Opioids and Migraine: Opioid Awareness and Frequency of Use among Turkish Migraineurs

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Abstract. Despite the inadequate evidence of efficacy and safety of opioid use for the treatment of migraine, it has been reported that patients with moderate to severe migraine headaches are prescribed opioids. Migraineurs may experience serious health impacts from opioids such as headache-related disability, psychiatric and cardiovascular comorbidities. The reduction of the risk of opioid abuse and prevention of an opioid epidemic are important public health challenges. The aim of this study was to assess the awareness of opioid therapy for migraine and the frequency of use among Turkish patients with episodic and chronic migraine. Materials and methods: consecutive migraine patients were enrolled in this cross-sectional study. A semi-structured questionnaire was developed and used by the researchers to assess the patients’ awareness of an opioid treatment option and the frequency of use of opioids for migraine treatment. Results. One hundred two patients were enrolled, of which 72 had episodic migraine and 30 had chronic migraine. All subjects reported that they had not been offered or prescribed any kind of opioids by general practitioners and neurologists for their headache. Besides, only 7 % of patients declared that they had heard of opioid treatment for migraine but they had never consulted their doctors about its effects. Conclusions. Our findings demonstrated that opioids were not preferred as an option for acute or preventive migraine treatment by Turkish migraineurs and their physicians. The reduction of opioid prescription will help to prevent the development of medication overuse and opiate-induced headaches and drug addiction.

Key words: opioid; migraine; headache; episodic migraine; chronic migraine; prescription; drug abuse; drug addiction; frequency of use

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Мигрень является одной из самых частых патологий неврологической сферы с высоким социоэкономическим бременем. Даже несмотря на то, что механизм патогенеза мигрени не полностью понят, известно, что триттеры мигрени включают в себя изменения в сердечно-сосудистой системе, глубокие и субдуральные структуры [1, 2]. Патогенез мигрени и клинические характеристики могут варьироваться от пациента к пациенту и от приступа к приступу [3]. Многие анальгетики, включая нестероидные противовоспалительные препараты (NSAIDs), мигрени профилактика зависит от таких препаратов как бета-блокеры, антиконвульсанты, антидепрессанты, и наоботуллинум токсин А [4]. Фактическое интенсивное использование в течение 3 недель может быть оценено при помощи 1-10 балльной шкалы. В исследовании приняли участие 102 пациента, из них 72 — с эпизодической мигренью и 30 — с хронической мигренью. Мы исследовали частоту использования опиоидных препаратов и информированность о применении опиоидов у турецких пациентов с мигренью. Выводы: изучение и оценка безопасности и риска фармакотерапии. 2019;7(3):139–145. https://doi.org/10.30895/2312-7821-2019-7-3-139-145

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**MATERIALS AND METHODS**

**Study population and design**

Исследование протокол было утверждено Рабочей группой по этике Региональной группы University of Health Sciences, Sisli Hamidiye Etfal Research and Training Hospital and carried out in accordance with the Declaration of Helsinki. Written informed consent were obtained from all the participants. In this cross-sectional, clinic-based study, patients older than 18 years with episodic migraine (n = 72) and chronic migraine (n = 30) who had been followed in a neurology outpatient clinic from August 2018 to December 2018 were recruited prospectively. The diagnosis of headache was made based on neurologist examination, neuroimaging studies, and all the diagnoses were made according to The International Classification of Headache Disorders, 2018 (ICHD-3) [10].

Данные на демографических и клинических характеристиках, такие как возраст, пол, уровень образования, уровень работы, дневная физическая активность, наличие головной боли, тяжесть головной боли (по шкале 1-10), частота и тип головной боли в днях, присутствие медикаментозного наркоза, и тип лечения были отмечены. Результаты всех исследований в клинических и нейрологических исследованиях были нормальными. Пациенты, которые были ранее диагностированы с помощью любой другой хронической боли (например, неврологических расстройств, другой мигрени, эндокринных расстройств, неврологических расстройств, рака, и т. д.), пациенты с другими типами головной боли, а также пациенты с коморбидными расстройствами мигрени, такие как мигрень с напряжением, тоннель-тип головной боли или другие типы головной боли, были исключены.
The researchers relied on their professional experience to develop a semi-structured questionnaire consisting of 4 questions related to the aim of this study. The survey was conducted to assess the patients’ awareness of opioid treatment and the frequency of opioid use for migraine.

