–10]. In ICHD-3, MOH is defined

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as patients with preexisting primary headaches, mostly migraine and tension-type headaches, who have 15 or more headache attack days/month and who have headaches that have developed as a consequence of the regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medications) for more than 3 months [2]. It is important to note here that many patients with primary headaches do not have MOH, even with the frequent use of analgesics. Prior studies showed that patients who take regular painkillers for other pain conditions, such as rheumatic arthritis and osteoarthritis, rarely develop MOH [11, 12]. In contrast, MOH can occur in patients with episodic migraines and who take regular analgesics for nonheadache pain [13, 14]. Based on these findings, MOH is believed to only develop in primary headache patients who display frequent symptomatic medication use.

Scher et al. recently challenged these findings because all the causal evidence linking MO and MOH is from clinical observation studies, some which have small sample sizes [15••]. Scher et al. mentioned two important points. First, there has been no well-designed trial with randomly assigned primary episodic headache patients who either overused or not symptomatic medications for acute headaches for a comparison of the incidence of MOH. Second, in a large sample size longitudinal study, the American Migraine Prevalence and Prevention (AMPP) study, the frequency of symptomatic MO was not associated with chronic migraine incidence after controlling for headache frequency [16]. In patients with chronic migraines, the frequency of symptomatic MO also did not predict chronic migraine remission [16, 17]. The authors suggested that patients who frequently use symptomatic medications could be suffering from the consequences of poor headache control. However, there was no increase in the overall risk of MOH in the groups using triptans and anti-inflammatory agents compared with the groups using acetaminophen or no painkiller in the AMPP study [16]. In contrast to the AMPP study, in a longitudinal, population-based study done in Taiwan, we found that analgesic overuse could predict persistent chronic daily headache after 2 years [10].

On the other hand, there is also some important evidence supporting the causal relationship between MO and MOH. The overuse of opioids and barbiturates is associated with migraine progression in both longitudinal population-based and clinic-based studies [16, 18, 19]. Triptans and nonsteroidal anti-inflammatory agents increased the risk of MOH in patients who experienced headaches for 10 days a month at baseline in the AMPP study [16, 18]. In the Nord-Trøndelag Health (HUNT) studies, which are a longitudinal population-based study, 26,197 participants without chronic daily headaches completed an 11-year follow-up. Of these participants, 201 (0.8%) developed MOH and 246 (1.0%) chronic daily headaches (CDH) without MO. The authors demonstrated that several risk factors for MOH did not increase the risk for CDH without MOH, suggesting these are pathogenetically distinct [20]. Prior studies showed that episodic and chronic migraine patients had a low serum level of nociceptin but a high serum level of calcitonin gene-related peptide (CGRP) [21, 22]. However, Munksgaard et al. found normal serum levels of nociceptin and CGRP in MOH patients [23]. This evidence indicates that MOH is different from the other primary headaches and that MO seems to not only be the consequence of poor headache control. Indeed, as seen by these studies, the causal relationships between MO and MOH are complex. Both the causal hypothesis (excessive symptomatic medication use causes MOH) and the reverse causation hypothesis (MO is the consequence of frequent headaches) may play certain roles in different individuals.

Risk Factors of MOH

The HUNT studies provided the most evidence for the risk factors for developing MOH; in this 11-year longitudinal study, the following risk factors were found: headache frequency of 7–14 days per month at baseline, age younger than 50, migraine history, low education level, chronic musculoskeletal complaints (MSCs), gastrointestinal complaint, high Hospital Anxiety and Depression Scale (HADS), insomnia, daily smoking, inactive physical activity (< 3 h hard physical activity per week) and regular use of tranquillisers [20]. In this study, migraine was the strongest risk factor for MOH. The combination of chronic MSCs, gastrointestinal complaints and a high HADS score (HADS A and/or HADS D) had a five times higher risk of developing MOH. A very strong association (OR 19.4) was found in headache patients with a frequency of 7–14 days per month at baseline [20]. The risk of a low education level and socioeconomic status [24–27] and higher depression scores [27] were also reported in other clinical studies. Family history of MOH or other forms of substance abuse were associated with a higher risk of MOH as well [28]. Several genetic risk factors were reported for MOH. The homozygote D/D ACE polymorphism correlated positively with the duration of MOH [29]. Also, the Val66Met BDNF polymorphism predicted the consumption of analgesic use [30].

