Clinical features of medication overuse headache following overuse of different acute symptomatic medications: A preliminary study

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Research article

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Abstract

Background Medication overuse headache (MOH) is a growing problem worldwide and is defined as daily or near-daily headache in patients with a primary headache disorder who overuse acute medications. There is debate about whether there are differences in the clinical features and risks of MOH induced by different drugs. Here we investigated the clinical characteristics of patients with MOH following overuse of different acute headache drugs such as triptans and other medications.

Methods A multicenter cross-sectional observation study, REgistry for Load and Management of MEdicAtion OveruSE Headache (RELEASE), prospectively collected demographic and clinical data from 114 consecutive patients with MOH according to the International Headache Society criteria between May 2020 and January 2021. We calculated the mean duration until onset of MOH from chronic daily headache (MDMOH), mean monthly frequency of severe headache (MMFSH), mean monthly frequency of seeking medical services (MMFMedS), and mean monthly intake frequency (MMIF) as well as headache impact and neuropsychological tests in patients with MOH after overuse of acute headache drugs.

Results A total of 105 eligible MOH patients was included in this study. The patients showed overuse of triptans (31/105, 29.5%), ergotamines (8/105, 7.6%), simple or combination analgesics (37/105, 35.2%), opioids (1/105, 0.9%), and combination of two of more drugs (28/105, 26.7%). The MDMOH was significantly longer for the analgesics group (10.6 years) than the ergotamines (4.1 years), triptans (4.3 years), or multiple drugs group (4.8 years) (p = 0.011, Kruskal–Wallis test). The MMFMedS was lower for the analgesics group (0.37 days per month) than the multiple drugs (0.85 days) or triptans (0.58 days) group (p = 0.008, Kruskal–Wallis test). The MMFSH was significantly lower in the triptans group (7.4 days per month) than in the analgesics (14.4 days) or multiple drugs group (13.7 days) (p = 0.005, Kruskal–Wallis *test*). The MMIF was higher in the multiple drugs group (25 days per month) than the triptans (18.1 days) or analgesics (19.5 days) group (p = 0.007, Kruskal–Wallis test).

Conclusion Data from this prospective multicenter study suggest that the clinical characteristics of MOH depend on the type of overused symptomatic headache medications.

Background

Medication overuse headache (MOH) is a chronic secondary headache disorder caused by frequent or regular consumption of analgesics or acute symptomatic headache medications in patients with a primary headache disorder most commonly related to migraine or tension-type headache (TTH).[1] The prevalence of MOH in the general population worldwide is approximately 1%; however, the condition is much more frequent in individuals with chronic headache disorders, with a prevalence of 30–70%.[2-5] MOH has emerged as a serious public health problem worldwide and is associated with large amounts of disability and financial costs.[6, 7] In recent years, awareness of the impact of the personal, social, and economic burdens caused by MOH has increased.[8] According to the Global Disease Burden Study 2015, headaches were the most prevalent neurological disorder, and MOH was among the most prevalent disabling condition after tension-type headache and migraine.[9] Epidemiological data, however, showed that the loss of productive time from paid or household work due to headache was 1.5 to up to 16 times greater with MOH than in migraine or TTH.[10-14] In some reports, the majority of patients with MOH is classified as severely disabled, and their quality of life is much worse than that of patients with episodic headaches.[7, 15-17] In a recent assessment of the costs of headache disorders in Europe, the total national annual costs were calculated as approximately EUR 40 billion related to MOH, which was approximately three times greater than the costs for migraine and 10 times greater than costs for TTH.[18, 19]

Several large-scale, population-based, longitudinal studies of MOH have been conducted to analyze the risk factors that lead to development of MOH.[20-23] The HUNT study, which has been conducted longitudinally over 11 years, suggested multiple risk factors for inducing MOH, including frequency of headache from 7 to 14 days per month, age under 50 years, history of migraine, low education level, chronic musculoskeletal complaints, gastrointestinal problems, high anxiety and depression level, insomnia, smoking, physical inactivity, and regular use of tranquilizers.[20] The risks of low socioeconomic status and education level and high psychiatric comorbidities in MOH have been reported in other studies.[21, 22] A family history of MOH or other substance abuse is also associated with a high risk of MOH.[23] A prospective study with 98 MOH patients reported that patients overusing triptans at lower doses developed MOH faster compared with those using other drugs such as ergotamines or analgesics.[24] Another study reported that patients with MOH caused by the combination of triptans and analgesics experienced more frequent and severe headaches compared with patients who overused only triptans.[25] However, the relevance of clinical characteristics and the prognosis of patients with MOH according to class of overused medications remain uncertain and controversial, as few large-scale longitudinal studies have been performed. The REgistry for Load and Management of MEdicAtion OveruSE Headache (RELEASE) is a multi-center, observational registry study in six neurology clinics of the tertiary care hospitals in Republic of Korea. From May 2020 to Dec 2021, we plan to enroll 500 patients who meet the diagnostic criteria of MOH according to the third edition of the International Classification of Headache Disorders (ICHD-3).[1] The purposes of this registry were to analyze epidemiological profiles and the clinical characteristics and risks for MOH, as well as to determine real world MOH treatment status and the best therapeutic approach to MOH. In the current study, we preliminarily analyzed the data from RELEASE collected between May 2020 and January 2021. We characterized the clinical features of MOH according to class of acute headache medications, as triptans, ergotamines, simple and combination analgesics, and opioids.

