Investigation of Prophylactic Drug Use Adherence in Patients with Migraine

Migren Hastalarında Profilaktik İlaç Kullanımına Olan Uyumun Araştırılması

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ABSTRACT

Objective: Adherence to drug use; it is a crucial part of patient care and clinical briefing. Non-compliance with prescribed treatment regimens is an important and common behavioral health problem for treating chronic diseases. In our study, we aimed to investigate the rate of adherence to medication use in migraine patients taking prophylactic drugs, the factors affecting it, and the reasons for decreased compliance.

Methods: Eighty patients diagnosed with migraine and using prophylactic treatment for migraine were included in the study. Detailed sociodemographic and clinical histories were obtained at the first interview. The scores obtained by applying the Beck Anxiety and Depression Inventory were recorded for each patient. The patients were evaluated with weekly visits for four weeks; adherence was examined using the tablet counting method.

Results: In our study, 70% of our patients who received prophylactic drugs for migraine were non-compliant with the treatment; it was observed that the three most common causes were forgetting to take medication, drug side effects, and drug expiration. It was observed that low education level, being married, diet and exercise incompatibility, and high sleep problems, depression, and anxiety symptoms affected the adherence to prophylactic drug use in a statistically significant and negative way.

Conclusion: To increase the patient's compliance with the treatment regimen, all potential barriers to compliance must be considered. Measures that consider the factors under the patient's control and the interaction between patient and physician and patient-health care will have the greatest impact on improving adherence. This will lead to better clinical outcomes and decrease morbidity and health expenditures.

Keywords: Migraine, drug, treatment, prophylactic treatment, compliance, tablet counting method, health

ÖZ

Amaç: İlaç kullanımına olan bağlılık; hasta bakımının ve klinik bilgilendirmenin çok önemli bir parçasıdır. Reçete edilen tedavi rejimlerine uyumsuzluk, kronik hastalıkların tedavisinde önemli ve yaygın bir davranışsal sağlık sorunudur. Çalışmamızda profilaktik ilaç kullanan migren hastalarında ilaca uyum oranları, etkileyen faktörler ve azalan uyum nedenlerinin araştırılması amaçlandı.

Yöntemler: Çalışmaya migren tanısı alan ve migren için profilaktik tedavi kullanan 80 hasta dahil edildi. İlk görüşmede detaylı sosyo-demografik ve klinik öykü alındı. Beck Anksiyete ve Depresyon Envanteri uygulanarak elde edilen puanlar her hasta için kaydedildi. Hastalar dört hafta boyunca haftalık ziyaretlerle değerlendirildi; adherans tablet sayma yöntemi ile incelendi.

Bulgular: Çalışmamızın sonucunda migren nedeniyle profilaktik tedavi alan hastalarımızın %70'inin tedaviye uyumsuz olduğu; ilaç kullanımında uyumsuzluğa yol açan en sık 3 sebebin ilaç almayı unutma, ilaç yan etkisi ve ilacın bitmesi olduğu görüldü. Uyuma etki eden faktörlere bakıldığında; eğitim seviyesinin düşüklüğü, evli olmak, diyet ve egzersiz uyumsuzluğu ve uyku problemi, depresyon ve anksiyete belirtilerinin fazla olmasının profilaktik ilaç kullanımına olan uyumu istatistiksel olarak anlamlı şekilde etkilediği görüldü.

Sonuç: Hastanın tedavi rejimini takip etme uyumunu artırmak için uyumun önündeki tüm olası engeller göz önünde bulundurulmalıdır. Uyumun iyileştirilmesinde en büyük etkiyi, hastanın kontrolünde olan faktörleri ve hasta-hekim ve hasta-sağlık hizmetleri arasındaki etkileşimi dikkate alan önlemler alacaktır. Bu, daha iyi klinik sonuçlara ve morbidite ve sağlık harcamalarında azalmaya yol açacaktır.

