

Evaluation of patients presenting with headache to the emergency outpatient clinic

Mustafa Ay¹, Veysel Erden²

¹Department of Intensive Care, Antalya Training and Research Hospital, Antalya, Turkiye

²Department of Anesthesiology and Reanimation, İstanbul Training and Research Hospital, İstanbul, Turkiye

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ABSTRACT

Aims: This study aimed to explore the factors contributing to headache presentation in patients by recognizing headache as a symptom of various potential ailments. It is crucial to understand these factors for appropriate assessment and treatment planning in patients with headaches. Additionally, this study investigated patients preferences for headache management, which is an understudied aspect in the field.

Methods: In 2012, a two-month study was conducted at an emergency department outpatient clinic to assess the general characteristics, severity, frequency, duration, and location of headache episodes among patients presenting with headache complaints. The study analyzed various parameters, including the different types of pain, such as throbbing, stabbing, and burning, as well as the impact of headaches on daily performance, medication use, specific medications taken, and alternative treatment methods via a headache questionnaire.

Results: The survey results revealed that 21.7% of the patients described their pain as extremely severe, 52.2% as severe, and 26.1% as distressing. Pain descriptions were predominantly throbbing (79.4%) and pain (62.2%), with sensations of pressure (20%), stabbing (18.3%), pulsating (13.3%), burning (10.6%), and constriction-like a band (2.8%). The localization of pain was bilateral in 15.0% of patients, unilateral in 18.3%, around or behind the eyes in 28.3%, and in the neck or back of the head in 38.3%. Headaches were found to affect the work life of 40.6% of patients, 20% reported no impact, and 39.4% experienced occasional interference. No significant statistical difference was observed regarding the intensity, frequency, and duration of pain, and its impact on work life with respect to sex. The usage of non-prescription medication was high (92.8%), whereas prescription medication usage was 57.8%. Regarding alternative treatment methods, massage therapy was used by 53.6% of the patients and herbal treatments by 17.8%.

Conclusion: This study examined the frequency and handling of headaches among patients visiting an emergency department. The results indicate that headaches affect both sexes equally, with a marginal prevalence in females. To provide better care, addressing patients' preferences and experiences is important. As patients rely on non-prescription medications and alternative therapies, concerns regarding healthcare accessibility arise. A combination of medication management, patient education, and non-pharmacological therapies is necessary to achieve better outcomes and decrease the burden on healthcare systems.

Keywords: Emergency patient, epidemiology, headache, prevalence, headache evaluation

INTRODUCTION

The prominence of headache disorders has escalated significantly in public health discussions, with over a decade and a half of consistent evidence revealing the profound impact of these conditions on individuals, societies, and healthcare systems globally.¹ The Global Burden of Disease (GBD) studies, notably GBD 2010 and GBD 2015, have positioned headaches, particularly tension-type headaches (TTH) and migraines, as leading contributors to global disability-adjusted life years (DALYs), surpassing all other neurological disorders.²

Headaches are one of the most common complaints in emergency departments (EDs), accounting for a notable 1-4%

of all visits. This clinical manifestation ranges from benign to life-threatening, presenting a considerable diagnostic and management challenge for healthcare providers. The urgency and complexity of headache disorders in emergency settings necessitate a comprehensive understanding of their prevalence, diagnostic evaluations, and treatment strategies.^{1,3}

Differentiating primary headache disorders from secondary, potentially life-threatening conditions is crucial and complex in emergency care. Data suggest that secondary headaches, which constitute approximately 5% of severe headache cases in the ED, can be both life threatening and severely disabling.

Corresponding Author: Mustafa Ay, mustafaayidil@hotmail.com

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Despite this, most headaches diagnosed in EDs are benign. A broad range of headache types, coupled with varying presentations and individual patient factors, can complicate the clinical decision-making process. Emergency clinicians must balance the need for immediate diagnostic procedures such as neuroimaging and lumbar puncture against the need for efficient and targeted treatment.^{1,4}

Headache questionnaires are useful tools for epidemiological studies to comprehend the prevalence and impact of headaches on populations. They serve as clinical instruments to obtain detailed information about a patient's headache experiences and differentiate between various types of headaches. The questionnaire followed a systematic approach to collect relevant information for the diagnosis and management of headache disorders. For research purposes, standardized questionnaires are used to quantify the impact of headaches on a patient's quality of life and to measure outcomes in clinical studies.⁵⁻⁸

This study aimed to systematically evaluate the clinical characteristics and treatment methods applied to adult patients presenting with headache complaints to the emergency department via a structured questionnaire. Additionally, we intended to collect the necessary clinical and epidemiological data to overcome the challenges encountered in the diagnosis and management of patients presenting with headaches to the ED.

