Medication-overuse headache: clinical profile and management strategies

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ABSTRACT

يعتبر الصداع الناجم عن الإفراط في استخدام الأدوية من أنواع الصداع الثانوية ، وله نتائج وعواقب صحية على الأفراد المصابين وعلى موارد الرعاية الصحية. ويتم تعريفه على أنه صداع يحدث للمريض لمدة 15 يومًا أو أكثر شهريًا لمريض مصاب بمرض الصداع الأولي وذلك بسبب الإفراط المتكرر في استخدام أدوية الصداع من مختلف الانواع لأكثر من 3 أشهر. يصيب الصداع الناجم عن الإفراط في استخدام الأدوية 1-2% من سكان العالم خلال عمر الإنتاجية. يمكن أن تساعد التطورات الجديدة في علوم الصداع وتطوير خيارات الأدوية الجديدة المخصصة لعلاج أمراض الصداع جنبًا إلى جنب مع فهم السمات السريرية والفيزيولوجية للمرض على تحسين النتائج الصحية للمرضى وتقليل العبء على نظام الرعاية الصحية. في هذا العمل نهدف إلى مراجعة مرض الصداع الناجم عن الإفراط في استخدام الأدوية وتحديد السمات السريرية وأساليب العلاجية الحديثة لهذا المرض.

Medication-overuse headache (MOH) is a disabling secondary headache disorder, with challenging consequences for affected patients and health care resources. It is defined as headache that occurs on ≥ 15 days per month in a patient known to have primary headache disorder due to regular overuse of acute or abortive headache medication for more than 3 months. MOH affects 1-2% of the world's population in their productive age. New advances in headache neurosciences and development of new treatment options specific for headache, along with an understanding of the clinical profile and pathophysiological mechanisms of MOH, can help improve patient outcomes and decrease the burden on the health care system. This work will review MOH, identify updated clinical assessments and recent management approaches.

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Medication-overuse headache (MOH) is defined by the International Classification of Headache Disorders 3rd edition (ICHD-3) as the occurrence of headache on 15 or more days/month in a patient with a known history of primary headache disorder. The ICHD-3 goes on to describe it is a condition that develops because of regular overuse of symptomatic or acute headache medication (on 10–15 or more days/month, depending on the class of medication) for more than 3 months.[1] The objective of this work is to review MOH and to identify its updated clinical assessments and recent management approaches.

Historical background. A report in 1963 of 52 patients who had headaches after taking ergotamine for prolonged periods, showed 71% developed signs and symptoms of toxicity, which reversed when the drug was discontinued.[2] In 1990, similar observations were made regarding triptans.[3] In 1998, the term "drug-induced headache" was introduced by the International Headache Society in the ICHD-1 for the first time. In 2004 in the ICHD-2, the term was changed to "medication-overuse headache" to highlight the impact of regular and longtime use of specific medications resulting in headache, and to differentiate it from headaches as side effects, caused by other headache-triggering medications.[4,5](However, the criteria specified that MOH can only be diagnosed once the headache disappears, after the offending agent is removed Otherwise, it was defined as probable MOH, leading to difficulties in clinical practice. In 2006, the requirement that headache can be definitively diagnosed only once it disappears was eliminated and that criterion was retained in the recent ICHD-3 guideline.[1,6]

Epidemiology. Medication-overuse headache occurs in 2% of women, and 1% of men worldwide.[7,8] It is most prevalent in people in their 40s, and about 50%

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of patients with chronic headaches have associated MOH.[6,8] Medications commonly implicated in MOH are paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), ergots, triptans, and opioids.[6,9]

Disease burden. The MOH has a broad impact on physical and psychological health. A recent study assessing the burden of MOH concluded those who overuse acute medications were more likely to have moderate to severe depression, moderate to severe anxiety, moderate to severe headache-related disability, and a higher incidence of emergency department and urgent care use for headache within the past 6 months.[10-13]

Pathophysiology. The pathophysiology of MOH is still not fully understood. In animal studies, Green et al[14] observed multiple changes in the physiological process in the central nervous system (CNS) after repetitive administration of analgesics. Data showed using triptans for long durations can result in susceptibility to cortical spreading depression (CSD) due to decreased threshold.[15,16] Long-term exposure to analgesics was found to increase the neuronal excitability in the amygdala's central nucleus, which may lead to the development of depression or anxiety.[17,18]