Anahtar Sözcükler: Migren, ilaç, tedavi, profilaktik tedavi, uyum, tablet sayma yöntemi, sağlık

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INTRODUCTION

Migraine is a multifactorial neurovascular syndrome characterized by headache attacks in individuals with genetic susceptibility (1). Migraine headache, which occurs in approximately 10% of the adult population, is the most common type of headache and ranks first in prevalence among semi-headaches (2). Migraine is seen approximately three times more frequently in women than in men (3). It is most commonly encountered in the second and third decades of life, and the age range within which the attacks are most common is 35-45 years. While the disease usually progresses in attacks, migraines become chronic in approximately 4% of patients (4). Migraine affects people in the most productive period of their lives and therefore causes significant loss of the workforce (5). According to data from the World Health Organization (WHO), migraine is among the top 20 diseases that cause severe loss of work force in the world (6). Migraine imposes heavy financial obligations for countries because of both the loss of workforce and the high cost of treatment. Patients with migraine describe pain attacks of varying severity and frequency. Various treatments, including antihypertensive beta-blockers, antidepressants, anti-epileptic drugs, and anti-CGRP monoclonal antibodies, can be administered for prophylaxis. There is no universally accepted guideline for prophylactic treatment, but patients with 3 attacks per month are generally candidates for prophylactic treatment (4,7). Patient tolerance is an important component of prophylactic treatment success.

Compliance or adherence refers to the course of a patient's prescribed and planned treatment in terms of time, dose, and frequency. Compliance with drug use in chronic treatments has been investigated for many chronic diseases, and poor compliance (<80% of the recommended treatment) has been associated with poor prognosis in many disease groups (8). Treatment compliance is a crucial part of patient care and is indispensable for achieving clinical goals. In a 2003 report on drug compliance published by the WHO, it was concluded that increasing the effectiveness of compliance has positive effects on health and may have a greater impact than specific medical treatments (10). Non-adherence to prophylactic treatments and behavioral lifestyle changes complicate treatment plans and are known barriers to successful treatment responses (11). Adherence or compliance is determined by the proportion of doses received in the schedule, often compared with the drug doses prescribed in a specific period. This rate is observed in observational studies and can be determined by researchers recording the number of drug doses taken by patients or by monitoring systems that determine drug intake. Drug counting by comparing the doses of drugs taken by patients with the amount of drugs prescribed in a given period contributes to accurate measurement of compliance (9). Treatment compliance is important for the success of the treatment of migraine and other headaches, but studies of compliance in cases of migraine and other headaches are insufficient. Research conducted to date has shown that the rates of compliance with both acute and prophylactic migraine treatment are low (12).

According to the WHO, there are many factors that lead to poor treatment compliance and they can be grouped into 5 categories: socio-economic factors, treatment-related factors, patient-related factors, health system- and healthcare-related factors, and disease-related factors (10) (Table 1).

It is difficult to objectively determine the compliance with drug therapy. In defining compliance, direct and indirect methods are used, each with different advantages and disadvantages. Direct methods include the evaluation of blood pressure levels, urinary wastes and breakdown products, drug metabolites, and various other markers, whereas indirect methods include the review of treatment outcome, patient notification, records of the number of drug doses or compliance with appointments, prescription follow-up, and the physician's opinion (13,14).

In the present study, to evaluate the compliance of patients receiving prophylactic migraine treatment, drug counting (number of tablets consumed) was used as an indirect and objective method. This approach makes it possible to cooperate more closely with patients, and if a decrease in compliance was observed upon monitoring drug intake, the reasons for non-compliance were sought.

MATERIALS AND METHODS

Our study was evaluated by the Gazi University Faculty of Medicine Clinical Research Ethics Committee, and ethics committee approval was obtained (approval number: 207, date: 11.04.2016).