Methods

Subjects

This study included patients from the RELEASE study. Inclusion criteria were as follows: (*i)* age 18 years old or older, (*ii)* patients who met criteria for MOH of ICHD-3[1], and (*iii)* patients agreed and were able to voluntarily give written informed consent. Patients with any serious ongoing medical, neurological, or psychiatric conditions who were unable to cooperate or had difficulty understanding the questionnaires were excluded.

Study design

This study used the data of the RELEASE study. The RELEASE study is a multi-center cross-sectional observational registry study with longitudinal follow-up in neurology clinics of the tertiary hospitals in Korea from May 2020. During the baseline assessment (Visit 1), demographic characteristics, medical history, and clinical features of primary headache and MOH were collected: *(i)* frequency, intensity, and duration of headache and *(ii)* type of overused medications and preventive drugs as well as frequency and duration of drug intake, effects, and tolerability. Classification of MOH was based on ICHD-3: triptans (code 8.2.2), ergotamine (code 8.2.1), non-opioid analgesics (code 8.2.3) or combination analgesics (code 8.2.5), opioids (code 8.2.4) and multiple drugs classes (code 8.2.6).[1] We investigated the time at first primary headache, the time when headache more than 15 days per month began to persist for more than 3 months, and the time when medication overuse began. We also determined the time of primary headache onset, chronic daily headache (CDH) onset, and MOH onset. We calculated each duration of primary headache, CDH, and MOH from onset. The mean duration from CDH until onset of MOH (MDMOH) was calculated by subtracting the duration of MOH from the CDH duration. The mean monthly frequency of severe headache (MMFSH) was determined as the number of headaches each month equivalent to 7 points or more on a numeral rating scale. The mean monthly frequency of seeking medical services (MMFMedS) was defined as the number of outpatient clinic visits each month, including both regular and unscheduled visits. The mean monthly intake frequency (MMIF) was defined the number of days per month when patients take acute symptomatic medications; one day was recorded even if medication was taken several times a day. This information was obtained from structured standardized questionnaires and patient diaries. All items in the standardized questionnaires were filled out during interviews conducted in detail by a skilled researcher at each visit, and headache diaries were provided to all patients at the time of study enrollment. Through the headache diary, we tried to obtain more accurate information on intake of acute symptomatic medications and frequency of headaches; in patients who did not regularly complete the headache diary, data were obtained through additional questionnaire items. If there was a discrepancy between the headache diary and the results of the questionnaire conducted at the hospital, the headache diary record was selected because we cannot rule out the effect of recall bias on the results. During the one-month follow-up, we evaluated headache-related (HIT-6 and MIDAS) and mood-related (PHQ-9 and GAD-7) parameters.

Self-reported questionnaires

We evaluated headache impact and conducted neuropsychological evaluations using self-reported questionnaires such as Headache Impact Test-6 (HIT-6), Migraine Disability Assessment (MIDAS), Patients Health Questionaire-9 (PHQ-9), and General Anxiety Disorder-7 (GAD-7). Reassessments were performed at 1-month, 3-month, and 2-year follow-ups by interviews using a standard questionnaire. In this result, we only analyzed day of enrollment (Visit 1) and one-month follow-up (Visit 2) data (Figure 1). We used the standardized questionnaires including the impact of headache on patient disability and psychiatric comorbidities at each follow-up visit.

Headache Impact Test-6 (HIT-6) The HIT-6 measures a wide range of functional impairments caused by headache.[26] The HIT-6 includes six questions relating to the previous four weeks, and each question is scored as never (6 points), rarely (8), sometimes (10), very often (11), or always (13). The total score can range from 36 to 78, and the severity of headache is categorized into four levels: ≥60, severe impact; 56–59, substantial impact; 50–55, some impact; and ≤49, little to no impact.[27]

Migraine Disability Assessment (MIDAS) The MIDAS includes 5 items and evaluates the impact of migraine on performance in activities at work, school, or home during the previous 3 months.[28] The MIDAS score was calculated by combining the number of days for each of five questions relating to the impact of all headaches, with headache-related disability of daily life graded as follows: grade 1, little or no disability (score 0–5); grade 2, mild disability (6–10); grade 3, moderate disability (11–20); and grade 4, severe disability (≥21).

Patient Health Questionnaire-9 (PHQ-9) The PHQ-9 evaluates the frequency of depressive symptoms over the past 2 weeks with nine questions; each question is rated as never (0 points), on several days (1), on more than half of days (2), or nearly every day (3).[29] The overall points range from 0 to 27, and the level of depression is determined as follows: 0–4,minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; or ≥20, severe. Seven points is the cutoff value for major depressive disorder.