The questions are listed below:
1. Do you know any prescription opioids used for pain relief?
2. Do you know any prescription opioids used for migraine type headaches?
3. Would you consider using opioid therapy for your migraine headache if it was prescribed by your doctor?
4. Have you been prescribed opioids for your migraine headache?

Statistical Analysis
Statistical analysis was performed using SPSS Statistics for Windows, version 23.0 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics (mean, standard deviation, and frequency) were used to assess the demographic and clinical characteristics. Student’s t-test was used to compare the mean values obtained for the two patient groups. The Chi-square test was used for categorical variables. A p value of <0.05 was considered to be statistically significant.

RESULTS

One hundred two patients were enrolled, of which 72 had episodic migraine and 30 had chronic migraine. The mean age of the patients was 38.22 ± 9.06, 79 % of the patients were female. Twenty-three patients with chronic migraine had medication overuse headache (MOH). There were no statistically significant differences in age, gender, education level, marital status, income, duration of migraine between the episodic and chronic migraine groups (all p values > 0.05). Details of demographic and clinical characteristics of the subjects are given in Table 1.

The most commonly used analgesic for acute migraine attack treatment was paracetamol followed in order of frequency by non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and caffeine combination tablets, and triptans. In the chronic migraine group, beta blockers (propranolol and metoprolol) were the most commonly used drugs for preventative treatment of migraine followed in order of frequency by antiepileptic drugs (topiramate, sodium valproate and lamotrigine), antidepressants (amitriptyline and venlafaxine), botulinum toxin injections, anesthetic blockade of the greater occipital nerve, and calcium channel blockers (flunarizine). Acute and preventive migraine treatments used by all the patients including the patients with chronic migraine are listed in Table 2.

According to the guidelines of the Turkish Ministry of Health on the prescription of opioids, both specialists and general practitioners are allowed to prescribe opioids. All the subjects who took part in the study reported that they had not been offered or prescribed any kind of opioids by general practitioners, emergency physicians and neurologists for their headache. Besides, only 8 (7 %) patients declared that they had heard about the use of opioids for the treatment of migraine but they had never consulted their doctors about this. Table 3 summarises the responses of episodic and chronic migraine patients to the questionnaire aimed at assessing the patients’ awareness of an opioid treatment option and the frequency of opioid use for migraine treatment.

Table 1. Demographic and clinical characteristics of the patients with episodic and chronic migraine

| Characteristics of the patients | Episodic migraine | Chronic migraine | P value |
|---------------------------------|-------------------|------------------|--------|
| Number                          | 72                | 30               | -      |
| Age (years)                     | 36.7 ± 12.1       | 42.8 ± 11.4      | 0.178* |
| Gender (female/male)            | 57/15             | 23/7             | 0.065**|
| Education                       |                   |                  |        |
| Primary school                  | 22                | 11               | 0.719**|
| High school                     | 24                | 9                |        |
| University                      | 26                | 10               |        |
| Income                          |                   |                  |        |
| None and minimum wage           | 38                | 18               | 0.316**|
| More than minimum wage          | 34                | 12               |        |
| Marital status                  |                   |                  |        |
| Single                          | 29                | 8                | 0.172**|
| Married                         | 43                | 22               |        |
| Duration of headache (years)    | 13.68 ± 5.78      | 14.5 ± 6.22      | 0.231* |
| Number of headache days per month| 4.1 ± 2.9        | 21.2 ± 4.8       | 0.012* |

Note. * Student’s t-test was used for comparison of the mean values.
** The Chi-square test was used for categorical variables.

Примечание. * Для сравнения средних величин использовали t-критерий Стьюдента.
** Для категориальных переменных использовали критерий хи-квадрат.
DISCUSSION

The results of our study demonstrated that opioid therapy was not used as an option for acute or preventive migraine treatment by Turkish migraineurs. Furthermore, it was discovered that opioids were not prescribed and used by general practitioners, neurologists and emergency physicians. None of the patients had been prescribed opioids for their headache. This suggests that migraine chronicity had no connection with opioid use. Some studies report that both patients and physicians tend to avoid such drugs in the treatment of pain due to opioophobia in patients with chronic pain [8, 9, 11]. Opioophobia, defined as the irrational fear and prejudice against using opioids, is found among doctors because of the serious side effect profile of these drugs and the need for close follow-up, and among patients due to their fear of stigmatization and being addicted to the drug [9]. The research on opioophobia in Turkish patients is based on identification of opioid use for managing chronic cancer pain [9, 11, 12]. Although these stud-