METHODS

Study Design and Data Collection

A cross-sectional study was conducted by administering a "Headache Questionnaire" to 180 participants who presented to the Emergency Outpatient Clinic of Istanbul Education and Research Hospital between September and October 2012. Individuals with mental retardation, cancer pain, or diagnosed rheumatic diseases were excluded from the study. Demographic characteristics, such as age, sex, and occupation, of the included participants were assessed.

The Headache Questionnaire used for data collection was a brief, easily applicable assessment tool designed to evaluate the severity, frequency, duration, and location of headache episodes. Types of pain (throbbing, pain, weight, stabbing, pulsating, burning, and belt-like), the impact of headaches on daily performance, use of prescription or non-prescription medications, specific medications taken, and the use of alternative treatment methods were among the queried parameters. This questionnaire was administered to patients only once **Table 1**.

Ethical Considerations

Institutional approval was obtained in this thesis study. Ethics committee approval is not required for this study since it is produced from a thesis before 2020. The purpose of the study was clearly explained to the participants by the researcher and written informed consent was obtained. This article has been written in accordance with the principles of the Helsinki Declaration for medical research.

Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In the evaluation of the data, descriptive statistical methods (mean, standard deviation, frequency distributions, and percentage distributions) were utilized in conjunction with chi-square and Fisher's exact tests for comparisons of

qualitative data. The results were considered statistically significant at p of less than 0.05.

Table 1. Headache questionnaire

Patient's name:	Age:	Gender:	Education status:	Job:
1) Describe your typical headache attack.				
2) Number the severity of your pain. No pain (0) Very mild (2-4) Discomforting (5-6) Severe (7-8) Extremely severe(9-10)				
3) How often do your headaches occur? Every day Every week (if every week, how many times a week) Less than once a month				
4) Do your headaches affect your performance at work? Does it prevent you from doing your Daily activities? Yes No Sometimes				
5) How long did your last headache last? Minutes Hours Days				
6) Which of the following best describes your headache? (You can tick more than one option) 1 Weight 2 Throbbing 3 Painful 4 Belt style 5 Burning 6 Palpitating 7 Freezing sensation 8 Stabbing				
7) Where does your pain occur? On both sides of the head On one side of the head Behind or around the eyes. On the neck or back of the head				
8) Is your headache accompanied by any of the following findings? (You can tick more than one option) 1 Nausea 2 Nasal congestion 3 Sensitivity to loud noise 4 Sensitivity to light 5 Dizziness 6 Drooping eyelids 7 Loss of strength 8 Clouding of consciousness 9 Flashes of light 10 Loss of vision 11 Tears 12 Heart palpitations 13 Shortness of breath 14 Numbness, tingling 15 Blurred vision 16 Fatigue 17 Dazed feeling 18 Crying				
9) Which of the following triggers your headache? (You can tick more than one option) 1 Menstrual period 2 Odors 3 Medications. 4 Alcohol 5 Exercise 6 Foods 7 Smoking 8 Changes in weather (Low pressure systems or storms) 9 Stress 10 Other.....				
10) Did you have warning symptoms such as low or high energy, restlessness before your headache? Yes No				
11) Have you had or are you experiencing any of the following? Uncontrolled blood pressure Heart attack or cardiovascular disease Stroke Reynaud's disease Stroke or transient ischemic attack Abnormal heartbeat (arrhythmia) Pregnancy				
12) Which of the following over-the-counter medications did you use for your headache? 1 Acetaminophen 2 Aspirin 3 Ibuprofen 4 Excedrin 5 Naprosyn 6 Paracetamol 7 Other.....				
13) Have you ever used prescribed medication to stop your headache? Which ones did you use? What are the consequences?				
14) Have you ever used prescribed medication to prevent your headache? Which ones did you use? What are the consequences?				
15) Have you tried alternative treatment methods to relieve your headache? 1 Massage therapy Yes, (if yes, did it work?) -No 2 Behavioral therapy Yes, (if yes, did it work?) -No 3 Acupuncture Yes, (if yes, did it work?) -No 4 Herbal treatments Yes, (if yes, did it work?) -No 5 Treatment with spine massage Yes, (if yes, did it work?) -No				