Generalized Anxiety Disorder-7 (GAD-7) The GAD-7 is a seven-item questionnaire designed for diagnosis of generalized anxiety disorder.[30] GAD-7 is used to assess the frequency of anxious symptoms over the past 2 weeks. Each item is scored as not at all (score 0), on several days (1), on more than half the days (2), or nearly every day (3). Cumulative scores range from 0 to 21, and the level of anxiety is determined as follows: 0–4, minimal; 5–9, mild; 10–14, moderate; or ≥15, severe. A cutoff score of 5 indicates generalized anxiety disorder.

The Korean versions of HIT-6, MIDAS, PHQ-9 and GAD-7 were previously validated. [31-34]

Statistical analysis

Univariate categorical variables, such as sex, and presence of current illness were compared using the Chi-square test or Fisher's exact test. The comparison between groups of overuse medications with regard to clinical features and MDMOH, MMFMedS, MMFSH, and MCMIF as well as the clinical and neuropsychological parameters of HIT-6, MIDAS, PHQ-9, and GAD-7 of Visit 1 were performed by the nonparametric method of the *H* test (Kruskal–

Wallis). Post hoc tests were performed by pairwise *U* test (Mann–Whitney). The mean scores of HIT-6, MIDAS, PHQ-9, and GAD-7 evaluated on Visit 1 were compared with those at Visit 2 using Wilcoxon signed rank test. The significance level was set to $p<0.05$, and Statistical Package for Social Sciences software (SPSS, Inc., Chicago, IL, USA) was used for all data analysis.

Results

Patient population

The demographic and clinical characteristics of the patient population are listed in Table 1. Among the 114 patients who satisfied the criteria for MOH based on the ICHD-3,[1] nine who overused more than two drug classes but not individually overused were excluded (Figure 1). A total of 105 patients were enrolled between May 2020 and January 2021, and there were 93 women (88.6%); the mean patient age was 46 years (range from 18 to 80 years). Most participants had migraine as primary headache (97.1%, [102/105]). Among 102 patients with migraine, 20 (19.6%) patients had migraine with aura and 82 (80.4%) patients had migraine without aura. The remaining 3 (2.9%) had TTH as primary headache.

Of 105 patients who completed one-month follow-up, most patients (73.3%, 77/105) overused one category of medications, while 24.8% (26/105) and 1.9% (2/105) of the patients simultaneously took two and three categories of medications, respectively. Table 2 summarized the categories of the overused acute symptomatic medications and their clinical features. The patients reported overuse of triptans (29.5%, 31/105), ergotamines (7.6%, 8/105), non-opioid analgesics (15.2%, 16/105), combination (20.9%, 22/105) analgesics, opioids (0.9%, 1/105), or two or more drugs in combination with overuse of each individual drug class (26.7%, 28/105). Almost all patients (75/105, 71.4%) were taking preventive medications at the time of enrollment in this study including beta-blockers (31/105, 29.5%), calcium channel blockers (20/105, 19.1%), antiepileptic drugs (49/105, 46.7%), tricyclic antidepressants (21/105, 20%), serotonin-norepinephrine reuptake inhibitors (2/105, 1.9%), or angiotensin II receptor blockers (4/105, 3.8%). OnabotulinumtoxinA (25/105, 23.8%) and anti-CGRP (calcitonin gene-related peptide) monoclonal antibodies (8/105, 7.6%) also were used. Patients started the appropriate treatments at the time of recruitment for the study; many of the patients stopped overused acute headache medications immediately (44.8%), while others reduced the drug intake dosage or frequency (41.9%) or chose to maintain the current acute medications (13.3%). Patients who maintained the use of overused drugs tried to reduce drug use and manage with preventive medications and other prophylactic treatments including injections.

Clinical characteristics of MOH according to overused medications at initial visit

The age and sex of the patients as well as headache onset and MOH onset age were not different between the groups (Table 1). The CDH duration was significantly longer in the analgesics group (11.4 years) compared with the triptans (5.6 years) and multiple drugs groups (6.3 years) (Table 1). The mean duration of drug overuse (MOH duration) was 1.1 years (range, 0.25 to 11.2 years), and MOH duration was not different among four groups of overused medications. The MDMOH was longer in the analgesics group (10.6 years) than the triptans (4.3 years, $p=0.003$, Mann–Whitney *U* test) and multiple drug classes (4.8 years, $p=0.013$, Mann–Whitney *U* test). The MMFMedS for visiting a headache clinic was lower for the analgesics group (0.37 days per month) than for the multiple drug classes (0.85 days, $p=0.007$, Mann–Whitney *U* test) or triptans (0.58 days, $p=0.009$, Mann–Whitney *U* test) group. However, the MMFSH was significantly lower in the triptans group (7.4 days per month) than the analgesics (14.4 days, $p<0.001$, Mann–Whitney *U* test) or multiple drug classes (13.7 days, $p=0.025$, Mann–Whitney *U* test) group. The MMIF was significantly higher in the multiple drug classes (25 days per month) than in the triptans (18.1 days, $p=0.001$, Mann–Whitney *U* test) or analgesics (19.5 days, $p=0.005$, Mann–Whitney *U* test, Table 1) group.

The prevalence of vascular risk factors such as hypertension, diabetes, hyperlipidemia, and heart diseases were not significantly different between the overused medication groups (Table 1).

