



The Interplay of Chronic Migraine and Medication Overuse Headache

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Abstract

Objective: The interplay of chronic migraine and medication overuse headache (MOH) can significantly impact a person's quality of life. The primary objective of this study was to examine the relationship between chronic migraine as a previous headache disorder and the subsequent development of MOH in the group of 800 new diagnosed patients.

Methods: The study cohort revealed that MOH was predominantly caused by the transformation of chronic migraine, with a staggering 74% of cases showing this association.

Results: The study showed a positive correlation between the duration of chronic migraine and the impact of MOH ($p \leq 0.05$). The underscores the profound effect that MOH can have on an individual's quality of life. Migraine is showed as a risk factor for development of MOH. Migraine was singled out as a risk factor for the overall aspect of health in MOH sufferers ($p = 0.05$), the study found that the duration of the earlier migraine was positively correlated with the impact of MOH ($r = 0.327$, $p = 0.003$). The impact of MOH on daily life was assessed as significant, correlating with the duration of the migraine ($p \leq 0.05$).

Interpretation: In summary, by addressing both the primary and secondary headache disorders, clinicians can help patients with chronic migraine achieve a better quality of life and long-term control of their debilitating condition.

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Background

Chronic Migraine

Chronic migraine is a common condition, affecting approximately 1 in 50 people. The diagnosis of chronic migraine implies that a patient has a history of migraine headaches and is now experiencing headaches at least 15 days per month^{1,2}. Effective management of chronic migraine involves a multifaceted approach, including the prescription of a daily preventive medication to reduce headache frequency, aggressive acute treatment of headaches that occur despite the preventive medication, and the identification and treatment of any underlying conditions that may be contributing to chronic headaches. The medical conditions that most commonly exacerbate chronic migraines are sleep disorders, mood disorders (typically depression, anxiety, or both), hormonal influences (pregnancy, recent childbirth, use of oral contraceptives), and overuse of pain medications¹. An analgesic is any medication used to relieve pain, whether it be a simple over-the-counter (OTC) medication like acetaminophen or a strong opioid ("narcotic"). Patients with chronic headaches often take analgesics frequently to relieve their pain and enable them to carry out their daily activities [1-4]. Unfortunately, virtually all medications—whether prescription or OTC—taken by migraine sufferers to treat acute headaches can exacerbate headaches if taken too frequently over a period of weeks or months. Some of the most commonly used are acetaminophen, compounds containing acetaminophen plus caffeine, butalbital-containing compounds, and hydrocodone. Even the triptans, which are commonly used to treat acute migraine, can also cause medication overuse headache (MOH) [5, 6].

Medication-overuse headaches (MOH), also known as analgesic rebound headaches, drug-induced headaches, or medication-misuse headaches, are a common neurologic disorder that can cause immense disability and suffering, and can transform episodic headache disorders into chronic headache disorders [1, 2].

The interplay of chronic migraine and medication overuse headache can significantly impact a person's quality of life [5]. The constant presence of headaches and the need for frequent medication use can lead to physical and emotional distress, decreased productivity, and limitations in daily activities [4]. Both chronic

migraine and medication overuse headaches are believed to stem from the same underlying pathophysiology of altered pain processing in the brain. In both conditions, there is a dysregulation of pain signals, leading to an increased sensitivity to pain and a decreased ability to modulate pain. This shared mechanism is what makes medication overuse headache a common consequence of treating chronic migraines with frequent analgesic use. It is essential for healthcare providers to address both the chronic migraine and medication overuse headache to improve the overall well-being of the patient [5-7].

Aim of the Study

The primary objective of this study was to examine the relationship between chronic migraine as a previous headache disorder and the subsequent development of MOH. By elucidating the connection between these two conditions, the researchers sought to gain valuable insights that could inform more effective prevention and management strategies for patients at risk of experiencing this debilitating secondary headaches.

Methodology and Findings

Patients and Methods

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Niš and was conducted as an observational, one-year cross-sectional study.