RESULTS

This study included 180 patients presenting with headaches to an emergency outpatient clinic. The cohort comprised of 49 male (27.2%) and 131 female (72.8%). The mean age of the male patients was 42.47 ± 12.72 years, ranging from 20 to 68 years, while the mean age for female patients was 42.06 ± 13.2 years, ranging from 18 to 81 years. Overall, the mean age of all patients was calculated to be 42.17 ± 13.04 years, with an age range of 18 to 81 years.

The distribution of educational status among our patients was as follows: 18 (10.0%) were not literate, 80 (44.4%) had a primary education, 32 (17.8%) had a middle school education, 34 (18.9%) had a high school education, and 16 (8.9%) had university degrees. The occupational distribution was diverse, including 10 (5.6%) retirees, 92 (51.1%) housewives, 31 (17.2%) laborers, 17 (9.6%) civil servants, 6 (3.3%) students, and 24 (13.3%) from the private sector.

In terms of pain severity, 39 patients (21.7%) reported extremely severe pain, 94 patients (52.2%) reported severe pain, and 47 patients (26.1%) described their pain as uncomfortable. When asked about the frequency of headaches, 37 patients (20.6%) reported daily occurrences, 66 (36.7%) weekly, and 77 (42.8%) less than once a month. Regarding the impact of headaches on work performance, 36 (20%) answered 'No, 73 (40.6%) answered Yes, and 71 (39.4%) answered Sometimes'. Duration of the last headache was reported as 'minutes' by 6 patients (3.3%), 'hours' by 120 patients (66.7%), and 'days' by 54 patients (30%).

The types of headaches described were throbbing (79.4%), painful (62.2%), pressure (20%), stabbing (18.3%), pulsating (13.3%), burning (10.6%), and band-like (2.8%). The location of the headaches varied, with 27 patients (15.0%) experiencing bilateral headaches, 33 (18.3%) unilateral, 51 (28.3%) behind or around the eyes, and 69 (38.3%) in the neck or back of the head.

The distribution of comorbid diseases and the events triggering the headache were investigated and are presented in Table 2 and Table 3.

Table 2. Distribution of diseases and conditions accompanying headache

Condition/disease	n	%
Hypertension	40	22.2
Cardiovascular disease	8	4.4
Stroke	0	0.0
Raynaud's disease	1	0.6
Stroke or transient ischemic attack	2	1.1
Arrhythmia	8	4.4
Pregnancy	92	70.2

In the study, 104 patients (57.8%) used prescribed medications to alleviate their headaches. Moreover, most patients used non-prescription drugs for headache relief. The distribution of non-prescription drug use was as follows: paracetamol was the most commonly used, with 97 patients (53.9%) reporting its use. This was followed by 'Other' non-prescribed medications, reported by 89 patients (49.4%). Aspirin was administered to 26 patients (14.4%). Naprosyn was used in 4 patients (2.2%). Ibuprofen was reported in 3 patients (1.7%).

No usage of Acetaminophen or Excedrin was reported. In total, 167 patients (92.8 %) used some form of nonprescription medication for their headaches.

Apart from medical therapy, patients have reported alternative therapy for headache relief (Table 4).

Gender-based comparisons showed no significant difference in the general features of headaches. Only the presence of a burning-type headache was significantly higher in males, with 9 cases (18.3%), than in females, who reported 10 cases (7.63%), resulting in a statistically significant difference (p=0.037) (Table 5).