Headache impact and neuropsychological investigations

The mean score of HIT-6, which reflects the impact of headaches conducted on the day of enrollment (Visit 1), was 65.2 in the overall patient group and was not significantly different between the groups (Table 1). However, sub-analysis revealed that HIT-6 was significantly lower in the triptans group than the multiple drugs group (62.9 *versus* 67.4, $p \leq 0.05$, Mann–Whitney *U* test) (Table 1). The scores of MIDAS and the neuropsychological tests of depression (PHQ-9) and anxiety (GAD-7) were not significantly different between the groups at Visit 1 (Table 1). To assess the treatment responses in the different overused drugs groups, we followed the patients after one month with appropriate management. At one month later (Visit 2), the triptans group improved significantly in every parameter of HIT-6 ($p=0.001$, *Wilcoxon signed rank test*), MIDAS ($p=0.028$, *Wilcoxon signed rank test*), PHQ, and GAD7 ($p=0.004$ and $p=0.008$, respectively, *Wilcoxon signed rank test*) compared with the first visit day (Visit 1) with appropriate management (Figure 2). The analgesics group also showed significantly improved scores of HIT-6 ($p=0.000$, *Wilcoxon signed rank test*), MIDAS ($p=0.005$, *Wilcoxon signed rank test*), and PHQ-9 ($p=0.031$, *Wilcoxon signed rank test*) at one month after (Visit 2) with appropriate treatments (Figure 2). A reduction by a severity category of ≥1, generally defined as clinically relevant, was observed in the triptans group at 62% for PHQ-9 and 50% for GAD-7 and in the analgesics group at 30% for PHQ-9. In the group overusing multiple drugs, however, only the HIT-6 score was significantly improved (*$p=0.015$, Wilcoxon signed rank test*); the ergotamines group did not show improvement in any of these parameters after one month of treatment.

Discussion

The current study focused on the epidemiological profiles of MOH and the clinical characteristics and risks depending on overused medications in 105 patients. As in many other studies of MOH, the majority of our patients (88.6%) was women who had migraine as their primary headache (97.1%). Most

of our patient group overused simple or combination analgesics (35.2%), followed by triptans (29.5%), and the combination of triptans and analgesics (18.1%). The high frequency of patients using analgesics can be attributed to the over-the-counter drugs that are readily available in primary care. Therefore, analgesics and triptans, which are now widely used, might be one of the most important causes of MOH, and ergotamines might be no longer be a major cause of MOH. Analysis of the clinical features and risks of MOH depending on the type of overused drugs revealed that triptans have better efficacy against the severity and impact of headache, but patients taking triptans developed MOH faster, even with lower intake frequency, than other drugs. In contrast, compared with triptans, simple and combination analgesics did not reduce the frequency of severe headaches, but the duration to develop MOH was longer. In contrast, patients overusing multiple drugs reported more frequent severe headaches, similar to the patients who overused analgesics, compared with the triptans or ergotamines groups, but they developed MOH in a shorter period of time, similar with that of the triptans or ergotamines group. In addition, the frequency of drug intake in the multiple drug classes group was higher than in the triptans and analgesics groups. Because triptans and analgesics were the most commonly overused drugs in the multiple drugs overusing group, this group can reflect the overuse properties of each drug, with a short duration to induction of MOH as well as frequent severe headache. In contrast, the analgesic overuse patients reported severe headaches but visited headache clinics less frequently compared with the triptans or multiple drugs group. Therefore, while triptans can be an efficient medication for controlling chronic headache disorders, they induce MOH at lower doses with a shorter period of time compared with other drugs. These findings suggest that repeated excessive use of triptans might be lowering the threshold and contributing to trigger MOH. These results are consistent with several previous studies.[24, 25] Overuse of triptans leads to MOH faster (1.7 years) and with lower dosages (18 single doses per month) compared with ergotamines and analgesics.[24] Although the mean monthly intake frequency was almost same in the previous and current studies, there was a difference in the years of development of MOH, which is estimated to be affected by factors such as sample size, race, and the subtype of triptans overused. Higher frequency of drug intake and more frequent severe headaches reported in the multiple drug classes group is in context with another study finding that combination therapy of multiple medications and a large number of medication intake can convert headaches to more severe and frequent clinical symptoms in patients with MOH.[25]