The serotonergic system was also affected by the use of analgesics for a long time, which leading to neuronal hyperexcitability, trigeminal nociception enhancement, and CSD due to an increase in the expression of serotonin 2A (pro-nociceptive) receptor binding sites and lowering of the production of serotonin in the CNS.[15]

Data from a study reported by Cargnin et al[19] showed variations in genes in the dopaminergic gene system (*DRD2*, *DRD4*, *SLC6A3*), and genes related to dependence of drug pathways (*ACE*, *HDAC3*, *WSF1*, *BDNF*). These genetic traits were considered potential risk factors for susceptibility to MOH with multi-drug consumption.[18-20]

Data from Pellesi et al[21] have reported the detection of high concentrations of different serum bands in patients with MOH in comparison to controls. Those include Hemopexin, alpha-1-acid glycoprotein 1, apolipoprotein A4 and haptoglobin which have been reported previously in an animal model of neuropathic pain. It was suggested that it was consequence of enduring neural damage and sensitization of the trigeminal nociceptive pathways due to over exposure to acute headache medication. Furthermore, additional proteins were isolated in patient with MOH: Alpha-1-antitrypsin, immunoglobulin heavy constant alpha 1, retinol binding protein and transthyretin.[21]

Structural changes have been reported in the CNS. Increased gray matter volume mainly in the periaqueductal grey area, hippocampus, posterior cingulate cortex, thalamus, cerebellum, fusiform gyrus, and ventral striatum. Orbitofrontal cortex (OFC), anterior cingulate cortex, left middle occipital gyrus, anterior cingulate cortex, insula and precuneus had lesser gray matter volume.[18] However, functional changes have been reported as well in the CNS (mesocorticolimbic system, the salience network, the fronto-parietal attention network, the default network, and the memory processing network).[22]

Clinical profile. The character of MOH is difficult to differentiate from other forms of chronic daily headache. The headache's character and associated symptoms of MOH are not defined in ICHD-3 criteria. However, MOH are refractory, daily, severe, have no specific location, are changeable on different days, and are associated with asthenia, nausea, irritability, anxiety, and concentration difficulties.[23] An interaction between susceptible patient and a therapeutic medication used excessively is considered MOH.[1]

Diagnosis. A detailed history is essential for headache evaluation, including the medication history. The ICHD-3 diagnostic criteria in **Table 1** is used to consider the diagnosis of MOH. The onset of headache usually is gradual, and the nature of the headache is often typical, such as tension or migraine, and can be more frequent and intense.[24] Patients with MOH usually report neck pain and headaches in the morning due to poor quality of sleep or overnight drug withdrawal.[25,26] **Table 2** compares the different diagnostic criteria of ICHD.

It is important to consider the red flags for secondary headaches — such as cerebral venous thrombosis and idiopathic intracranial hypertension, which can present in chronic headache with medication overuse — when taking a patient's history and performing the physical examination. Hemicrania continua, giant cell arthritis, and new daily persistent headache can also be presented with chronic headaches. The choice of which appropriate investigation to follow depends on the consideration of secondary headache diagnosis and the strength of suspicion. Computerized tomography and magnetic resonance imaging can be used to rule out tumors, venous thrombosis, high intracranial pressure, and pachymeningitis for most secondary headaches.[27] Psychiatric disorders such as anxiety and depression can be associated with MOH; it has been suggested they occur in patients with MOH because of the headaches, not because of personality traits.[6,28,29]

Management. Role of counseling. Educating patients, the general population, and healthcare providers

Table 1 - The ICHD-3 diagnostic criteria for medication overuse headache.

- Headache occurring on ≥15 days/month in a patient with pre-existing headache disorder
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache*
- Not better accounted for by another International Classification of Headache Disorders (ICHD-3) diagnosis
*Regular intake of simple analgesics for ≥ 15 days /month or ergotamine, opioids, and triptans for ≥10 days/month

Table 2 - Comparison between all the diagnostic criteria of medication overuse headache by the International Classification of Headache Disorders (ICHD) 1, 2, and 3.

