https://doi.org/10.1590/0004-282X-ANP-2020-0547

Medication overuse headache and awareness

Cefaleia por abuso de medicação e conscientização

Zeynep Tuncer ISSI[1], Hayriye DURAN[2], Mehmet Emin KUŞ[2], Nil HELVACIOĞLU[2], Hülya ELLIDOKUZ[3], Vesile ÖZTÜRK[1]

ABSTRACT

Background: Medication overuse headache (MOH) is the worsening of an underlying headache due to the overuse of its acute treatment. Unintentionally, healthcare professionals may contribute to this condition. Health professionals play an important role in preventing this increasingly frequent and difficult-to-treat condition. **Objective:** To investigate MOH awareness among physicians with headache through a survey conducted among medical doctors on our university campus. **Methods:** This was an observational cross-sectional study about MOH awareness. The total number of medical doctors working in the Dokuz Eylül University Health Campus was provided by the administrative unit. A total of 18 questions were prepared and administered on a voluntary basis to obtain information about MOH awareness. **Results:** A total of 312 medical doctors were surveyed, including 198 (63.5%) from internal medical sciences, 81 (26%) from surgical medical sciences, and 33 (10.5%) from basic medical sciences. Half of the physicians in our sample were unaware of MOH. Our results showed that awareness of MOH, was quite low even among medical doctors. **Conclusions:** MOH causes both labor and financial losses to countries and impairs the quality of life of patients. Preventing excessive use of medications by raising awareness among doctors is an important step to prevent the development of MOH.

Keywords: Headache Disorders; Headache Disorders, Secondary; Migraine Disorders; Awareness; Socioeconomic Factors.

RESUMO

Antecedentes: A cefaleia por uso excessivo de medicamentos (CEM) é o agravamento de uma cefaleia subjacente devido ao uso excessivo do seu tratamento agudo. Involuntariamente, os profissionais de saúde podem contribuir para essa condição. Os profissionais de saúde desempenham um papel importante na prevenção dessa condição cada vez mais frequente e de difícil tratamento. **Objetivo:** Investigar a conscientização da CEM entre médicos com dor de cabeça por meio de uma pesquisa realizada entre médicos em nosso campus universitário. **Métodos:** Este foi um estudo transversal observacional sobre a consciência da CEM. O número total de médicos que trabalham no Campus de Saúde da Universidade Dokuz Eylül foi fornecido pela unidade administrativa. Um total de 18 questões foram preparadas e aplicadas de forma voluntária para obter informações sobre a conscientização da CEM. **Resultados:** Um total de 312 médicos foram pesquisados, incluindo 198 (63,5%) das ciências médicas internas, 81 (26%) das ciências médicas cirúrgicas e 33 (10,5%) das ciências médicas básicas. Metade dos médicos de nossa amostra desconhecia a CEM. Nossos resultados mostraram que o conhecimento sobre a CEM era bastante baixo, mesmo entre os médicos. **Conclusões:** A CEM causa perdas laborais e financeiras aos países e prejudica a qualidade de vida dos pacientes. Prevenir o uso excessivo de medicamentos por meio da conscientização dos médicos é um passo importante para prevenir o desenvolvimento da CEM.

Palavras-chave: Transtornos da Cefaleia; Transtornos da Cefaleia Secundários; Transtornos de Enxaqueca; Conscientização; Fatores Socioeconômicos.

INTRODUCTION

Medication overuse headache (MOH) is the worsening of an underlying headache due to the overuse of its acute treatment. All drugs used to treat headache attacks, such as non-steroidal anti-inflammatory drugs or triptans, can cause MOH as well as other attempts to relieve headaches[1,2]. Patients with MOH may have several types of underlying primary headaches, such as migraine or tension-type headache, cluster-type headache, posttraumatic headaches, or headaches secondary to the decrease or increase in intracranial pressure[2].

[1]Dokuz Eylül University Faculty of Medicine Hospital, Department of Neurology and Pain Management, Izmir, Turkey.

[2]Dokuz Eylül University Faculty of Medicine Hospital, Izmir, Turkey.

[3]Dokuz Eylül University Faculty of Medicine Hospital, Oncology Institute Preventive Oncology Department, Izmir, Turkey.