The pharmacological mechanism of the clinical differences among the overused drugs has not been determined. MOH following triptan overuse could be explained by alteration in the serotonin (5-hydroxytryptamine, 5-HT) pathways in the various stages involved in headache development.[35] In animal experiments, chronic exposure of medications has been shown to affect the development of cortical spreading depression (CSD) by enhancing the excitability of cortical neurons and altering 5-HT receptor expression. The hyperexcitability of cortical neurons can make the cerebral cortex more susceptible to CSD development, subsequently promoting the trigeminal nociceptive process.[36] The alterations in cortical activity, such as increased stimulation responses, are indicative of neuronal hyperexcitability and have been reported in several neurophysiological studies of MOH patients.[37-40] Drug abuse can lead to decreased level of 5-HT, and a relative deficiency of 5-HT results in up-regulation of the excitatory 5-HT_{2A} receptor and altered intracellular signaling, which can increase the susceptibility to CSD.[35, 41] Some studies have suggested that repeated and continuous use of triptans contributes to facilitation and sensitization of the central and peripheral trigeminal nociceptive pathways by down-regulating serotonin receptors $5\text{-HT}_{1B/D}$, resulting in neural adaptations that lower the thresholds to migraine triggers.[42-44] Moreover, one study revealed that the onset time of MOH was shorter in patients treated with second generation 5-HT agonists such as zolmitriptan and naratriptan compared with patients taking first generation 5-HT agonists including sumatriptans.[45] The new 5-HT agonists, which have significantly higher affinity and intrinsic activity at the 5-HT receptor site, increase treatment options for migraine; however, the improved pharmacological profiles can cause a faster onset of MOH with lower dosages.[45] These features are in line with several clinical studies, including the current report, which revealed that MOH caused by triptans will develop faster at lower drug doses than will that caused by other drugs.

Evidence has been presented to support the clinical characteristics seen in patients with analgesics overuse MOH. Cyclooxygenases reinforce their prominent role in the inflammatory process through strong up-regulation.[46] Conversely, repeated and sustained exposure to analgesics results in down-regulation of these enzymes, with similar effects to those of downregulated receptor levels, which are the main pharmacological targets of analgesics.[5] However, this mode of enzyme regulation is slower and needs longer exposure to drugs compared with receptor regulation,[47] which supports that analgesics overuse patients take more time to develop MOH than do those with triptan overuse. In a study conducted with median-nerve somatosensory evoked potential (MNSEP) to identify sensitization patterns, all MOH patients showed an increased amplitude of MNSEP after initial stimulation, and the MNSEP amplitude was larger in patients with excessive use of analgesics than in patients with excessive use of triptans.[39] Trigeminal and somatic nociceptive systems were evaluated using pain-related evoked potentials (PREP) in patients with MOH.[37] Amplitudes of both trigeminal and somatic PREP were increased in all MOH patients, and MOH patients overusing analgesics showed a reduced latency of somatic PREP compared with MOH patients overusing triptans.[37] These reports provide support for the stronger headache intensity reported by patients with analgesics overuse MOH. Several reports have suggested that cortical neuronal excitability changes, central sensitization including the trigeminal nociceptive system, alteration in pathways associated with serotonin and dopamine expression, and the cannabinoid system affect the pathophysiology of MOH.[35, 48-50] In these studies, a specific substance or a single stimulation method was used as a drug-like prolonged repetitive trigger for MOH, but multiple reaction pathways, rather than one, were altered simultaneously or sequentially. Therefore, cross-sensitization can occur between overused drugs, suggesting that common mechanisms underlie the development of sensitization to drugs that target different neurotransmitters.[51] In addition, the overlap and accumulation of various pathways will further strengthen the pathophysiological triggering mechanism of MOH. This can account for the clinical phenotype of patients with MOH from overuse of multiple drugs that progressed to MOH in a shorter period of time and exhibited more frequent severe intensity of headache. Discontinuation of overused drugs is presumed to lead an inverse reaction of the sequential mechanism, which generates MOH. The difference in the remodeling mechanism represented by synaptic plasticity versus enzymatic modulation affects the withdrawal process as well, supporting the current study, which showed faster and more effective improvement in the triptan overuse group compared with other drug overuse groups.

Few prospective randomized controlled studies on the treatment of MOH have been reported.[5, 52] Whether acute headache medications should be discontinued and whether the preventive drugs should be started immediately or after withdrawal of acute symptomatic medication is a controversial issue in management of MOH.[53-56] Although debated, detoxification by abrupt withdrawal of the overused drugs is the treatment of choice for MOH.[57, 58] Cessation of the overused acute headache drugs was the main strategy for management of our MOH patients, and this approach can help reduce headache frequency or intensity and improve patient quality of life. Patients with triptans-induced MOH showed significant improvement at one month of follow-up after individual management in headache impact (HIT-6) and headache-related disability (MIDAS) scores as well as symptoms of depression (PHQ-9) and anxiety (GAD-7) measures (Figure 2). The improvement in these parameters suggests that patients with triptan-induced MOH can maintain drug (triptans) discontinuation and recover from MOH faster and easier and experience less frequent recurrence of MOH compared to other drug-induced MOH patients. Analgesic overuse MOH patients showed improvements in HIT-6, MIDAS, and PHQ-9 scores after one month. In patients with overuse of multiple drugs, however, only the HIT-6 score was improved. Ergotamine overuse patients did not show improvement in parameters after one month of treatment. Because of the short-term follow-up of one month, the impacts of headache and accompanying psychiatric symptoms could not be determined accurately, and long-term observation of treatment responses should be investigated in future study.