ICHD-1	ICHD-2	ICHD-3
A- Occurs after daily dose of a substance for ≥ 3 months.	A- Headache present on ≥ 15 days/month fulfilling criteria C and D.	A- Headache occurring on ≥ 15 days/month in a patient with pre-existing headache disorder
B- A certain required minimum dose should be indicated.	B- Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.	B- Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache*
C- Headache is chronic (≥ 15 days/month).	C- Headache has developed or markedly worsened during medication overuse.	C- Not better accounted for by another International Classification of Headache Disorders (ICHD-3) diagnosis.
D- Headache disappears within 1 month after withdrawal of the substance.	D- Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication.	*Regular intake of simple analgesics for ≥ 15 days / month OR ergotamine, opioids, and triptans for ≥ 10 days/month.

Table 3 - Treatment strategies for patients with MOH.

A-	Education of the general population and healthcare providers with general practitioners intervention
B-	Management strategies for MOH:
C-	Abrupt withdrawal: treatment of choice for triptans, ergots, simple and combination analgesics, and NSAIDs
D-	Gradual withdrawal: best for the overuse of opioids, barbiturates, and benzodiazepines
E-	Outpatient management is recommended for committed, motivated patients, taking non-opioid and non-barbiturate medications, and who do not have any comorbidities. Inpatient care management is usually considered because of failed outpatient management, overuse of barbiturates, opioids or benzodiazepines, or those with medical or psychiatric comorbidities, and with severe withdrawal symptoms such as vomiting
F-	Valproate, nabilone, onabotulinumtoxin A, topiramate, and amitriptyline are used as prophylactic management

about MOH and analgesic overuse — especially when headache sufferers take it for any primary headache disorders — can prevent the development of MOH.[6] New information campaigns for patients at risk before the onset of MOH have important role in the management of headache.[15] Headache centers in Germany provide a brochure about MOH, which has proved effective in the prevention of developing MOH in those with frequent usage of medications and migraine.[15] Primary health care counselling has a major role in the prevention of MOH as well as the initial treatment, while general practitioners (GP) can educate patients about proper usage of medication and modifiable risk factors, such as physical inactivity, stress, obesity, and smoking.[30] Intervention by a GP was found to be effective in the management of MOH, according to the Norwegian Akerhus study.[25] They compared those patients who received GP counselling with those who did not; there was a significant decrease in headache and the frequency of medication usage with those who received counseling. Thus, education by a GP is effective, preventing the need for withdrawal from medications, and can be demonstrated after 16 months.[25,31]

Strategies. Management strategies for withdrawing from drug overuse can be abrupt or gradual. Abrupt, sudden removal is considered the treatment of choice for triptans, ergots, simple and combination analgesics, and NSAIDs. Gradual withdrawal is best for the overuse of opioids, barbiturates, and benzodiazepines.[32-34]

Danish guidelines recommend the total cessation of all medications within 2 months.[6,35] Withdrawal symptoms such as headache, nausea, vomiting, hypotension, sleep disturbance, and tachycardia generally last for 2-10 days.[15,36] **Table 3** summarizes treatment strategies for patients with MOH.

Inpatient or outpatient? Outpatient management, considered more cost effective, is recommended for committed, motivated patients, who are taking non-opioid and non-barbiturate medications, and do not have any physical or psychiatric comorbidities. Inpatient management is considered when outpatient management has failed; barbiturates, opioids or benzodiazepines have been overused, or with the patient has medical or psychiatric comorbidities, or experiences severe withdrawal symptoms such as vomiting. For that reason, inpatient care will ensure compliance and adherence, and the health care provider can decide the most appropriate treatment for withdrawal symptoms including intravenous administration.[33,37,38] Non-pharmacological management, such as behavioral strategies can be applied in inpatient settings for patients with dependence and psychological symptoms.[39-41]

Prophylactic management. The European Federation of Neurological Sciences recommends that if prophylactic therapy has started before or at the time of abrupt withdrawal of the overused medication, preventive therapies should be at the lowest doses, then dosage can be titrated up with time. The choice of treatment depends on the medication used, patient preferences, the type of primary headache disorder, comorbidities, and adverse effects.[42] A meta-analysis of randomized controlled trials (RCTs) on the effects of prophylactic therapies confirmed the efficacy of valproate, nabilone, onabotulinumtoxin A, topiramate, and amitriptyline. The results of RCTs with patients affected by chronic migraine and MOH suggest the use of onabotulinumtoxin A and topiramate without early discontinuation.[43] Another RCT in 2020 compared 3 treatment strategies: withdrawal with preventive treatment, preventive without withdrawal treatment, and withdrawal with postponed optional preventive treatment. Study results recommend the use of withdrawal and the preventive treatment strategy for MOH.[44]