Among patients aged 18 years who presented to the General Neurology Outpatient Clinic and Headache Outpatient Clinic of the Gazi University Faculty of Medicine's Neurology Department between 2016 and 2017, 80 patients who were diagnosed with migraine according to the ICHD-III beta diagnostic criteria and received prophylactic treatment for migraine were included in the study. Patients who did not require prophylactic treatment for migraine headaches and received only acute treatment were not included in the study. Patients with secondary headaches who could not attend follow-up appointments or could not be contacted at specified times during the study period were also excluded.

Table 1. Factors affecting adherence to treatment

Categories	Factors
Demographics features	Age, race, gender, occupation, educational status, and health information
Disease	Disease type, duration and severity, presence of complications, frequency of hospital use, satisfaction with healthcare providers, and quality of care
Treatment	Dose, type of drug, presence of other drugs, drug supply, diet required by the treatment, and presence of side effects
Behaviour	Doctor- patient interaction, patient's level of knowledge, illness, and treatment beliefs, caregiver knowledge, and beliefs
Economic features	Economic situation, health insurance and insurance type, and treatment and drug prices

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Eighty patients diagnosed with migraine who met the inclusion criteria were included in the study. Informed consent was first obtained in writing from the patients who agreed to be included in the study, and detailed clinical information was obtained. In the first appointment, patients were interviewed according to this form, which included questions about age, gender, educational status, marital status, duration of illness, frequency of migraine attacks, presence of chronic migraine, duration of headaches, factors that trigger or alleviate headaches, presence of aura and/or prodrome, presence of concomitant diseases, sleep patterns, previous surgery or serious illnesses, smoking, compliance with exercise and healthy diet, total number of drugs used daily, migraine drugs used, and total doses for all drugs for 1 week. Neurological examinations of the patients were performed, and any abnormal findings were recorded. At the same time, the presence of the greater occipital nerve (GON) and trigger point tenderness were examined for each patient. Scores obtained from applications of the Beck Anxiety Scale and Beck Depression Scale were recorded for all patients in the same interviews. One week after the first meeting, patients were interviewed again and the number of drug dosages remaining in their pill boxes or bottles was determined. The same interviews were repeated three additional times at 1-week intervals, and patients were asked the number of remaining drug doses each time. If there were any variations in the patients remaining drug doses during this period, the reasons for the variations were learned and recorded. These reasons included forgetting to take one's medicine, leaving home without drugs, not taking drugs due to side effects, running out of drugs, misunderstanding directions, difficulty in swallowing medicine, doubting the necessity of the drugs, difficult drug use, and dislike of taking medicine. The weekly doses of the drugs used by the patients for migraine headache were calculated and recorded.

Statistical Analysis

Statistical evaluation of the data was performed using IBM SPSS Statistics 23.0. Descriptive and frequency assessments were used to evaluate the patients' demographic data. For age, gender, occupation, marital status, educational status, duration of illness, total number of drugs used daily, number of migraine drugs used daily, types of migraine drugs used, headache duration, and monthly frequency of headache attack, Pearson's chi-square test, Yates' corrected chi-square test, and Fisher's chi-square test were used to compare relationships with migraine type, reasons for dose adjustment, comorbidities, causes of headache relief, exercise and diet compliance, and smoking. The conformity of continuous variables to normal distribution was evaluated using visual methods (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). While statistical analysis of patient groups with and without treatment compliance was performed according to Beck Depression Scale scores, Beck Anxiety Scale scores, and total number of drugs used daily, the Mann-Whitney U test, a non-parametric test, was used for variables that did not show normal distribution. Statistical significance was set at $p<0.05$.