Psychiatric comorbidity such as depression and anxiety is prevalent highly in patients with MOH, as with other chronic headache disorders, compared with the general population or patients with episodic headache.[59] However, the prevalence of psychiatric comorbidity in MOH patients did not show differences according to type of overused medications in the current study. One month after treatment, the neuropsychiatric measurements for depression and anxiety symptoms showed remarkable improvement in the triptan and analgesic overuse groups. The mechanism for improvement in both headache and neuropsychiatric outcomes is uncertain; however, successful MOH treatment to reduce headache might lead to relief of depression and anxiety. Although it might be related to the individual pharmacological mechanisms of each drug, the different outcomes for different overused drugs remain to be determined. Cessation of overused medications with additional preventive managements, including botulinum toxin or anti-CGRP antibody injections, might be associated with neuropsychological improvement as well as reduction in headache frequency and intensity. The presence of psychiatric comorbidity contributes to progression from drug use to abuse and from headache to rebound headache, which is related to headache chronification in MOH.[60, 61] Therefore, early detection of MOH and initiation of treatment can prevent the vicious cycle in which comorbid psychiatric diseases worsen MOH. All of these aspects must be considered in the treatment of MOH since they are synergistic with each other and each affects the other.

There are, however, some limitations to consider with the current study. First, since only patients who visited tertiary hospitals were included, and patients who did not agree to participate in the study even if they met the inclusion criteria were excluded, selective participation cannot be ruled out. In addition, some patients did not keep a headache diary on a regular basis, and data were obtained through additional questionnaire items, so we cannot rule out that recall bias may have influenced our results. Third, the use of other acute pain medications for the treatment of other pain conditions was not accurately assessed. Therefore, the effects of prescribed pain medications for medical conditions other than headache may not have been included in this study. Finally, caution is needed to generalized the results because the sample size is small, especially patients with ergotamines overuse MOH.

Conclusion

Taken together, our study suggests that the clinical presentations of MOH might depend on the type of overused symptomatic headache medication. Use of triptans induces MOH in lesser doses and in shorter periods of time; however, withdrawal from triptans is shorter and easier compared with that from analgesics, ergotamines, and multiple drug classes. Use of analgesics takes more time to develop MOH, but these patients suffer headache pain more frequently than do triptan overuse patients. Patients overusing multiple drugs develop MOH quickly, report more frequent severe headache with frequent medical visits, and do not show significant improvement after stopping the drugs. Upon completion of the RELEASE study, the impact of drug overuse and treatment outcome will be stated in the final report.

Abbreviations

CDH: Chronic daily headache; CGRP: Calcitonin gene-related peptide; CSD: Cortical spreading depression; GAD-7: General Anxiety Disorder-7; HIT-6: Headache Impact Test-6; ICHD-3: The third edition of the International Classification of Headache Disorders; MDMOH: Mean duration until onset of MOH from chronic daily headache; MIDAS: Migraine Disability Assessment; MMFMedS: Mean monthly frequency seeking medical services; MMFSH: Mean monthly frequency of severe headache; MMIF: Mean monthly intake frequency; MNSEP: Median-Nerve Somatosensory Evoked Potential; MOH: Medication overuse headache; OTC: Over-the-counter; PHQ-9: Patients Health Questionaire-9; PREP: Pain-Rrelated Evoked Potentials; TTH: tension-type headache; 5-HT: 5-Hydroxytryptamine

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Institutional Review Board at Jeonbuk National University Hospital (IRB 2020-06-028-003) and at each participating centers. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

There is no conflict of interest to declare in relation to this manuscript.

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Authors' contributions

S-Y Oh, J-J Kang, and MK Choo designed and directed the project. H-K Park and S-J Cho contributed to collect and analyze the data. S-Y Oh and J-J Kang took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis, and the final manuscript.

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Tables

Table 1. Demographic and clinical features in medication overuse headache patients according to class of headache drug.