New therapy modalities. CGRP and their role. Recent studies looked at the prophylactic effect of anti-calcitonin gene-related peptide receptor (anti-CGRP) monoclonal antibodies (MAB) in MOH. A prospective study in 2021 with 316 patients started anti-CGRP MAB as a migraine prophylaxis for 6 months. They noticed a >50% reduction in headache frequency regardless of the presence of MOH, concluding anti-CGRP MABs are probably an effective prophylactic treatment for migraine patients with MOH; and they were safe and well-tolerated.[45,46] They did not support that one anti-CGRP MAB is better than another for MOH (erenumab vs. galcanezumab). They also did not support dual therapy with concomitant botulinum toxin-A instead of monotherapy. Anti-CGRP MABs were considered safe, facilitate acute medication discontinuation, reduce headache frequency, and reduce usage of acute medication.[47]

Future potential of the new medication. In terms of acute therapy, FDA approval of both small molecule CGRP receptor antagonists, such as ubrogepant, and the serotonin (5-HT) 5-TH1F receptor agonist, such as lasmiditan, for the management of migraine, may have the potential to lower the MOH risk profile, which is supported by preclinical and preliminary clinical data.[47,48]

More detailed studies for real-world evidence of the efficacy of these new medications can improve our understanding and management possibilities of using these therapies.

Conclusion. Proper approach for MOH is crucial, as well as the need for appropriate clinical assessment and a treatment strategy for the overused medication. It is equally important that patients be made aware of MOH. Overall, it is a challenging disorder, and appropriate assessment with clinical profile utilizing updated diagnostic criteria will help in the diagnosis and management of MOH. Treatment strategies vary by medication. Abrupt and sudden removal is considered the treatment of choice for triptans, ergots, simple and combination analgesics, and NSAIDs. Gradual withdrawal is best for the overuse of opioids, barbiturates, and benzodiazepines. Further research is needed to evaluate new acute therapy safety and efficacy of new medications in patients with MOH.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed. Sage Publishing; 2018. Available from: https://www.ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf
2. Horton BT, Peters GA. Clinical manifestations of excessive use of ergotamine preparations and management of withdrawal effect. Report of 52 cases. ***Headache*** 1963; 2: 214-217.
3. Dodick DW. Migraine. ***Lancet*** 2018; 391: 1315-1330.
4. Al-Quliti KW, Assaedi ES. New advances in prevention of migraine. Review of current practice and recent advances. ***Neurosciences (Riyadh)*** 2016; 21: 207-214.