Study Population

Our database of head screen patients included more than 800 patients. For this research, we included only those with voluntary written informed consent to participate. The patients completed sociodemographic and medical questionnaires, which included demographic information; educational level; marital status; family and work status; number of family members; residence; personal history; presence of other illnesses; presence of previous (primary and/or secondary) headaches (type, characteristics, duration, frequency, type and effectiveness of symptomatic and preventive therapy); and habits and risk factors (physical activity, cigarette smoking, use of alcohol, caffeine, etc.). The study was conducted in the Headache Center of the Neurology Clinic at the Clinical Center in Niš during 2021-2022 (January-December). The Clinical Center in Niš is a tertiary healthcare institution to which approximately 2,5 million inhabitants from the area of southeastern Serbia gravitate.

MOH Group

This group included all patients in whom MOH was first diagnosed during the period of this study after their voluntary consent to participate in the study. The diagnosis of MOH was made according to the diagnostic criteria of the Headache Classification Committee of the International Headache Society (2018)^x. The secondary etiology of the headache was ruled out after complete diagnostic processing (computed tomography/magnetic resonance imaging of the endocranium, etc.). For all patients, the diagnosis of MOH was made by the same doctor, a specialist in neurology and pain medicine, who manages the Headache Center at the Clinical Center Nis. At this clinic, patients were referred for examination by primary care physicians or specialists in neurology, internal medicine, or related specializations. This group was consisting of 183 patients. Data are presented in Table 1.

The following data related to MOH and previous chronic headache were collected from these patients: duration of headache; frequency (number of days with headache in one month); location of pain (frontal, temporal, parietal, and occipital); lateralization (unilateral and diffuse); character of pain (muffled and pulsating pain); intensity of pain (using a numerical scale for pain assessment); presence of related symptoms and signs (nausea/vomiting, photophobia, phonophobia, diplopia, neck and shoulder stiffness, blurred vision, tinnitus, and hypoxia); type of analgesic therapy used; use of preventive therapy; frequency of use of this therapy (number of days in one month); and therapeutic efficacy (assessment of pain intensity reduction/associated symptoms). Detailed data regarding headache characteristics are presented in our previous paper [7]. Data are presented in Table 2. Data about total health related quality of life (as average of sum of physical and mental score) are presented in Tables 3-5.

Control Group

The control group (CG) was selected from among the companions (relatives, friends) of all patients who were examined at the Headache Center during the period of this study after their voluntary consent to participate. These individuals were included consecutively (in order) up to the predicted number (according to the number of patients in the MOH group). The preconditions for their inclusion were

that they did not have a headache in their personal life history (at least in the last two years), that they did not have serious somatic or mental illnesses and that they did not use any chronic therapy.

Instruments

The quality of life was assessed using the Short Form (SF)-36 questionnaire. The SF-36 questionnaire has previously been approved for use in the Serbian language and has shown good internal consistency (ranging from .80 to .90) (<https://eprovide.mapi-trust.org/about/about-proqolid>). The SF-36 consists of 36 questions that evaluate eight dimensions of health: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. In each domain, higher scores (range 0–100) reflect better self-perceived health per unit. The physical composite score (PCS) represents the mean value of the scores in the first four domains, and the mental composite score (MCS) represents the mean value of the scores in the last four domains. The total score (TS) was calculated as the mean physical composite score (PCS) and the mean mental composite score (MCS)⁸. The test was applied at the time of MOH diagnosis (MOH group) or consent to participate in the study (control group).