Clinical features of MOH patients	Medication group					*p* value				
	Triptans (n=31)	Ergotamines (n=8)	Analgesics (n=37)	Multiple drug classes (n=28)	Total (n=104)	4 groups[K]	T *vs.* E[M]	T *vs.* A[M]	T *vs.* M[M]	M *vs.* A[M]
Sex, female, n (%)[P]	26 (83.9)	7 (87.5)	32 (86.5)	28 (100)	105 (93)	0.196	1.000	0.762	0.054	0.065
Age (years)	42.26±11.6	43.75±19.4	47.54±14.8	49.18±10.3	46.12±13.3	0.224	0.772	0.220	**0.025***	0.503
Headache onset age (years)	23.13±12.0	19.50±12.4	26.65±13.7	22.32±12.9	23.88±12.9	0.253	0.401	0.273	0.693	0.137
MOH onset age (years)	38.81±10.6	39.25±16.4	41.89±14.7	42.75±11.1	41.00±12.7	0.728	0.772	0.627	0.251	0.491
Primary headache duration (years)	19.76±14.7	24.95±14.0	21.53±13.1	27.42±13.3	22.85±13.9	0.116	0.295	0.562	**0.033***	0.050
Chronic daily headache duration (years)	5.57±6.4	5.78±4.6	11.35±11.0	6.28±6.7	7.84±8.6	**0.043***	0.364	**0.011***	0.465	**0.035***
MOH duration (years)	1.15±1.6	2.25±3.8	0.68±0.7	1.40±2.3	1.13±0.2	0.433	0.401	0.465	0.709	0.271
Mean duration from chronic daily headache to MOH onset (years)	4.34±5.8	4.09±4.1	10.59±11.0	4.82±5.4	6.68±8.3	**0.011****	0.720	**0.003****	0.569	**0.013***
Mean monthly frequency of seeking medical services (days)	0.58±0.5	0.79±0.5	0.37±0.6	0.85±0.9	0.59±0.6	**0.008****	0.235	**0.009****	0.349	**0.007****
Mean monthly frequency of severe headache (days)	7.42±4.8	8.88±7.4	14.38±8.7	13.68±10.1	11.69±8.6	**0.005****	0.645	**0.000*****	**0.025***	0.484
Mean monthly intake frequency (days)	18.10±7.7	19.63±10.6	19.49±7.7	25.00±6.9	20.57±8.1	**0.007****	0.483	0.415	**0.001****	**0.005****
Headache-related scales at the first visit										
Headache Impact Test-6	62.97±8.7	63.63±9.1	65.68±8.0	67.39 ±5.6	65.17±7.8	0.236	0.720	0.244	**0.036***	0.410
Migraine Disability Assessment	68.06±85.5	31.25±23.8	71.27±75.1	63.29 ±68.9	65.09±74.1	0.650	0.421	0.596	0.814	0.591
Patient Health Questionaire-9	10.61±6.1	6.13±4.1	11.00±6.5	11.32 ±8.3	10.59±6.8	0.334	0.073	0.941	0.879	0.926
General Anxiety Disorder-7	7.26±5.3	4.38±3.3	6.84±6.3	8.04 ±7.1	7.10±6.1	0.615	0.184	0.508	0.903	0.576
Comorbid diseases[P]										
Hypertension, n (%)	8 (25.8)	1 (12.5)	8 (21.6)	7 (25)	24 (23.1)	0.865	0.653	0.685	1.000	0.749
Diabetes,n (%)	1 (3.2)	1 (12.5)	2 (5.4)	1 (3.6)	5 (4.8)	0.723	0.289	1.000	0.942	1.000
Hyperlipidemia, n (%)	6 (19.4)	0 (0)	5 (13.5)	7 (25)	18 (17.3)	0.348	0.313	0.531	0.755	0.335
Heart diseases, n (%)	1 (3.2)	0 (0)	0 (0)	0 (0)	1 (0.9)	0.498	1.000	0.456	1.000	.

Values are mean ±SD

T; Triptans, E; Ergotamines, A; Analgesics, M; Multiple drugs

K; Kruskal–Wallis test, M; Mann-Whitney U test, P; Pearson's chi-square test

Table 2. Categories of acute symptomatic medications overused.

Type of overuse medications	Medication group, n=105
Triptans	31 (29.5%)
Sumatriptan	8 (7.6%)
Almotriptan	1 (0.9%)
Zolmitriptan	7 (6.7%)
Naratriptan	7 (6.7%)
Frovatriptan	8 (7.6%)
Ergotamines	8 (7.6%)
Ergotamine	8 (7.6%)
Analgesics	37[a] (35.2%)
Simple analgesics	16[b] (15.2%)
Acetaminophen	12 (11.4%)
Aspirin	1 (0.9%)
Naproxen	2 (1.9%)
Ibuprofen	3 (2.8%)
Loxoprofen	1 (0.9%)
Combinations	22 (20.9%)
OTC with caffeine	18 (17.1%)
OTC without caffeine	4 (3.8%)
Opioids	1 (0.9%)
Tramadol	1 (0.9%)
Multiple drugs	28 (26.7%)
Triptans & Analgesics	19 (18.1%)
Triptans & Ergotamines	1 (0.9%)
Triptans & Opioids	2 (1.9%)
Ergotamines & Analgesics	2 (1.9%)
Opioids & Analgesics	2 (1.9%)
Triptans & Analgesics & Opioids	2 (1.9%)

OTC = Over the counter

a One patient in the analgesics category overused both simple analgesics and combination agents.

b Three patients took two kinds of simple analgesics.