Risk Factors of MOH Relapse

Several risk factors were found to be associated with the relapse of MOH after detoxification treatment: higher depression scores [31•] and a longer duration of chronic headache [32] and higher number of headache days per month [32] predicted relapse into overuse within 1 year. Migraine

predicted a lower relapse rate than did patients with a tension-type headache at the primary headache diagnosis [31•]. As for genetic risk factors, MOH patients with rs4680G allele carriers or the catechol-O-methyltransferase rs6269G-rs4680G haplotype were associated with a lower risk of relapse after detoxification therapy. In addition, the carrier SLC6A4 variant—encoded the serotonin transporter polymorphism—was found to have a poor outcome, including unsuccessful withdrawal therapy and relapse within 12 months of follow-up after successful detoxification [33].

Comorbidities

Comorbidity means that two medical diseases develop in the same patients at higher rates than if these diseases were to occur by chance. In MOH patients with a secondary headache, it seems difficult to clarify the boundary between comorbidity and the risk factors. It is not surprising that most research has reported psychiatric disorders as comorbidities of MOH. In a study from six EU countries and based on results using the HADS, MOH was found to be associated with depression and anxiety. Anxiety was found to have a 10.4-fold increase in males and 7.1-fold in women compared with the no headache control patients [34]. In the COMOESTAS project, 40% of MOH patients had depression and 57.7% anxiety [35]. A similar result was also reported in the Brief Intervention for Medication Overuse Headache (BIMOH) study, showing that MOH patients had a significantly higher anxiety scale based on the HADS [36]. In the SAMOHA study, the Beck Depression Inventory, Beck Anxiety Inventory and a direct psychiatrist interview by Modified Mini International Neuropsychiatric Interview (M-MINI) were used for psychopathological assessment; the authors compared the psychiatric disturbances between MOH, episodic migraine and heathy control groups. The frequency of moderate to severe anxiety was significantly higher in MOH patients than in episodic migraine patients, as well as in heathy controls. However, the frequency of depression in MOH was higher than that in healthy control patients but not in episodic migraine patients [37]. In the same study, the Leeds Dependence Questionnaire (LDQ) score and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score were administered. Clinically relevant obsessive-compulsive disturbances for drug abuse assessed by the Y-BOCS appeared to have a higher representation in the MOH group, while the prevalence of this trait in the EM group was comparable to that of healthy controls [37]. Similar results were also reported in one Italian clinic-based study [38]. However, it is still controversial whether obesity is associated with MOH. One Danish cross-sectional population-based survey showed obesity was significantly associated with MOH [39], but this was not the case in the Nord-Trøndelag health studies [20]. Physical inactivity was also controversial regarding its association with MOH; it was reported to be related to MOH in one study but not another one [39, 40]. Of note, daily smoking and stress were also reported as being comorbid with MOH [41].

Burden

The quality of life of patients with MOH is much worse than that of patients with episodic headaches [5, 18, 41, 42]. Because of the loss of productivity, absenteeism and direct medical costs, MOH can be very costly. In the Eurolight study, the annual cost of MOH is €3561 per patient, almost three times higher than that of episodic migraine and 10 times that of tension-type headache [43]. In this study, the indirect cost accounts for about 90% of the total costs [43]. Indeed, the overall cost is €5–10 billion in Italy, Spain and France. In a recent Italian study, the detailed total cost of MOH patients without adequate treatment was €2835 on a 3-month basis, which was higher in males than females (€3885 vs. €2631); here, the indirect cost accounted for about 80% of the total cost. This result, though, is much higher than the costs found by the Eurolight study. The authors suspected the discrepancies resulted from the methodology of cost calculation because the variables of medication price, such as NSAIDs, triptans and opioids, and loss of productivity were both calculated in detail in this Italian study. They suggest that the cost addressed in previous studies was likely underestimated because the average medication price was only roughly calculated and only a loss of work of more than half a day was included [43].