### Table 2. Acute and preventive migraine treatments used by the patients

| Drugs for acute migraine attack treatment | All patients* \((n = 102)\) | Drugs for preventive treatment of migraine | Patients with chronic migraine* \((n = 30)\) |
|------------------------------------------|-----------------------------|--------------------------------------|-------------------------------------|
| Paracetamol                              | 54 (53 %)                   | Beta-Adrenergic Blockers             | 10 (33 %)                           |
|                                          |                             | - propranolol                        | 8 (26 %)                            |
|                                          |                             | - metoprolol                        | 2 (7 %)                             |
| Non-steroidal anti-inflammatory drugs    | 42 (41 %)                   | Anti-Epileptic Drugs                | 8 (26 %)                            |
| - ibuprofen                              | 10 (10 %)                   | - topiramate                        | 4 (13 %)                            |
| - etodolac                               | 8 (7 %)                     | - valproate                         | 2 (6 %)                             |
| - flurbiprofen                           | 8 (7 %)                     | - lamotrigine                       | 1 (3 %)                             |
| - diclofenac - Na                        | 5 (6 %)                     | - others                            | 1 (3 %)                             |
| - dexketoprofen                          | 5 (5 %)                     |                                      |                                     |
| - others                                 | 6 (5 %)                     |                                      |                                     |
| Combined analgesics                      | 12 (11 %)                   | Tricyclic antidepressants           | 6 (20 %)                            |
| (paracetamol and caffeine)               |                             | - amitryptiline                     | 6 (20 %)                            |
| Triptans                                 | 10 (9 %)                    | Botulinum toxin injection           | 4 (13 %)                            |
| - eletriptan                             | 6 (5 %)                     | Pericranial nerve blocks            | 4 (13 %)                            |
| - frovatriptan                           | 4 (4 %)                     | Calcium channel blockers            | 2 (6 %)                             |
|                                          |                             | - flunarizine                       |                                     |

*Note. \(n\) — number of patients.
*Some patients had more than one acute and/or preventive treatment.

### Table 3. The responses of the patients with episodic and chronic migraine to the questionnaire on patients’ awareness and use of opioids for their headache

| Questions                                                                 | Patients with episodic migraine \((n = 72)\) | Patients with chronic migraine \((n = 30)\) |
|---------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Names of prescription opioids for pain relief known by patients           | Morphine                                      | Morphine                                    |
|                                                                           | Fentanyl transdermal                         | Fentanyl transdermal                        |
|                                                                           | Tramadol                                      |                                             |
| The number of patients who knew/heard of migraine treatment using opioids | 5 (6 %)                                       | 2 (6 %)                                     |
| The number of patients who might consider using opioids if prescribed by doctors | 70 (97 %)                                    | 30 (100 %)                                  |
| The number of patients who used opioids for migraine                      | None                                          | None                                        |

*Note. \(n\) — number of patients.

### Table 2. Препараты для купирования и профилактики приступов мигрени, используемые пациентами

| Препараты для купирования и профилактики приступов мигрени, используемые пациентами |
|-------------------------------------------|
| All patients* \((n = 102)\) | Drugs for preventive treatment of migraine | Patients with chronic migraine* \((n = 30)\) |
|-------------------------------------------|
| Paracetamol                              | Beta-Adrenergic Blockers                      |
|                                          | - propranolol                                 |
|                                          | - metoprolol                                  |
| Non-steroidal anti-inflammatory drugs    | Anti-Epileptic Drugs                          |
| - ibuprofen                              | - topiramate                                   |
| - etodolac                               | - valproate                                    |
| - flurbiprofen                           | - lamotrigine                                  |
| - diclofenac - Na                        | - others                                      |
| - dexketoprofen                          |                                             |
| - others                                 |                                             |
| Combined analgesics                      | Tricyclic antidepressants                     |
| (paracetamol and caffeine)               | - amitryptiline                               |
| Triptans                                 | Botulinum toxin injection                     |
| - eletriptan                             | Pericranial nerve blocks                      |
| - frovatriptan                           | Calcium channel blockers                      |
|                                          | - flunarizine                                  |