ZTI https://orcid.org/0000-0002-3109-3073; HD https://orcid.org/0000-0002-8834-3037; MEK https://orcid.org/0000-0001-8121-2176; NH https://orcid.org/0000-0003-4726-9886; HE https://orcid.org/0000-0001-8503-061X; VO https://orcid.org/0000-0002-9784-6779

Correspondence: Zeynep Tuncer Issı; Email: zzeyneptuncer@gmail.com.

Conflict of interest: There is no conflict of interest to declare.

Authors' contributions: All authors: contributed to the study conception and design, commented on previous versions of the manuscript and read and approved the final manuscript, material preparation, data collection and analysis were performed; ZTI: write the first draft of the manuscript.

Received on December 12, 2020; Received in its final form on February 19, 2021; Accepted on March 22, 2021.

CC BY

The latest MOH criteria were published in the third edition of the International Classification of Headache Disorders (ICHD-3) (Table 1). MOHs are headaches that last for at least 15 days each month and patients should have had excessive medication for at least 3 months. Most of the times, these headaches disappear after the cessation of medication[3,4].

Studies performed with the new criteria based on the methods used in previous studies will be useful for future population-based prevalence studies. There are still gaps in MOH's global prevalence prediction[1,5,6]. The prevalence rates of MOH in adults generally range from 0.5 to 2.6% (with different rates such as 4.9% reported by Shahbeigi et al.[5] and 7.2% reported by Ayzenberg et al.[6]).

Different pathophysiologic mechanisms are thought to play a role in the development of MOH. Genetic factors, suppression of the antinociceptive system, decrease and loss of function in trigeminal ganglion serotonin receptors as a result of chronic triptan use, decrease in serotonin synthesis in the dorsal Raphe nucleus, and a serotonin transporter protein gene polymorphism are among hypotheses. There is growing evidence that central sensitization plays an important role in the pathophysiology of chronic headache[7,8,9,10,11,12].

Risk factors for MOH development have been evaluated in cohort studies. In general, compared with patients with episodic migraine, patients with migraine and MOH are more likely to be of the female sex, have lower levels of educational attainment, be married, be unemployed, have migraine remission during pregnancy, be menopausal, have constipation, not use oral contraceptives, have higher use of healthcare resources, and be on polypharmacy compared with patients with episodic migraine. Patients with MOH have lower incomes and lower levels of education than the general population[13].

The most important factor in the development of MOH is the lack of awareness and understanding on the part of patients and physicians. If MOH is clinically suspected, it can only be retrospectively verified. Diagnosis may take longer than three months because prolonged observation is needed after the medication has been discontinued[14].

Psychological factors, especially patient anxiety, are important factors of MOH. Migraineurs use drugs for prophylactic purposes unnecessarily, even though most do not have frequent attacks, because they fear that migraine may cause labor loss or hinder their social activities[7]. Most analgesic combinations include barbiturates or caffeine and can predispose to physical or psychological addiction. A recent population-based study has shown that caffeine can be a moderate risk factor for chronic headaches and combinations containing caffeine should not be used[15].

There are no studies on this subject in Turkey. Thus, the aim of was to investigate awareness of MOH through a survey conducted among medical doctors on our university campus.

Table 1. Third edition of the International Classification of Headache Disorders.

ICHD-3 diagnostic criteria of MOH
A. Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder.
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache. – Regular intake of opioids, ergotamine or triptans on ≥10 days per month; – Regular intake of non-opioid simple analgesics on ≥15 days per month; – Regular intake of multiple drug classes or combination analgesic use ≥10 days per month without overuse of any individual drug.
C. Not better accounted for by another ICHD-3 diagnosis.

ICDH-3: Third Edition of the International Classification of Headache Disorders; MOH: medication overuse headache.

METHODS

This was an observational cross-sectional study about MOH awareness in the Dokuz Eylül University Health Campus, İzmir, Turkey. The number of medical doctors working on campus was provided from the administrative unit. A total of 1,170 medical doctors in the Health Campus were stratified according to their duties. In cases where the frequency was unknown, 50% frequency level and 5% error margin were accepted and it was calculated that at least 289 people should be included at a 95% confidence interval (95%CI). Considering the possible losses, the number of physicians to be surveyed was planned to be approximately 300, stratified by the number of professors, associate professors, assistant associate professors (a degree between professor and associate professor in Turkey), specialists, and residents in each department using the stratified sampling method. The doctors working in the Department of Neurology were excluded from the study due to a high expected awareness.