Statistical Analysis

No power calculations were conducted to determine the sample size for this particular study. The data are presented as the mean±standard deviation or as counts and percentages. Unpaired Student's t test or the Mann–Whitney test was used to compare continuous data, as appropriate. Analysis of variance (ANOVA) or the Kruskal–Walli's test was performed for continuous data among three or more groups, as appropriate. The chi-square test or Fisher's test was used for analysis of categorical data. An exploratory logistic regression analysis (entry method) was also conducted to further assess the significant associations between demographic, clinical and headache-related characteristics and quality of life. From these analyses, those variables with $p < 0.10$ were retained for the subsequent multivariable model (backward Wald method). Logistic and linear regressions were performed, and the Hosmer–Lemeshow test was performed to estimate the calibration ability of the models. A complete case analysis was performed. A p value was set at $p < 0.05$. All the statistical analyses were performed using R software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The basic data are presented in Table 1. The study cohort consisted of 183 patients (111 men and 72 women) who were first diagnosed with MOH. The diagnoses of MOH and migraine are based on ICHD criteria^x. The mean age of the study participants was 41.5 ± 10.6 years. The data revealed that the average duration of MOH until diagnosis was 5.1 ± 5.5 years, indicating that this secondary headache disorder often goes unrecognized and untreated for an extended period.

The study cohort revealed that MOH was predominantly caused by the transformation of chronic migraine, with a staggering 74% of cases showing this association. This emphasizes the strong relationship between these two conditions, where the excessive use of acute headache medications to manage chronic migraine can result in the development of MOH.

The data from the study indicated that MOH often goes miss diagnosed and untreated for an average duration of 5.1 ± 5.5 years. The impact of MOH on patients' daily lives was found to be significant, as reflected by a high Headache Impact Test (HIT) score of 65.4 ± 5.5 . This underscores the profound effect that MOH can have on an individual's quality of life, emphasizing the importance of early recognition and proper management. By including all variables with a significance level of $p < 0.1$ in the univariate model in the analysis of the multivariate model, migraine was singled out as a risk factor for the overall aspect of health in MOH sufferers ($B = -0.69$, 95%CI -1.16 - -0.22, $p = 0.005$) Table 3. This suggests that the longer an individual has been suffering from chronic migraine, the more severe the consequences of medication overuse can be. Therefore, clinicians must be vigilant in educating patients with chronic migraine about the risks of medication overuse and the importance of adherence to preventive therapy, in order to prevent the development of this secondary, and potentially more disabling, headache disorder. The data revealed that the average duration of MOH until diagnosis was 5.1 ± 5.5 years, indicating that this secondary headache disorder often goes unrecognized and untreated for an extended period. Interestingly, the impact of MOH on the patients' daily lives was assessed as significant, with a high Headache Impact Test (HIT) score of 65.4 ± 5.5 . The study showed a positive correlation between the duration of chronic

migraine and the impact of MOH, suggesting that the longer a person experiences chronic migraine, the more severe the consequences of medication overuse can be. This highlights the crucial role of healthcare providers in educating patients about the risks of medication overuse and the significance of adhering to preventive therapy to prevent the development of this secondary headache disorder.

Interestingly, the impact of MOH on the patients' daily lives was assessed as significant, with a high Headache Impact Test (HIT) score of 65.4 ± 5.5 . This underscores the profound and debilitating effect that MOH can have on an individual's quality of life, and highlights the need for early recognition and appropriate management of this condition. Table 1.

As we found here MOH was most commonly generated by the transformation of chronic migraine, affecting 74% of the patients. The study found that common (51%) and combination analgesics (48.2%) were the medications most frequently overused, with patients consuming them 15 to 25 days per month. Importantly, the impact of MOH on the patients' daily life was assessed as significant, with a HIT score of 65.4 ± 5.5 . Furthermore, the duration of the earlier chronic headache correlated with the impact of MOH, as indicated by the moderate positive correlation ($r = 0.327$, $p = 0.003$). Table 2-7.

The results presented here indicate that impairments of the PCS, MCS, and TS are present in patients suffering from MOH. All examined aspects of health were impaired in patients with MOH, compared with healthy subjects, regardless of age, regardless of place of residence, in patients with higher education, in patients who are married and unmarried, regardless of work status, regardless of smoking status, regardless of the habit of drinking caffeinated beverages and regardless of physical activity. It has been shown that impairment of the TCS is more pronounced in MOH with migraine. and in patients with MOH who do not consume alcohol compared to healthy women and healthy subjects who do not consume alcohol.