Table 3. Comorbidities and triggers associated with headache

Symptom/Trigger	n	%
Comorbidities		
Fatigue	138	76.7
Sensitivity to loud noises	102	56.7
Light sensitivity	82	45.6
Nausea	80	44.4
Dizziness	67	37.2
Tearing of eyes	41	22.8
Blurred vision	38	21.1
Dazed feeling	30	16.7
Nasal congestion	29	16.1
Numbness and tingling	16	8.9
Photopsia (flashing lights)	13	7.2
Palpitations	13	7.2
Crying	12	6.7
Loss of strength	8	4.4
Vision loss	8	4.4
Ptosis (drooping eyelid)	7	3.9
Shortness of breath	2	1.1
Clouding of consciousness	0	0.0
Triggers		
Stress	152	84.4
Exercise	51	28.3
Weather changes	40	22.2
Menstruation	36	27.5
Smoking	13	7.2
Odors	12	6.7
Foods	8	4.4
Alcohol	4	2.2
Medications	0	0.0

Table 4. Distribution of alternative methods used for headache relief

Alternative method	Effective (n)	Effective (%)	Not effective (n)	Not effective (%)
Massage therapy	58	32.2	38	21.1
Herbal treatments	13	7.2	19	10.6
Behavioral therapy	0	0.0	0	0.0
Acupuncture	0	0.0	0	0.0

There were no significant differences in the use of alternative therapies for headaches between the male and female participants. A total of 48.98% of male participants and 45.80% of female participants did not use massage therapy to alleviate headaches, with 32.65% of male and 32.06% of female participants finding it effective. 18.37% of males and 22.14% of females tried massage therapy but did not find it effective. Most participants did not use herbal remedies, with 87.76% males and 80.15% females reporting no use. Among those who found herbal treatments effective, 6.12% of males and 7.63% of females used them.

Table 5. Gender-based comparison of headache intensity, frequency, duration, and description

Description	Male (%)	Female (%)	*p
Headache intensity			
Discomforting	30.61	24.43	0.313
Severe	55.10	51.15	
Extremely severe	14.29	24.43	
Headache frequency			
Daily	22.45	19.85	0.588
Weekly	30.61	38.93	
Less than once a month	46.94	41.22	
Impact on work performance			
No impact	26.53	17.56	0.115
Yes impact	28.57	45.04	
Sometimes impact	44.90	37.40	
Duration of last headache			
Minutes	6.84	2.29	0.214
Hours	71.43	64.89	
Days	22.45	32.82	
Headache description			
Weighty feeling	20.41	19.85	0.933
Throbbing	71.43	82.44	0.104
Painful	55.10	64.89	0.228
Belt-Like	2.85	3.05	0.713
Burning	18.37	7.63	0.037*
Pulsating	14.29	12.98	0.818
Freezing sensation	0.00	0.00	
Stabbing	21.43	21.37	0.085

*Chi-square test

Statistically significant differences were observed in the intensity of pain and distribution of medication use ($p=0.003$). Triptans were notably higher in the extremely severe pain group, and non-medication use was higher in the discomforting pain group. Differences were also observed in the duration of last headache and medication use ($p=0.040$). NSAIDs were more frequently used by those with headaches lasting days, whereas those with pain lasting minutes had a higher tendency to avoid medication. Table 6 shows the detailed relationship between the intensity and duration of headaches and corresponding medication use among the participants.

DISCUSSION

The current study enrolled 180 patients who sought treatment for headaches at an emergency outpatient clinic. Of these, 72.8% were female, which aligns with previous studies that reported a higher prevalence of headaches in females. The average age of the participants did not vary significantly between sexes, and the prevalence of headaches appeared to be consistent across different age groups. This study found that headache prevalence was not influenced by socioeconomic status, which further emphasizes the universal nature of headache disorders. Pain severity was described as severe or extremely severe by more than half of the patients, highlighting the significant impact of headache on individuals. The study also noted that headache disorders can be chronic, with many patients experiencing frequent and long-lasting headaches, thus emphasizing the need for ongoing management strategies.

Our study found that most headaches reported by our participants were throbbing and located on one side of the head, which is consistent with previous findings on migraine headaches.^{9,10} However, we also observed a significant number of bilateral and posterior headaches, indicating that tension-type headaches were common. This highlights the need for a nuanced approach to characterize headache in clinical practice. Additionally, hypertension was the most common comorbidity, whereas pregnancy showed a strong correlation with headache occurrence, warranting further investigation of the potential links between these factors and headache pathology.