A total of 18 questions were prepared and distributed on a voluntary basis to obtain information about MOH awareness. Permission to perform the survey was obtained from the Dokuz Eylül University, Faculty of Medicine. The study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University in March 2016.

The surveys were completed at the end of May 2016. An informed consent was obtained from all subjects when they were enrolled. Participants had a right to decline participation or to turn down specific questions without having to give any explanation. The questionnaire was administered by doctors in a study room. The purpose of interview was explained and the interview lasted from 5–15 minutes. All respondents were asked background questions concerning sex, age, educational level, and the faculty they graduated from. Then, they were asked if anyone in their family had headaches, and if they did, what the frequency of the

headaches was. Questions were asked about analgesic preferences, the reason for the preference, the frequency of use, and the side effects. Later, they were asked if they had heard about MOH, which analgesics were used and how often were they used to cause this condition, and the answers were noted. We wanted to confirm whether they had heard of MOH or if they were aware of the circumstances that led to it.

The results are presented as means and standard deviations (SD) or 95%CIs. The differences between means were tested using the independent samples t-test. The percentages were compared using the Pearson chi-square or *Odds Ratios* (ORs). The significance level was set to $p<0.05$. All statistical analyses were performed using the IBM SPSS software version 22.0.

RESULTS

A total of 312 medical doctors were surveyed, including 198 (63.5%) from internal medical sciences, 81 (26%) from surgical medical sciences, and 33 (10.5%) from basic medical sciences. Of the physicians surveyed, 149 (48%) were female and 163 (52%) were male. MOH awareness was similar between the sexes. The age ranged from 23 and 64 years, with an average of 37.44±11.32 years. According to their duties, 89 were full professors, 31 were associate professors, 10 were assistant professors, 39 were specialists, and 143 were residents.

Eighty-eight percent of participants reported having headaches, and 57.4% reported at least one person in their family having headaches. The frequency of physicians with symptoms of headache is shown in Table 2.

Simple analgesics were most commonly used medication, and ergotamine, triptan, opioid, and combined analgesics were used less frequently. Of the participants, 51% used analgesics for headaches and other pains, 25.6% used analgesics only for headaches, and 15.7% for pains other than headaches; 7.4% did not use analgesics. The frequency of analgesic use is given in Table 3.

Bleeding (88.8%), gastric ulcer (95.2%), kidney damage (88.5%), liver damage (84.9%), and rash (72.8%) were the most common adverse effects; anemia (38.8%), anorexia (30.1%), headache (42.6%), and palpitation (26%) were the less common. Forty-nine percent of the physicians in our sample were unaware of MOH. The answers to our question about what frequency of medication use causes headaches are presented in Table 4.

Physicians who had had a headache before and those whose family members (at least one person) had experienced a headache were more aware of MOH. Physicians with headaches were significantly more aware of MOH than those without headaches (54.2 and 35.1%, respectively). Awareness of MOH was similar between the sexes (53.7 for women and 50.3% for men).

Younger physicians and those at the beginning of their career were more aware of MOH than older physicians and residents were more aware of MOH than specialists.

There was no significant difference in MOH awareness between physicians who graduated from medical schools in major cities such as Izmir, Ankara, and Istanbul, and physicians who graduated from more peripheral medical schools ($p=0.245$).

DISCUSSION

Epidemiological studies show that painkiller drugs are used excessively and unnecessarily all over the world, most notably in developing countries. According to data, 1–3% of the general population use analgesics every day, and 7% use

Table 2. Frequency of physicians who reported headaches.

	Number of individuals	Percentage
Less than 1 day in a month	37	11.9
1–2 days in a month	121	38.8
1–3 days in a week	113	36.2
4–5 days in a week	37	11.9
6–7 days in a week	2	0.6
Total	312	100

Table 3. Frequency of analgesic use.

	Number of individuals	Percentage
No use	23	7.4
Less than 1 day in a month	117	37.5
1–2 days in a month	126	40.4
1–3 days in a week	38	12.2
4–5 days in a week	3	1
6–7 days in a week	5	1.6
Total	312	100

Table 4. Answers to our question about what frequency of medication use causes headaches.