5. Al-Quliti, KW, Alhujeily R, Aljarbou OM, Al-Rasheedi RS, Alrewaithi B. Knowledge, attitude, and practice among pharmacists for migraine management in Al-Madinah Al-Munawarah. ***Int J Med Dev Countries*** 2022; 6: 340-347.
6. Kulkarni GB, Mathew T, Mailankody P. Medication overuse headache. ***Neurol India*** 2021; 69: S76-S82.
7. Aurora SK, Brin MF. Chronic Migraine: An Update on Physiology, Imaging, and the Mechanism of Action of Two Available Pharmacologic Therapies. ***Headache*** 2017; 57: 109-125.
8. Viana M, De Icco R, Allena M, Sances G, Højland JR, Katsarava Z, et al. Clinical subtypes of medication overuse headache - Findings from a large cohort. ***Headache*** 2019; 59: 1481-1491.
9. Lundqvist C, Gossop M, Russell MB, Straand J, Kristoffersen ES. Severity of analgesic dependence and medication-overuse headache. ***J Addict Med*** 2019; 13: 346-353.
10. Schwedt TJ, Buse DC, Argoff CE, Reed ML, Fanning KM, Hussar CR, et al. Medication overuse and headache burden: results from the CaMEO Study. ***Neurol Clin Pract*** 2021; 11: 216-226.
11. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. ***Lancet Neurol*** 2018; 17: 954-976.
12. Bottiroli S, Allena M, Sances G, De Icco R, Avenali M, Fadic R, et al. Changes in anxiety and depression symptoms associated to the outcome of MOH: A post-hoc analysis of the Comoestas Project. ***Cephalalgia*** 2018; 38: 646-654.
13. Vandenbussche N, Paemeleire K, Katsarava Z. The many faces of medication-overuse headache in clinical practice. ***Headache*** 2020; 60: 1021-1036.
14. Green A, Gu P, De Felice M Dodick D, Ossipov M, Porreca F. Increased susceptibility to cortical spreading depression in an animal model of medication-overuse headache. ***Cephalalgia*** 2014; 34: 594-604.
15. Vandenbussche N, Laterza D, Lisicki M, Lloyd J, Lupi C, Tischler H, et al. Medication-overuse headache: a widely recognized entity amidst ongoing debate. ***J Headache Pain*** 2018; 19: 50.
16. Schwedt TJ, Chong CD. Medication overuse headache: pathophysiological insights from structural and functional brain MRI research. ***Headache*** 2017; 57: 1173-1178.
17. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. ***J Headache Pain*** 2019; 20: 117.
18. Diener HC, Dodick D, Evers S, Holle D, Jensen RH, Lipton RB, et al. Pathophysiology, prevention, and treatment of medication overuse headache. ***Lancet Neurol*** 2019; 18: 891-902.
19. Cargnin S, Viana M, Sances G, Tassorelli C, Terrazzino S. A systematic review and critical appraisal of gene polymorphism association studies in medication-overuse headache. ***Cephalalgia*** 2018; 38: 1361-1373.
20. Katsarava Z. Medication-overuse headache (MOH). In: Mitsikostas DD, Paemeleire K, editors. Pharmacological Management of Headaches. Headache. Cham (China): Springer; 2016. https://doi.org/10.1007/978-3-319-19911-5_19
21. Pellesi L, Guerzoni S, Baraldi C, Cainazzo MM, Pini LA, Bellei E. Identification of candidate proteomic markers in the serum of medication overuse headache patients: An exploratory study. ***Cephalalgia*** 2020; 40: 1070-1078.
22. Kristoffersen ES, Straand J, Vetvik KG, Benth JS, Russell MB, Lundqvist C. Brief intervention for medication overuse headache in primary care. The BIMOH study: A double blind pragmatic cluster randomised parallel controlled trial. ***J Neurol Neurosurg Psychiatry*** 2015; 86: 505-512.
23. Scher AI, Rizzoli PB, Loder EW. Medication overuse headache: An entrenched idea in need of scrutiny. ***Neurol*** 2017; 89: 1296-1304.
24. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine Progression: A Systematic Review. ***Headache*** 2019; 59: 306-338.
25. Al Quliti KW. Prevalence of depressive symptoms and its correlates in primary headache patients with a history of head-neck trauma. ***Neurosciences (Riyadh)*** 2022; 27: 181-186.
26. Al-Quliti K. Stress and Its Correlates in Migraine-Headache Patients with a Family History of Migraine. ***Behavioral Sciences*** 2022; 12: 65.
27. Westergaard ML, Glümer C, Hansen EH, Jensen RH. Medication overuse, healthy lifestyle behaviour and stress in chronic headache: results from a population-based representative survey. ***Cephalalgia*** 2016; 36: 15-28.
28. Kristoffersen ES, Straand J, Russell MB, Lundqvist C. Lasting improvement of medication overuse headache after brief intervention—A long term follow up in primary care. ***Eur J Neurol*** 2017; 24: 883-891.
29. Diener HC, Antonaci F, Braschinsky M, Evers S, Jensen R, Lainez M, et al. European Academy of Neurology guideline on the management of medication-overuse headache. ***Eur J Neurol*** 2020; 27: 1102-1116.
30. Nielsen M, Carlsen LN, Munksgaard SB, Engelstoft IMS, Jensen Rn, Bendtsen L. Complete withdrawal is the most feasible treatment for medication-overuse headache: A randomized controlled open-lable trial. ***Eur J Pain*** 2019; 23: 1162-1170.
31. Grazzi L, Grignani E, D'Amico D, Sansone E, Raggi A. Is medication overuse drug specific or not? Data from a review of published literature and from an original study on Italian MOH patients. ***Curr Pain Headache Rep*** 2018; 22: 71.
32. Engelstoft IMS, Carlsen LN, Munksgaard SB, Nielsen M, Jensen RH, Bendtsen L. Complete withdrawal is the most feasible treatment for medication-overuse headache: A randomized controlled open-label trial. ***Eur J Pain*** 2019; 23: 1162-1170.
33. Westergaard ML, Lau CJ, Allesoe K, Gjendal ST, Jensen RH. Monitoring chronic headache and medication-overuse headache prevalence in Denmark. ***Cephalalgia*** 2020; 40: 6-18.
34. Raggi A, Giovannetti AM, Leonardi M, Sansone E, Schiavolin S, Curone M, et al. Predictors of 12-months relapse after withdrawal treatment in hospitalized patients with chronic migraine associated with medication overuse: A longitudinal observational study. ***Headache*** 2017; 57: 60-70.
35. Bottiroli S, Allena M, Sances G, De Icco R, Avenali M, Fadic R, et al. Psychological, clinical, and therapeutic predictors of the outcome of detoxification in a large clinical population of medication-overuse headache: A six-month follow-up of the COMOESTAS Project. ***Cephalalgia*** 2019; 39: 135-147.
36. Carlsen LN, Munksgaard SB, Jensen RH, Bendtsen L. Complete detoxification is the most effective treatment of medication-overuse headache: A randomized controlled open-label trial. ***Cephalalgia*** 2018; 38: 225-236.