*Примечание. \(n\) — число пациентов.
*Nекоторые пациенты использовали несколько препаратов для купирования и/или профилактики приступов мигрени.*
ies include a number of different research methods and approaches, it can be concluded that over half of the patients with chronic pain have doubts about taking opioids and they are afraid of using morphine for their pain. According to the responses to the questionnaire we developed, a remarkable number of patients with migraine reported that they might use opioids if their doctors advised them to do so. It can be said that opiophobia in migraineurs is less common than opiophobia in patients with cancer pain. This can be explained by different pain mechanisms of migraine and cancer pain, patients’ clinical characteristics, comorbid disorders, cancer patients’ fear, and severity of pain. In addition, this is the first study exploring the frequency of Turkish migraineurs’ use of opioid analgesic drugs for migraine and headache relief. Our patients stated that they had not been informed about such a treatment alternative. The findings of the current study showed that chronicity of migraine, education level, gender, duration of headache, and medication overuse headache did not have any influence on the use of opioids for the acute and preventive (prophylactic) treatment of migraine.

Even though there is not enough evidence, opioids are recommended only as second or third-line therapy for migraine — following simple analgesics, NSAIDs and migraine-specific medications such as triptans for moderate to severe migraine pain, and they should be reserved for emergency department use or rescue medication with limited use [13]. It is reported that opioids are one of the most common medications for acute migraine treatment in the USA and Canada emergency rooms [6, 7]. However, opioid analgesics for migraine treatment are associated with more severe headache-related disability, psychiatric and cardiovascular comorbidities, costs, and greater health-care resource utilization [14]. In a study by S.V. Tornabene et al., the researchers evaluated the use and timing of opioids for the treatment of migraine headaches in the emergency department. They reported that patients who received opioids for headache stayed in emergency rooms longer than patients who did not [15]. T.W. Ho et al. investigated the effects of prior opioid use on rizatriptan efficacy. They demonstrated that prior opioid use was associated with lower triptan response in migraine attacks [16]. S.J. Tepper stated that acute opioid use results in failure of migraine prevention [17]. Moreover, opioids are responsible for migraine progression [14]. EFNS and NICE guidelines do not recommend opioids for acute treatment of migraine [5]. In this study, participants who visited the emergency department at least once for migraine attack treatment reported that they did not receive opioids.

Repeated morphine administration increases levels of calcitonin gene related peptide (CGRP) in the dorsal root ganglia in animal studies [18]. Upregulation of peripheral expression of CGRP in primary afferent neurons of trigeminal ganglion might be the most important reason for increasing levels of pro-nociceptive peptide involved in migraine pathogenesis triggering the frequency of attacks [19]. This mechanism might explain how opioids play a role in the chronification of migraine. It is well established that migraineurs are prone to developing chronic daily headaches namely chronic migraine or chronic tension-type headaches from opioid overuse [20, 21]. In addition, the overuse of opioids for the treatment of migraine is related to medication overuse headache. The use of opioids eight days a month is a risk factor of medication overuse headache [8]. Taking into account that the patients were not offered or prescribed opioid analgesics in the current study, we did not observe any association with chronification of migraine and medication overuse headache.

Awareness and motivation campaigns against excessive opioid use are carried out in written and visual media around the world. Several studies in developed countries have recently highlighted that opioid use is an important public health problem, and stated the necessity of limiting the use of opioids [22–24]. D.C. Buse et al. assessed opioid use and dependence and found that 16.6% of patients with chronic opioid use for migraine treatment met the dependence criteria and that these patients had more hospital admissions with more frequent recurrent complaints [25]. It is advisable that both patients and healthcare professionals should have realistic expectations of the intended benefits of treatment of chronic pain with opioids [26].

**CONCLUSION**

Opioid use is not a viable treatment option for Turkish patients with migraine. In order to raise awareness in our country, efforts are being made in many areas, including social media, to protect young people from such substances and addictions. At the same time, there are substance addiction treatment centres which provide support to individuals who are opioid addicts as a result of medical and non-medical use. As the present study is a single-centre study, its results are limited in scope and offer only a general reflection of the situation. However, our study was the first to evaluate both episodic and chronic migraine patients’ awareness of opioid use in the treatment of migraine and reflected the perspectives of Turkish physicians and patients. Further studies of awareness of the general public and healthcare professionals about opioid use for the management of other headache types is warranted. It would be useful to understand the prevalence of opioid use for migraine treatment in other countries as well as views and opinions of professionals regarding the prescription practice.

1 NICE clinical guideline of management of migraine (with or without aura). 2019. https://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura
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