Management

MOH is a heterogeneous and complex disorder. It can result from different categories of abortive medications, and in fact, the casual relationship is still controversial. Currently, there is no universal consensus on how to treat patients with MOH, and a specific treatment based on sufficiently powered randomised trials is still lacking. Most of the evidence comes from observational studies [44]. Nevertheless, the number of patients in these studies is usually small, and only some types of primary headache disorders are studied, mostly chronic migraine; moreover, certain types of overused medications are excluded. These limitations make it difficult to conclude what treatment strategies of the different treatment protocols are best.

Education

Many patients do not know that the overuse of symptomatic medications may end up with increasing headache frequencies and MOH [45]. It is intriguing that some patients may improve only after understanding the risk of the excessive use of symptomatic medications. The BIMOH study investigated the outcomes of MOH patients who received a brief intervention involving [1] feedback about individual risk of MOH and [2] how to reduce overuse. At 3 months after education, mean headache frequency was reduced to 7.3 days/month, and chronic headache condition was resolved in 50% of the patients [46]. A recent randomised controlled trial (RCT) asked MOH patients to receive the short and simple advice of outpatient detoxifications before randomisation to either a valproate or placebo group. In the observation period before randomisation, 38.6% patients intended for the RCT could not be included because they had already 'self-detoxified' [47•].

Withdrawal Treatment

Many clinical observation studies have reported an improvement in MOH after medication withdrawal [48–53]. However, Scher et al. challenged these results because of the lack of controls and a high dropout rate; they recalculated that the overall response rate of withdrawal treatment is only about 33%, leaving the question whether the response rate is greater than the percentage of patients who might have improved on their own. In addition, one study demonstrated that the effect of detoxification is not equal for every MOH patient. Patients with a complicated version of MOH, such as those with psychiatric problems or with a history of withdrawal failure, reported a much poorer discontinued rate in detoxification compared with simple MOH patients [50]. Recently, in a prospective, randomised, outpatient study on detoxification, MOH patients were separated into either a complete discontinuation of acute medication group or restriction group, that is, acute medications taken less than 2 days per week. The complete discontinuation method was shown to be a more effective detoxification programme than restricted drug use. However, in this study, preventive medications were allowed if necessary [54]. Importantly here, withdrawal symptoms do not occur in every MOH patient; the symptoms depend on both the duration and different acute medications and tend to occur much more frequently in patients on opioids and barbiturates but less so in those on triptans and anti-inflammatory agents. Withdrawal symptoms usually last for 1–2 weeks. The most common symptom is an initial worsening of the headache, accompanied by nausea, vomiting, hypotension, tachycardia, sleep disturbance, restlessness, anxiety and nervousness [55]. Antiemetic neuroleptics and steroids have usually been used to reduce the symptoms of the withdrawal phase. However, steroids seemed to not be effective when treating symptoms [56].