RESULTS

Descriptive Findings

Eighty patients, including 69 women (86.2%) and 11 men (13.8%) aged 20-66 years were included in our study. In terms of occupation, 52.5% of the patients were housewives, 32.5% were employed, 12.5% were students, and 2.5% were retired. Furthermore, 71.2% of the patients were married and 28.8% were single, and 48.7% of the patients were primary school graduates, 20% were high school graduates, and 31.3% were higher education graduates. While 55% of the patients had migraine headaches for ≤10 years, 22.5% had experienced migraines for 11-19 years and 22.5% for 20 years or more. Furthermore, 77.5% of the patients reported migraines without auras and 22.5% had migraines with auras. While migraine headaches progressed as attacks in 90% of the patients, they were continuous in 10%. Prophylactic migraine medication was used by 57.5% of the patients as a single medication per day, and the remaining patients were using additional drugs due to comorbid diseases in addition to preventive migraine medication. In the first clinical interview, 73.8% of the patients who underwent neurological examinations had tenderness in the GON region and many trigger points. It was determined that 48.8% of the patients did not comply with their diets and 51.3% did not exercise. The smoking prevalence was 16.2%. Sleep problems were reported by 56.2% of the patients; most these problems were difficulty in falling asleep, waking up early in the morning, and frequent interruption of sleep during the night. Another comorbid condition accompanied migraines in 37.5% of the patients. Beck Depression Scale scores indicated high-level depressive symptoms for 17.5% of the patients, moderate-level symptoms for 10%, and low-level symptoms for 30%. While 55% of the patients had low anxiety scores, high anxiety scores were obtained for 28.7% and moderate anxiety scores for 16.3%. Among patients using preventive migraine treatment, the most commonly used medication was amitriptyline at a rate of 29.1%, whereas 21.5% of the patients used topiramate, 19.3% used duloxetine, 16.1% used propranolol, and 7.5% used sodium valproate.

Patients were followed for 4 weeks, and it was observed that 30% of the patients had some remaining drug dosages in their pill boxes on a weekly basis that was compatible with appropriate drug use for 4 weeks. The remaining 70% were considered to have had non-compliance with their treatment because they took fewer drug dosages than they should have on a weekly basis (Table 2). During the 4-week follow-up period, patients with treatment non-compliance were asked about the reasons for the fluctuations in their drug dosages. Forgetting to take the medication was the most common reason at a rate of 55.8%. This was followed by drug side effects at a rate of 14.7%, the drug having ended at a rate of 11.3%, leaving home without the medication at a rate of 9%, and dislike of taking medication at a rate of 5.6% (Table 3).

Comparative Statistics

The gender, age, occupation, disease duration, presence of aura, monthly attack frequency, duration of attacks, presence of chronic migraine, smoking, presence of concomitant diseases, presence

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Table 2. Distribution of adherence to drug use by individuals participating in the study

Number		(%)
Compliance with drug use (n=80)		
Non-adherens	56	70.0
Adherens	24	30.0

Table 3. Distribution of reasons for changes in drug dose among individuals participating in the study

Reasons for dose change	Number	(%)
Forget	50	56.8
Side effects	13	14.7
End of the drug	10	11.3
Leaving the house without medication	8	9
Unlike taking medication	5	5.6
Misunderstanding directives	1	1.1
Doubts about the necessity of the drug	1	1.1
Total	88	100

of additional drugs used, and presence of GON and/or trigger point sensitivity were compared between the compliant and non-compliant patient groups. No statistically significant differences were found for any of these variables (p>0.05).

When the compliance statuses of the patients were compared according to marital status, 77.2% of married patients and 52.2% of single patients were found to be non-compliant with the proper usage of medication. Thus, single patients had a higher rate of treatment compliance, and marital status had a statistically significant effect on compliance (p=0.030). Comparing the level of education and compliance with treatment, it was found that 82.1% of primary school graduates and 44% of higher education graduates were non-compliant. The relationship between educational status and compliance was statistically significant, and treatment compliance increased as the level of education increased (p=0.003). While 82.2% of the patients who reported that they had sleep problems were non-compliant with the proper use of medication, 54.3% of the patients without sleep problems were found to be non-compliant, and the relationship between sleep patterns and compliance with preventive drug use was statistically significant (p=0.007). When the compliance statuses of the patients were evaluated according to their diet and exercise habits, 84.6% of the patients who did not pay attention to their diets were found to be non-compliant, and this difference was statistically significant (p=0.021). Similarly, 85.4% of migraine patients who did not exercise were non-compliant with the appropriate use of preventive medication, and there was a statistically significant difference when these patients were compared with those who exercised (p=0.009) (Table 4).