	Number of individuals	Percentage
I have no idea	153	49
More than 1 day in a week	11	3.5
More than 2 days in a week	41	13.1
More than 10 days in a month	43	13.8
More than 15 days in a month	33	10.6
Every day	31	9.9
Total	312	100

analgesic at least one day every week. Considering the secondary effects of chronic drug use on other organ systems (chronic renal failure due to combined analgesics, gastrointestinal ulcers due to NSAIDs), it is clear that MOH is a serious health problem globally[7,8,16].

Our results showed that MOH awareness among medical doctors was quite low. Only half of the physicians were aware of this condition. Although awareness was higher among younger physicians who just started the profession, it was still below what it should be.

It is important to note that the assessment of MOH in one Hospital in Turkey, may not be representative of the entire country.

In a study conducted in adults with home interviews in Turkey, the prevalence of MOH was 2.2% in women and 0.6% in men. Although MOH is common in middle-aged people especially women, the increasing recognition of MOH, even in adolescents, increases the importance of the subject. MOH is found in 4% of patients who come to neurology outpatient clinics with headaches in Turkey[17-19].

In 2012, Ertas et al. showed that the prevalence of headache between the ages of 18–65 years was 45–57.5%[18]. In another study performed on 459 individuals in Eskişehir, the prevalence of headache was 78.2%[20]. In a study conducted in rural areas with 11,549 individuals, the prevalence of headache was 42.8%[21]. In our study, the prevalence of headache among medical doctors was 88.1%, which was higher than the prevalence in Turkey, and the prevalence of headache in the family was 57.4%, which was more consistent with the prevalence in Turkey. In a study conducted in Oman, the prevalence of headache among 403 medical students was 98.3 and 96.8% among women and men, respectively, and similar to our study, and the prevalence of a family history of headache was 57.6%[22]. Although the prevalence of headache in our study was higher than that of general population, and despite the prediction that the physician population might be more prone to MOH due to easy drug access, it was surprising that only half of the physicians were aware of MOH.

Although access to drugs is easier for physicians, 40.4% of participants used drugs only 1–2 days per month, and 37.5% used in less than 1 day per month. We think that the low use of drugs despite the high headache prevalence in our study protected participants from MOH, despite the fact that they were unaware of MOH.

In the early 1980s, it was thought that only ergotamine could cause MOH; however, it was later determined that all analgesics, especially combined ones, could cause MOH.

The distribution of the drugs used by patients with MOH varies according to the period of studies and different regions. In a 2015 study conducted by Westergaard et al. İn Denmark, the most used medication was NSAIDs[23]. In a study in Spain that included 4,855 individuals over the age of 14 years, the most used medication was paracetamol (54%)[24]. Triptans and ergotamine are thought to cause MOH more than simple analgesics[25]. Simple analgesics must be used for longer periods and in larger amounts than others to cause MOH[24,26-28]. However, there are conflicting results about the shorter duration of time required for ergotamine and triptans to cause MOH[13]. In a population-based study in the United States of America, only opioids and barbiturates were shown to play a significant role in the development of chronic headache, including MOH[27]. Considering that up to 90% of patients with MOH take more than one drug for acute attack treatment, it is not possible to determine and distinguish the different characteristics of MOH subtypes according to medication overuse[13].

Triptans cause MOH more often in affluent countries[29,30]. Progression to MOH was shorter (1.7 years) in triptan users than in ergotamine (2.7 years) and analgesic (4.8 years) users[28]. Fortunately, withdrawal headaches are shorter for triptans and less treatment is needed during the detoxification period[31]. Caffeine, a non-selective adenosine receptor antagonist, promotes chronic headache through a possible modulation effect in neuronal-glial and vascular functions[3,15].

Overuse of general medication is defined as the foremost risk factor for MOH. In a large-scale study conducted in Norway, the risk of developing chronic headaches in patients with back pain was investigated. Weekly or daily analgesic users had a higher risk of developing chronic migraine, chronic non-migraine headache, and chronic neck pain in the follow-up. In a study conducted by Katsavara et al., chronic headache was found to be 20 times higher in those who used monthly acute headache treatment drugs for more than 10 days per month than those who used them for less than 5 days per month[12,32.]