Prophylaxis

It is not certain whether the combination of withdrawal and preventive medication is a better strategy for treating MOH. Trials on preventive medications are usually based on personal experience [44]. Despite it still being unclear when to start a preventive treatment in MOH patients, in most studies, the preventive treatment usually follows detoxification immediately. In the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study, onabotulinumtoxinA was designed for its preventive effect in chronic migraine (CM) with or without MOH. There was no early discontinuation protocol in the PREEMPT study. In the post hoc analysis for CM with the MO subgroup at week 24, the data showed a significant between-treatment group mean change from baseline, favouring onabotulinumtoxinA vs. placebo for headache days (primary endpoint: −8.2 vs. −6.2 days; $p < 0.001$) [57, 58]. Of note, the effect size did not differ (days vs. days in MO vs. no MO) between those with and without MO. Sandrini et al. demonstrated that early discontinuation combined with onabotulinumtoxinA treatment was superior to early discontinuation treatment alone [59]. Two randomised, double-blind, placebo-controlled parallel-group, multicentre trials for topiramate preventive effect in CM with or without MOH were conducted in Europe and the USA [60–62]. In the European trial, the post hoc analysis for the MO subgroup demonstrated that topiramate without early discontinuation significantly reduced the mean number of monthly migraine days compared with the placebo group. However, the reduction of the mean number of days per month of acute medication intake from baseline did not reach statistical significance compared with the placebo [60]. Therefore, preventive medications are effective in patients with MOH without withdrawal treatments.

Nonpharmacologic Treatments

In addition to medication treatment, nonpharmacologic treatments have value either in addition to or instead of pharmacologic treatment. Behavioural treatments combined with pharmacologic therapies (combined therapy)

have been demonstrated to significantly improve outcomes. A behavioural treatment was found to be a potentially effective choice for MOH patients. In a longitudinal study, Grazzi et al. demonstrated that pharmacologic therapy combined with biofeedback-assisted relaxation reduced the relapse rate of medication overuse in 3 years in comparison with patients receiving pharmacologic treatment alone [63•, 64•]. The BIMOH study provided evidence on benefit of a brief intervention (BI) for patients with MOH in primary care. In the BI group, trained general practitioners explained the information and personal risk of MOH, informed the patients of the possible gain from detoxification, suggested a medication diary record and helped set personal aims and plans to limit the use of symptomatic medications. Compared with the control group, the headache frequency of the BI group was significantly improved [36, 65•]. In the 16-month follow-up, the BI effect was persistent, showing a low relapse rate of MOH [65•]. Without preventive treatment, the BIMOH study demonstrated the efficacy of a behavioural intervention. In CM patients with MOH, the mindfulness-based treatment without prophylactic medications after withdrawal programme was demonstrated to have similar effects to patients who were administered medical prophylaxis [66]. In addition, the mindfulness-based treatment was associated with changes in the plasma levels of catecholamine and elusive amines similar to those observed in patients undergoing pharmacological prophylaxis [67].

Noninvasive stimulation of the vagal nerve (nVNS) was reported to treat a total of 348 migraine attacks in 15 patients with CM and MOH. The pain-free response at 2 h was 34.2%, while the headache response, defined as a reduction in the visual analogue scale at 2 h, was 50.8%. Rescue medications were only used in 17.6% of the headache episodes. There was no relapse of MO at 6 months in all patients [68]. On the other hand, the effect of occipital nerve stimulation was not consistent in two different studies [69, 70].

Conclusions

MOH is a severe, disabling disease with a high economic burden. The causal relationship or consequence between MO and MOH is still unknown, possibly because of the heterogeneous mechanisms of MOH. Currently, high-quality studies for various treatment protocols are still lacking, and some specific medications shown to have some efficacy have been found in post hoc analyses. Clinically, the risk factors of MOH should be monitored in order to prevent its development. In addition, it might be reasonable to add behavioural therapy to pharmacological withdrawal not only for better long-term withdrawal effects but also lower relapse rates. In the future, well-designed studies focusing on MOH with enough statistical power are warranted to help physicians make decisions when treating MOH patients.

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Compliance with Ethical Standards

Conflict of Interest Ping-Kun Chen declares no conflict of interest. Dr. Wang reports personal fees from Eli-Lilly, personal fees from Daiichi-Sankyo, personal fees from Pfizer, Taiwan, personal fees from Bayer and personal fees from Eisai, all outside of the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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