Stress has emerged as the primary instigator of headaches, which aligns with the well-documented association between stress and headache episodes. Factors such as weather changes and menstruation, identified as other triggers, underscore the complex nature of headache precipitants, as supported by existing research.^{8,9,11} The extensive utilization of non-prescription medications (92.8%) among participants suggests that many patients may be self-medicating, potentially due to barriers to healthcare access or a preference for self-management strategies. This trend may also reflect dissatisfaction with conventional treatments or a desire for holistic care approaches, as patients resort to alternative therapies. Paracetamol, widely used for self-medication (53.9%), aligns with its global reputation as a first-line pain

Table 6. Comparison of headache characteristics with prescribed medication use

Headache characteristic	No medication	Metamizole	NSAIDs	Paracetamol	SSRIs	Triptans	p
Intensity of pain							
Discomforting	51.10%	0.00%	34.00%	12.80%	0.00%	2.10%	0.003*
Severe	40.40%	1.10%	31.90%	17.00%	4.30%	5.30%	
Extremely severe	35.90%	0.00%	25.60%	10.30%	0.00%	28.20%	
Frequency of headaches							
Daily	45.90%	0.00%	35.10%	13.50%	0.00%	5.40%	0.319
Weekly	43.90%	1.50%	19.70%	18.20%	4.50%	12.10%	
Less than once a month	39.00%	0.00%	39.00%	11.70%	1.30%	9.10%	
Impact on work performance							
No	47.20%	0.00%	27.80%	16.70%	0.00%	8.30%	0.345
Yes	38.40%	0.00%	30.10%	12.30%	5.50%	13.70%	
Sometimes	43.70%	1.40%	33.80%	15.50%	0.00%	5.60%	
Duration of last headache							
Minutes	66.70%	0.00%	16.70%	0.00%	0.00%	16.70%	0.040*
Hours	45.80%	0.00%	29.20%	18.30%	0.80%	5.80%	
Days	31.50%	1.90%	37.00%	7.40%	5.60%	16.70%	

*Chi-square test, NSAID: Nonsteroidal anti-inflammatory drug

reliever due to its accessibility, efficacy, and safety profile when used appropriately. However, concerns over potential overuse or misuse have been raised given that headache disorders are a significant cause of emergency outpatient visits.^{12,13}

The findings indicated that a significant number of patients (49.4%) used 'other' non-prescribed medications to treat their headaches, suggesting that many individuals may be exploring various over-the-counter options or relying on traditional remedies not classified as conventional medications. This suggests that patients may seek alternative treatment because of unmet needs in professional healthcare or personal preferences for self-directed care. While a smaller percentage of patients (14.4%) used aspirin, along with Naprosyn (2.2%) and ibuprofen (1.7%), the absence of Acetaminophen or Excedrin use may indicate regional or cultural preferences in medication choices or awareness of their side effects or ineffectiveness. Regarding alternative therapies, massage therapy was found to be effective in 32.2% of those who tried it, indicating that non-pharmacological interventions could play a role in headache management strategies, particularly for patients who may not respond well to medical therapies or those seeking complementary approaches, that aligns with the previous studies.^{14,15}

The relatively low efficacy reported for herbal treatments (7.2%) and the lack of use of behavioral therapy and acupuncture may be indicative of a lack of awareness, accessibility, skepticism, or insufficient evidence supporting these methods. This also reflects the necessity for increased education and research on the effectiveness of various alternative therapies for headache.

In clinical practice, these findings underscore the need for healthcare providers to inquire about all forms of medication and alternative treatments patients utilize. This is crucial for preventing potential drug interactions, recognizing patterns of medication overuse headaches, and ensuring that patients are advised about the range of available effective treatments, both medical and alternative.

Reevaluating current headache management protocols and patient education practices may be necessary because of the high reliance on non-prescription medications. Medical professionals should provide more comprehensive guidance on the appropriate use of OTC drugs and investigate the reasons for low uptake or reported ineffectiveness of prescribed medications and alternative therapies. This approach could lead to more personalized and effective headache management plans, better patient outcomes, and fewer emergency department visits for headaches.