In our study, it was observed that simple analgesics were used more frequently, and ergotamine, triptan, opioid, and combined analgesics were used less frequently. The most commonly used drug was paracetamol, followed by NSAIDs. Although drug adverse effects were generally known, there was no awareness of sensorial neuropathy or cognitive slowness, which are specific abnormal conditions due to medication overuse.

In our study, 312 physicians were included and the percentage of awareness of MOH was 50.9%. In a study conducted by Lai et al. at Birmingham University, the awareness of MOH was found in 38% of individuals with health education[33]. Increased international awareness about the correct use of analgesics is important for prevention efforts against MOH [23].

The primary approach in MOH management is based on the discontinuation of overused medication[14]. Although there is limited evidence, headache experts recommend withdrawal therapy in MOH. The purpose of this treatment is to detoxify patients, stop chronic headaches, and provide responsiveness to acute or prophylactic medications[13].

Comorbidities have become an important factor in epidemiologic studies of headache. Subclinical obsessive-compulsive disorder is more common in patients with MOH than

in patients with episodic or chronic migraine. Anxiety and mood disorders are also more common in people with MOH. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4), two-thirds of patients with overuse of analgesic and acute migraine drugs meet the criteria for substance abuse disorders[17,34]. In patients with MOH, disability, depression, and anxiety can be further reduced by detoxification and prophylactic treatment[35]. The need for effective protection strategies such as behavioral therapies and early initiation of prophylactic drugs are emphasized. The role of different types of psychotherapy interventions is still unclear. Prospective treatment studies should compared drug, non-drug, and combination treatments[13].

Patients with MOH are more likely to have poorer quality of life than patients with episodic headaches or even daily chronic headaches[36]. MOH is an expensive disease that places a heavy economic burden on society. Some of MOH's financial impact include loss of work days, emergency department visits, getting permission from work for hospital visits, and unnecessary tests[29].

Diener et al. performed a systematic literature review with 7 PICO questions (P = population, I = intervention, C = control O = outcome) about information and education effectiveness for the prevention of MOH, pharmacological preventive therapy, education and counselling, preventive medical and non-medical treatment effectiveness, withdrawal from overused medications, and symptoms that subjects with MOH develop during medication withdrawal and also relapse after successful treatment of MOH[37].

A study on undergraduates found that 77% of the respondents had no awareness of MOH. Awareness of MOH was significantly higher in undergraduates in the field of health education (37.6%) than in other undergraduates (13.6%) in a survey performed on 485 undergraduates, 41% of whom were in the field of health education[33]. In a Norwegian study in which staff from 17 neurological departments participated, 143 of whom responded (86%), one third wrongly stated that the use of the most common headache prophylactics could lead to MOH[38].

After a four-month campaign for awareness of MOH in Denmark, Carlsen et al. concluded that large-scale awareness campaigns should be conducted using different communication technologies and collaborating with networks of health professionals and patient organizations. In that study, there was an increase in the percentage of people who were aware of MOH after the campaign (from 31 to 38%)[39].

Prevention of MHO, which leads to both material losses and deterioration of quality of life, should be the main goal, which is not possible without awareness of MOH. Without awareness, the diagnosis of MOH can be overlooked and treatment delayed, even with the most optimistic view. In order to prevent this and raise awareness of MOH among medical doctors, it is necessary to place more emphasis on this issue in medical education and to increase the frequency of in-service training.