37. Fischer MA, Jan A. Medication-overuse headache. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538150/
38. De Goffau MJ, Klaver ARE, Willemsen MG, Bindels PJ, Verhagen, AP. The effectiveness of treatments for patients with medication overuse headache; a systematic review and meta-analysis. ***J Pain*** 2016; 18: 615-627.
39. Carlsen LN, Munksgaard SB, Nielsen M, Engelstoft IMS, Westergaard ML, Bendsten L, et al. Comparison of 3 treatment strategies for medication overuse headache: A randomized clinical trial. ***JAMA Neurol*** 2020; 77: 1069-1078.
40. Diener HC, Marmura MJ, Tepper SJ, Cowan R, Starling AJ, Diamond ML, et al. Efficacy, tolerability, and safety of eptinezumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: Subgroup analysis of PROMISE-2. ***Headache*** 2021; 61: 125-136.
41. Dodick D, Tepper SJ, Diener HC, Tassorelli C, Lukas S, Evers S, et al. Efficacy of erenumab in chronic migraine patients with medication overuse and prior preventive treatment failure [abstract]. ***Neurol*** 2019; 92: S38.002
42. Tepper SJ, Diener HC, Ashina M, Brandes JL, Friedman DI, Reuter U, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. ***Neurol*** 2019; 92: e2309-e2320.
43. Caronna E, Gallardo VJ, Alpuente A, Torres-Ferrus M, Pozo-Rosich P. Anti-CGRP monoclonal antibodies in chronic migraine with medication overuse: real-life effectiveness and predictors of response at 6 months. ***J Headache Pain*** 2021; 22: 120.
44. Holland PR, Saengjaroentham C, Sureda-Gibert P, Strother LC. Medication overuse headache: Divergent effects of new acute antimigraine drugs. ***Cephalalgia*** 2020; 40: 889-891.
45. Navratilova E, Behravesh S, Oyarzo J, Dodick DW, Banerjee P, Porreca F. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. ***Cephalalgia*** 2020; 40: 892-902.
46. Van Hoogstraten WS, MaassenVanDenBrink A. The need for new acutely acting antimigraine drugs: Moving safely outside acute medication overuse. ***J Headache Pain*** 2019; 20: 54.
47. Rau JC, Navratilova E, Oyarzo J, Johnson KW, Aurora SK, Schwedt TJ, et al. Evaluation of LY573144 (lasmiditan) in a preclinical model of medication overuse headache. ***Cephalalgia*** 2020; 40: 903-912.
48. Silberstein S, Cohen JM, Seminerio MJ, Yang R, Ashina S, Katsarava Z. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. ***J Headache Pain*** 2020; 21: 114.