DISCUSSION

In this study, patients who required prophylactic treatment for migraine headaches were evaluated in terms of treatment compliance. We determined compliance with drug use in these patients, the factors affecting compliance, and the reasons for non-compliance. Therefore, we applied the tablet counting method

to the drug dosages of migraine patients receiving prophylactic treatment. Because of the evaluations performed for 4 weeks, it was determined that 70% of our patients were non-compliant with their treatments.

We concluded that the education levels of the patients affected compliance in a statistically significant way. As the level of education increased, treatment compliance also increased (p=0.003). Our findings are in agreement with the results of many other studies. In most previous studies, it was reported that education level affected adherence to medication schedules. In a study conducted by Leopold et al. (15) with patients with Parkinson's disease, many sociodemographic and disease-related factors were examined, as in our study, and it was reported that only gender and education level had significant effects on compliance. As the level of education increased, compliance with appropriate drug dosages also increased (15).

When our patients were evaluated in terms of compliance according to marital status, it was observed that single patients were statistically significantly more compliant with appropriate drug dosages than married patients (p=0.03). We know of no similar study in the literature to date addressing the effect of marital status on treatment compliance.

We also evaluated our patients in terms of the presence of sleep problems, exercise, and dietary habits. In accordance with the literature, the presence of sleep problems, low levels of exercise, and failure to maintain healthy dietary habits decreased treatment compliance among our patients. These findings were statistically significant for sleep problems, exercise, and diet (p=0.007, p=0.009, and p=0.021, respectively). Sleep disorders are common among individuals with migraines and have been found to increase the frequency of migraine attacks. Various sleep problems are frequently reported, particularly in patients with chronic migraine (16). Furthermore, one of the most common modifiable risk factors among migraine patients is obesity, which has been associated with the risk

Table 4. Comparison of patient groups who are compatible and non-compliant with drug use according to educational status, marital status, sleep patterns, and exercise and diet

	Compliance with drug use			
	Non-adherence		Adherence	
	Number	%	Number	%
Educational status (n=80)				
Primary school graduate	32	82.1	7	17.9
High school graduate	13	81.3	3	18.7
High education	11	44.0	14	56.0
p=0.003				
Marital status (n=80)				
Married	44	77.2	13	22.8
Single	12	52.2	11	47.8
p=0.030				
Sleep pattern (n=80)				
No problem	19	54.3	16	45.7
Problem	37	82.2	8	17.8
p=0.007				
Diet compliance status (n=80)				
Not attention	33	84.6	6	15.4
Partially	18	56.3	14	43.8
Attentive	5	55.6	4	44.4
p=0.021				
Exercise status (n=80)				
Not attention	35	85.4	6	14.6
Partially	17	54.8	14	45.2
Attentive	4	50.0	4	50.0
p=0.009				

of chronic migraine, especially in women of reproductive age. There are data supporting the argument that obesity leads to migraine chronicity by causing systemic inflammation and insulin resistance (17). Because obesity is also related to exercise habits, a sedentary lifestyle poses an indirect risk of migraines. Risk factors such as obesity, sedentary lifestyle, and sleep disturbances that complicate migraine control should be recognized and managed immediately to break the vicious cycle that accelerates the recurrence of these headaches. This is even more important considering the low levels of adherence to acute and/or preventive treatment among many migraine patients (18). Cognitive and behavioral interventions can improve patients' quality of life by promoting treatment compliance. In a study by Hepp et al. (19), regardless of the prophylactic agent prescribed for patients with chronic migraine, poor adherence to treatment was reported. At the end of 1 year, the patients' rate of compliance with treatment was found to be between 17% and 20%. Compared with previous studies evaluating compliance among patients with episodic migraines, compliance appeared to be lower among those with chronic migraines (19). Poor habits in terms of diet and exercise and the consequences of those habits increase susceptibility to chronic migraines, as do sleep disturbances, and

make it more difficult for patients to comply with treatment. Overall, the results obtained in this study were compatible with those reported in the literature. Although most our patients had episodic migraines, the high levels of risk factors among our patients seemed to worsen compliance.