References

1. Westergaard ML, Hansen EH, Glumer C, Olesen J, Jensen RH. Definitions of medication-overuse headache in population-based studies and their implications on prevalence estimates: a systematic review. Cephalalgia. 2014 May;34(6):409-25. https://doi.org/10.1177/0333102413512033
2. Munksgaard SB, Jensen RH. Medication overuse headache. Headache. 2014 Jul-Aug;54(7):1251-7. https://doi.org/10.1111/head.12408
3. Cheung V, Amoozegar F, Dilli E. Medication overuse headache. Curr Neurol Neurosci Rep. 2015 Jan;15(1):509. https://doi.org/10.1007/s11910-014-0509-x
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211. https://doi.org/10.1177/0333102417738202
5. Shahbeigi S, Fereshtehnejad SM, Mohammadi N, Golmakani MM, Tadayyon S, Jalilzadeh G, et al. Epidemiology of headaches in Tehran urban area: a population-based cross-sectional study in district 8, year 2010. Neurol Sci. 2013 Jul;34(7):1157-66. https://doi.org/10.1007/s10072-012-1200-0
6. Ayzenberg I, Katsarava Z, Sborowski A, Chernysh M, Osipova V, Tabeeva G, et al. The prevalence of primary headache disorders in Russia: a countrywide survey. Cephalalgia. 2012 Apr;32(5):373-81. https://doi.org/10.1177/0333102412438977
7. Kendir Ai, Beckmann Y, Seçil Y, Eryaşar G, Başoğlu M. İlaç Aşırı Kullanım Baş Ağrısı Klinik ve Tedavi Özellikleri. Turkiye Klinikleri J Neur. 2009;4(3):122-7.
8. Diener H-C, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol. 2004 Aug;3(8):475-83. https://doi.org/10.1016/S1474-4422(04)00824-5
9. Reuter U, Salomone S, Ickenstein G, Waeber C. Effects of chronic sumatriptan and zolmitriptan treatment on 5-HT1 receptor expression and function in rats. Cephalalgia. 2004 May;24(5):398-407. https://doi.org/10.1111/j.1468-2982.2004.00683.x
10. Tohyama Y, Yamane F, Fikre Merid M, Blier P, Diksic M. Effects of serotine receptors agonists, TFMPP and CGS12066B, on regional serotonin synthesis in the rat brain: an autoradiographic study. J Neurochem. 2002 Mar;80(5):788-98. https://doi.org/10.1046/j.0022-3042.2002.00757.x
11. Park JW, Kim JS, Kim YI, Lee KS. Serotonergic activity contributes to analgesic overuse in chronic tension-type headache. Headache. 2005 Oct;45(9):1229-35. https://doi.org/10.1111/j.1526-4610.2005.00247.x
12. Katsarava Z, Jensen R. Medication-overuse headache: where are we now? Curr Opin Neurol. 2007 Jun;20(3):326-30. https://doi.org/10.1097/WCO.0b013e328136c21c
13. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol. 2010 Apr;9(4):391-401. https://doi.org/10.1016/S1474-4422(10)70008-9
14. Smith TR, Stoneman J. Medication overuse headache from antimigraine therapy: clinical features, pathogenesis and management. Drugs. 2004;64(22):2503-14. https://doi.org/10.2165/00003495-200464220-00002

15. Scher AI, Stewart WF, Lipton RB. Caffeine as a risk factor for chronic daily headache: a population-based study. Neurology. 2004 Dec;63(11):2022-7. https://doi.org/10.1212/01.wnl.0000145760.37852.ed

16. Colás R, Munoz P, Temprano R, Gomez C, Pascual J. Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology. 2004 Apr;62(8):1338-42. https://doi.org/10.1212/01.wnl.0000120545.45443.93

17. Orhan EK, Baykan B. Ilaç Asiri Kullanimi Basagrisi: Sik Ve Önlenebilir Bir Basagrisi Nedeni/Medication Overuse Headache: The Reason of Headache That Common and Preventable. Noro-Psikyatri Arsivi. 2013;50(Suppl 1):47. https://doi.org/10.4274/Npa.y7264

18. Ertas M, Baykan B, Orhan EK, Zarifoglu M, Karli N, Saip S, et al. One-year prevalence and the impact of migraine and tension-type headache in Turkey: a nationwide home-based study in adults. J Headache Pain. 2012 Mar;13(2):147-57. https://doi.org/10.1007/s10194-011-0414-5

19. Baykan B, Ertas M, Karli N, Akat-Aktas S, Uzunkaya O, Zarifoglu M, et al. The burden of headache in neurology outpatient clinics in Turkey. Pain Pract. 2007 Dec;7(4):313-23. https://doi.org/10.1111/j.1533-2500.2007.00154.x

20. Arslantas D, Tozun M, Unsal A, Ozbek Z. Headache and its effects on health-related quality of life among adults. Turk Neurosurg. 2013;23(4):498-504. https://doi.org/10.5137/1019-5149.JTN.7304-12.0

21. Benbir G, Karadeniz D, Göksan B. Türkiye'nin doğu ve kırsal kesiminde yaşa ve cinsiyete göre baş ağrısı özellikleri ve alt tipleri. Ağrı. 2012;24(4):145-52. https://doi.org/10.5505/agri.2012.85579