By including all variables with a significance level of $p < 0.1$ in the univariate model in the analysis of the multivariate model, migraine was singled out as a risk factor for the overall aspect of health in MOH sufferers ($B = -0.69$, 95%CI -1.16 - -0.22, $p = 0.005$) Table 3.

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This suggests that the longer an individual has been suffering from chronic migraine, the more severe the consequences of medication overuse can be. Common (41%) and combination analgesics (48.2%) were the most frequently used medications, taken 15 to 25 days per month, contributing to the overuse that leads to MOH. Importantly, the impact of MOH on daily life was assessed as significant, correlating with the duration of the earlier chronic headache, Table 1. As we notice here in MOH patients with migraine ...

In summary, the close relationship between chronic migraine and medication overuse headache underscores the importance of vigilant patient education, early recognition, and a comprehensive management approach that includes preventative medication, acute treatment, and the avoidance of analgesic overuse. By addressing both the primary and secondary headache disorders, clinicians can help patients with chronic migraine achieve a better quality of life and long-term control of their debilitating condition.

By definition, medication-overuse headache occurs in people with primary headache who overuse acute medication. Most have a background of migraine or less commonly of tension-type headache. Rarely, it develops in people with cluster headache, although

typically there is also a background of migraine or a family history of migraine [8, 9]. Although any analgesic can cause medication-overuse headache, triptans and opioids appear to carry the most risk, and do so in a shorter period [5-10].

In clinical practice, medication-overuse headache most often develops in people with migraine (or less commonly tension-type headache) who report increased frequency or worsening of pre-existing headache or the development of new headache associated with medication overuse. Medication-overuse headache may be indistinguishable from the pre-existing headache. This can sometimes be difficult to untangle because the transition from episodic to chronic migraine or tension-type headache often induces more regular use of analgesics. A diagnosis of medication-overuse headache is therefore often retrospective, following drug withdrawal [11-15].

The results of our research confirm the results of earlier studies that MOH occurs mainly in middle age and more often in women [16, 17]. Interestingly, the largest percentage of patients in our study did not smoke or consume alcohol, while the majority of them were physically inactive and regularly consumed caffeinated beverages. In the literature reviewed, no significant studies were found, the results of which could be useful for comparison with the results obtained here. A study examining various risk factors for MOH revealed a correlation between physical inactivity and smoking and MOH onset [17]. Our results are partially consistent with those findings. Studies examining the characteristics of patients who have never had a headache in their lives have shown that they were men of younger ages who regularly consumed alcoholic beverages (unpublished results). Our findings on the inverse relationship between alcohol consumption and the occurrence of MOH are consistent with these findings. Although most patients with MOH do not have comorbidities, the incidence of cardiovascular, bone and joint diseases was significantly greater than that of other comorbid conditions. The reasons for these findings should be diagnoses in these patients) are the most common causes of secondary chronic headaches [18]. This headache, due to its chronic course, poses a risk of developing MOH. Previous studies have shown an association between disease involving the osseous joint system and MOH [18].

Although MOH can arise from all primary headaches, MOH is most often caused by the transformation of chronic migraine [19, 20]. The results of our study showed that the highest percentage of patients with MOH previously had chronic migraines. Our research has shown that MOH is most often caused by the excessive use of combined and ordinary analgesics (NSAIDs). The risk of MOH has previously been shown to be lower with triptans and ergotamine use than with NSAIDs [21]. Although they used prophylactic therapy, for the most part, patients with MOH did not achieve satisfactory therapeutic efficacy.

The high values obtained here on the scale of assessment of the impact of headaches on daily life activities are in agreement with the results of previous studies [22]. Research devoted to examining the pathophysiological mechanisms of MOH has shown morphometric and functional changes in regions crucial for the modulation of nociception (periaqueductal gray matter, posterior cingulate cortex, hippocampus, thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula, and precuneus) [23, 24]. These structures are involved in nociception modulation, cognition, and affective and addictive behavior. The mechanisms of central sensitization (hyperexcitability of pain modulation pathways) are considered crucial in the pathophysiology of MOH [25]. Bilateral, moderately severe pain accompanied by tightness in the neck and shoulders and the absence of so-called migraine features of MOH in our study (even though it is largely due to the transformation of previous chronic migraine) support the previously assumed mechanisms of central sensitization considered because arterial hypertension and spondylosis of the cervical spine the most common.