Figures

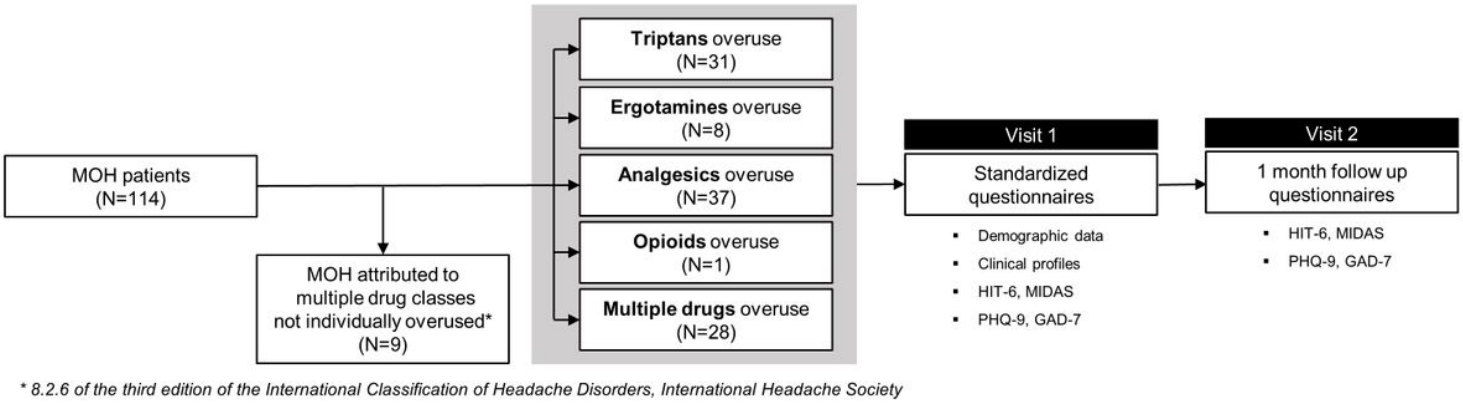

Figure 1

Study design and flow chart

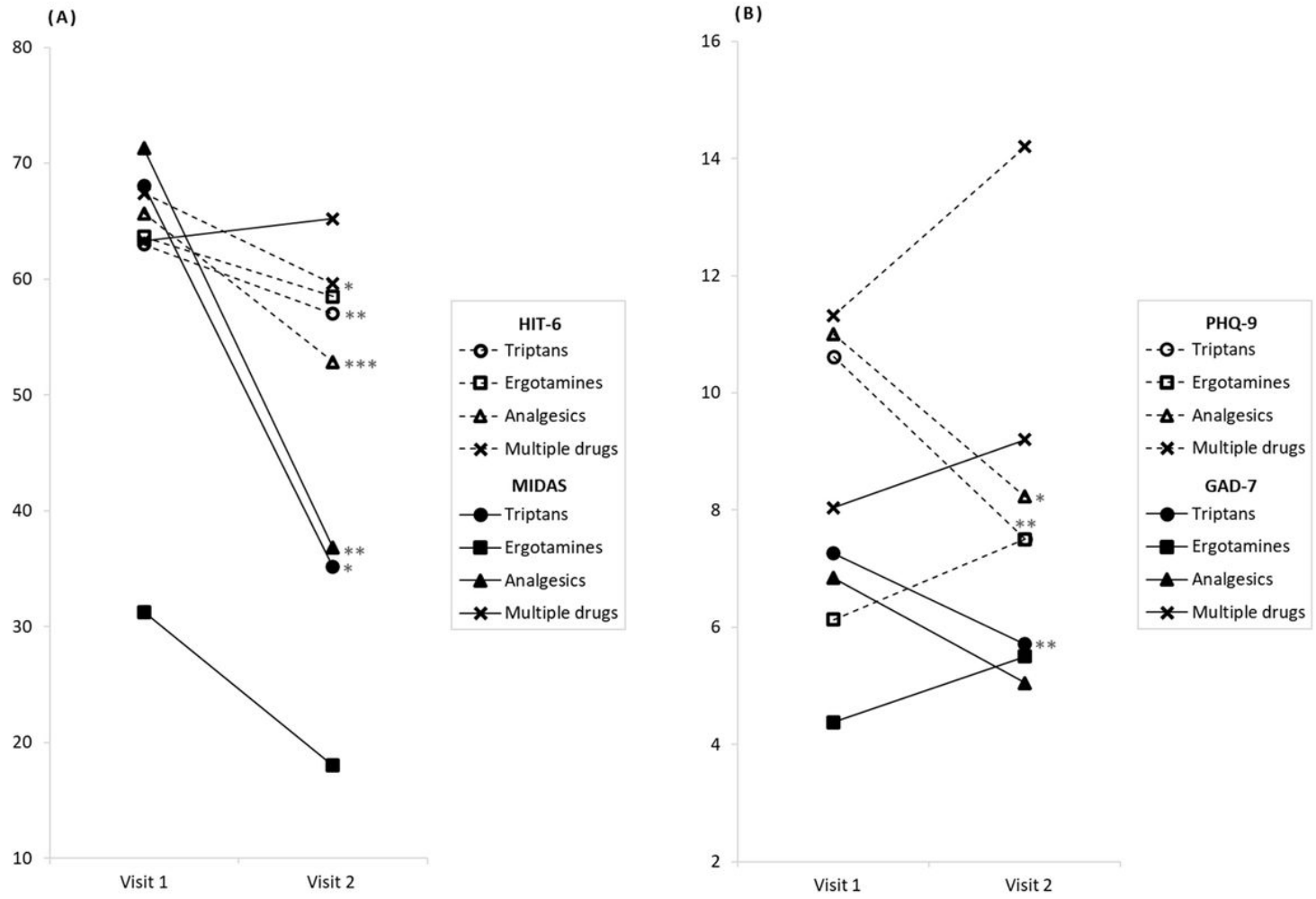

Figure 2

Comparison of questionnaires on enrollment day (Visit 1) and after 1 month (Visit 2). (A) HIT-6 and MIDAS and (B) PHQ-9 and GAD-7. *p < 0.05, **p < 0.01, ***p < 0.001