Compliance with prophylactic treatment was lower among patients with anxiety and depressive symptoms. The Beck Anxiety Scale and Beck Depression Scale scores of non-compliant patients were higher than those of compliant patients, and the differences were statistically significant (p=0.01 for both). Our findings are consistent with the data of many previous studies. Anxiety and depression adversely affect health and complicate the treatment of different illnesses. Mood disorders that impair an individual's energy, motivation, and cognitive functions may adversely affect the desire to be treated, the ability to continue treatment, and treatment compliance (20). Therefore, cognitive and behavioral interventions may improve treatment compliance and quality of life by improving patients' strategies for coping with psychosocial stress factors (18).

In our study, the reasons for non-compliance with prophylactic treatment among migraine patients were also investigated. The

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most common reason for non-compliance was forgetting to take one's medication, as reported by 56.8% of our patients. This was followed by aversion to the drug's side effects, reported by 14.7%, and expiration of the drug, reported by 11.3%. In a previous survey study, reasons for non-compliance with the appropriate use of drugs in general were questioned and results similar to ours were obtained. The most common reason for non-compliance was forgetting to take the medication (30%), and other reasons were the existence of other priorities (16%), knowingly skipping a dose (11%), lack of knowledge (9%), and emotional factors (7%) (21). In addition, the prescription of complex treatment regimens, insufficient information about side effects and benefits, patient lifestyle, and drug cost have been cited as reasons for non-compliance (22).

Study Limitations

Although the patients included in the present study showed typical demographic and clinical features of migraine patients and thus represented the target population well, the small sample size is a limitation of the study. Another limitation of this study is the tablet counting method used to measure compliance. Regardless of the measurement method chosen, no effort to monitor patients' drug usage at home perfect. Surveys may not accurately capture missed drug dosages or identify dosages taken at inappropriate times. Compliance measurements performed by counting the number of tablets, as we did in the present study, will indicate missed dosages but do not reflect the timing of the dosages (15). In future studies, the use of a combination of measurement methods would help reduce the effect of this limitation.

CONCLUSION

Appropriate compliance with prescribed medications is a crucial part of patient care and an indispensable point in achieving clinical goals because non-compliance leads to inferior clinical outcomes, increased morbidity and mortality rates, and unnecessary health expenditures. In our study, the tablet counting method, which is an indirect and objective measurement method, was used to evaluate the compliance of migraine patients with prophylactic drug treatment. Approximately 25-50% of adult patients with headaches does not comply with preventive treatment. In this study, non-compliance was observed in 70% of migraine patients receiving prophylactic treatment. The higher rate of non-compliance obtained in this study in comparison with the literature may be attributed to the low level of education of most of our patients.

All potential barriers to compliance must be considered to increase the patient's ability to follow the prescribed treatment regimen. Interventions that take into account factors under the patient's control and interactions among the patient, physician, and healthcare system will have the greatest impact on improved compliance. This will lead to better clinical outcomes and decrease mortality, morbidity, and unnecessary health expenditures.

Ethics

Ethics Committee Approval: Our study was evaluated by the Gazi University Faculty of Medicine Clinical Research Ethics Committee, and ethics committee approval was obtained (approval number: 207, date: 11.04.2016).

Informed Consent: Informed consent was first obtained in writing from the patients who agreed to be included in the study.

Authorship Contributions

Concept: E.C., T.T., Design: E.C., T.T., Data Collection or Processing: E.C., Analysis or Interpretation: T.T., Literature Search: E.C., T.T., Writing: E.C., T.T.

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