The impairment of the MCS is more pronounced in people suffering from MOH and are independent of gender and alcohol-related habits. In this study, the TS was impaired in patients with MOH compared to healthy subjects regardless of gender and in patients who did not consume alcohol, compared to healthy subjects of the same status. Previous research has shown a deterioration in the quality of life in patients with MOH compared to healthy subjects. It has also been shown that depression and anxiety are of particular importance in this impairment of quality of life as frequent comorbidities of MOH [26,27]. In the observational research, it was noticed that with

the discontinuation of overused medications in hospital settings, there is a significant improvement in the quality of life of patients with MOH and a reduction in the level of their psychological distress. It has also been shown that patients with greater MCS disorders and a higher degree of depression and anxiety have a less favorable outcome in reducing the number of days with monthly headaches and improving quality of life after discontinuation of excessive medication [27, 28]. There is a study that examined the quality of life in patients with MOH after discontinuation of excessive medication in relation to different modalities of secondary prevention and rehabilitation in hospital settings [29, 30].

The potential for developing MOH appears to vary based on the individual patient's unique biology and the specific medication in question. Some studies have suggested that triptans have the highest potential for causing MOH, while non-steroidal anti-inflammatory drugs (NSAIDs) have the lowest risk. Importantly, over-the-counter analgesics can be particularly "insidious" in this regard, as their ready availability and perceived safety can tempt patients to steadily increase their intake, ultimately leading to the entrapment of MOH [25-31].

The pathogenesis of medication-overuse headache is poorly understood but appears closely related to that of chronic migraine. Many people increase their analgesic use over time without necessarily realizing there is a problem; they often remain unaware of the long-term consequences until advised that they have medication-overuse headache. Therefore, education is important in preventing its development. The diagnosis is sometimes difficult and headache diaries may play an important role. Although some people can successfully wean medications themselves, this often requires support; clinicians should advise patients that they will probably get worse before they get better. Detoxification without access to any acute medication treatments is probably the most effective strategy. People taking simple analgesics and/or triptans can often achieve this as an outpatient. It is more difficult for those overusing opioid medications and if their use is substantial they may require detoxification as an inpatient [34-38]. Topiramate and botulinum toxin may help in managing medication-overuse headache, but the final goal should always be to reduce the frequency of acute headache medication use. The limitations of the study stem from the study nature. We believe that methodological requirements

reduce its shortcomings. The advantages of this study are clinically implicable conclusions that can be useful in both, primary and secondary prevention of MOH, and improving the quality of life in selected patients. Assessment of the degree of depression in MOH patients and its treatment could be useful for improving the quality of life of MOH patients. Psychological strategies aimed at evaluating and treating the depression could be useful in primary and secondary prevention of MOH and its devastating effects on patients' quality of life. Additional researches are required.

Conclusion

MOH results from the transformation of a previous chronic headache due to overuse of analgesic therapy. It affects the middle-aged population, mostly women, and affects all aspects of the patient's life. Despite defined therapeutic strategies for treatment, prevention of MOH is considered inviolable (patient education, limiting the use of analgesic therapy, especially in the at-risk group of patients (middle-aged women with chronic migraine)). However, further investigations of other potentially modifiable risk factors for the development of MOH and its course and outcome after certain therapeutic interventions are necessary.

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- The impact of MOH on daily life was assessed as significant, correlating with the duration of the migraine ($p \leq 0.05$).

Conclusion

In summary, by addressing both the primary and secondary headache disorders, clinicians can help patients with chronic migraine achieve a better quality of life and long-term control of their debilitating condition.

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