22. Deleu D, Khan M, Humaidan H, Al Mantheri Z, Al Hashami S. Prevalence and clinical characteristics of headache in medical students in Oman. Headache. 2001 Sep;41(8):798-804. https://doi.org/10.1046/j.1526-4610.2001.01146.x

23. Westergaard ML, Hansen EH, Glümer C, Jensen RH. Prescription pain medications and chronic headache in Denmark: implications for preventing medication overuse. Eur J Clin Pharmacol. 2015 Jul;71(7):851-60. https://doi.org/10.1007/s00228-015-1858-3

24. Feinstein AR, Heinemann L, Dalessio D, Fox JM, Goldstein J, Haag G, et al. Do caffeine-containing analgesics promote dependence? A review and evaluation. Clin Pharm Therap. 2000 Nov;68(5):457-67. https://doi.org/10.1067/mcp.2000.110974

25. Dodick DW, Silberstein S. How clinicians can detect, prevent and treat medication overuse headache. Cephalalgia. 2008 Nov;28(11):1207-17. https://doi.org/10.1111/j.1468-2982.2008.01737.x

26. Evers S, Gralow I, Bauer B, Suhr B, Buchheister A, Husstedt IW, et al. Sumatriptan and ergotamine overuse and drug-induced headache: a clinicoepidemiologic study. Clin Neuropharmacol. 1999 Jul-Aug;22(4):201-6.

27. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. Headache. 2008 Sep;48(8):1157-68. https://doi.org/10.1111/j.1526-4610.2008.01217.x

28. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener H-C. Features of medication overuse headache following overuse of different acute headache drugs. Neurology. 2002 Oct;59(7):1011-4. https://doi.org/10.1212/wnl.59.7.1011

29. Da Silva AN, Lake III AE. Clinical aspects of medication overuse headaches. Headache. 2014 Jan;54(1):211-7. https://doi.org/10.1111/head.12223

30. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. Neurology. 2008 Nov;71(22):1821-8. https://doi.org/10.1212/01.wnl.0000335946.53860.1d

31. Katsarava Z, Fritsche G, Muessig Ma, Diener H, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology. 2001 Nov;57(9):1694-8. https://doi.org/10.1212/wnl.57.9.1694

32. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J. Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. Neurology. 2003 Jul;61(2):160-4. https://doi.org/10.1212/01.wnl.0000069924.69078.8d

33. Lai JT, Dereix JD, Ganepola RP, Nightingale PG, Markey KA, Aveyard PN, et al. Should we educate about the risks of medication overuse headache? J Headache Pain. 2014 Feb;15(1):10. https://doi.org/10.1186/1129-2377-15-10

34. Hagen K, Linde M, Steiner T, Zwart JA, Stovner L. The bidirectional relationship between headache and chronic musculoskeletal complaints: an 11-year follow-up in the Nord-Trøndelag Health Study (HUNT). Eur J Neurol. 2012 Nov;19(11):1447-54. https://doi.org/10.1111/j.1468-1331.2012.03725.x

35. Bendtsen L, Munksgaard S, Tassorelli C, Nappi G, Katsarava Z, Lainez M, et al. Consortium COMOESTAS: Disability, anxiety and depression associated with medication-overuse headache can be considerably reduced by detoxification and prophylactic treatment. Results from a multicentre, multinational study (COMOESTAS project). Cephalalgia. 2014 May;34(6):426-33. https://doi.org/10.1177/0333102413515338

36. Lantéri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia. 2011 May;31(7):837-50. https://doi.org/10.1177/0333102411398400

37. 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 Jul;27(7):1102-16. https://doi.org/10.1111/ene.14268

38. Kristoffersen ES, Faiz KW, Winsvold BS. Neurology residents' knowledge of the management of headache. Cephalalgia. 2019 Oct;39(11):1396-406. https://doi.org/10.1177/0333102419847973

39. Carlsen LN, Westergaard ML, Bisgaard M, Schytz JB, Jensen RH. National awareness campaign to prevent medication-overuse headache in Denmark. Cephalalgia. 2018 Jun;38(7):1316-25. https://doi.org/10.1177/0333102417736898