The study findings on sex differences in headache characteristics and treatment approaches showed no significant disparities between males and females in most headache features. However, a notable exception was the occurrence of burning-type headaches, which was significantly more prevalent in males (18.3%) than in females (7.63%, $p=0.037$). This result is interesting, as it suggests possible sex differences in the experience of pain or the phenomenology of headaches, an area that warrants further exploration. Although migraine headaches, which are more common in women, are typically described as pulsating or throbbing, the finding of more burning-type headaches in men suggests a potential difference in the underlying pathophysiology or reporting bias, which requires further investigation.¹⁶⁻¹⁸

The effectiveness of alternative therapies varied among the study participants. Although approximately 32% of both men and women found massage therapy helpful, almost half of the participants did not use this nonpharmacological treatment option. This suggests a lack of awareness regarding the benefits of these therapies or a preference for pharmacological interventions. The reported low efficacy of herbal treatments among those who use them indicates that although some patients are exploring these options, they may not be widely perceived as effective. These findings are consistent with the literature, which often highlights the variability in patient responses to both pharmacological and non-pharmacological treatments, emphasizing the need for personalized treatment plans that consider patient preferences and experiences with different therapies.^{19,20}

This study highlights the need for better education on headache management for patients, as suggested by their preference for self-medication with OTC drugs. Clinicians should advise patients on the correct use of OTC medications and the risks of overuse, as well as guide them towards alternative therapies that can alleviate symptoms and improve overall well-being and work performance. The findings of this study can inform the development of educational materials and interventions aimed at promoting more effective self-management of headaches, potentially reducing the burden of headaches on individuals and the healthcare system.

The frequency of headaches also influences the use of medication, with nonsteroidal anti-inflammatory drugs (NSAIDs) being more commonly used by those whose headaches persist for several days. This may indicate a pattern of chronic tension-type headaches or poorly controlled migraines. Those with shorter headache episodes tended to avoid medication more often, possibly because of the natural resolution of their pain or belief that medication would not be effective. These data suggest that healthcare providers should personalize treatment recommendations based on the unique features of each headache presentation. For instance, patients with milder or shorter headaches may benefit from discussing the pros and cons of 'watchful waiting' or using non-pharmacological methods, such as relaxation techniques or biofeedback. Additionally, the higher reliance on NSAIDs among patients with longer-lasting headaches highlights the need to address the risk of medication overuse in patient education and headache management strategies.

Therefore, clinicians must engage with patients to ensure that the chosen treatments align with the severity, frequency, and impact of headaches while also considering patient preferences and the potential risks of medication overuse. The findings of this study emphasize the complexity of headache management and the necessity of personalized treatment approaches that account for the multifaceted nature of headache disorders.

Limitations

This study has some limitations.

1. Cross-sectional design: The study's cross-sectional nature allows for the observation of a snapshot in time, which can identify associations, but not causal relationships. This design limits the ability to determine progression or changes in headache characteristics or medication use over time.

2. Selection bias: Participants were drawn from an emergency outpatient clinic, which may not be representative of the general

population with headaches. This could lead to a selection bias, as the severity of headaches might be higher in an emergency care setting than in a primary care setting.

3. Exclusion criteria: The exclusion of individuals with mental retardation, cancer pain, or diagnosed rheumatic diseases could limit the generalizability of the findings to all patients with headache, as these conditions could also influence headache characteristics and treatment responses.

4. Self-reported data: The reliance on self-reported data in the “Headache Questionnaire” can introduce recall bias, as participants may not accurately remember or report the severity, frequency, or duration of their headaches.

5. Geographic and cultural factors: Conducted in a specific location, the study’s findings might not be applicable to different geographic or cultural settings where headache prevalence and treatment approaches could differ.

These limitations highlight areas for future research, such as longitudinal studies, broader participant selection, and in-depth analyses of treatment patterns and efficacy. Addressing these limitations in subsequent research can deepen our understanding of headache disorders and improve the care for those affected.

CONCLUSION

This study sheds light on the prevalence and management of headache disorders in patients attending an emergency outpatient clinic. The findings reveal that headaches affect both sexes equally, with a higher prevalence among females. The study also highlights the need for patient education on headache management, given the frequent use of prescribed and nonprescription medications. The distinctive finding that males are more prone to burning-type headaches warrants further research. Personalized care that considers patient preferences and experiences is crucial for effective headache management. Stress is a significant trigger emphasizing the need for comprehensive management strategies. The reliance on non-prescription medications and alternative therapies, such as massage, raises questions about accessibility to healthcare services. A holistic approach that combines medication management with patient education and non-pharmacological therapies is essential for improving patient outcomes and reducing the burden on the healthcare system.

ETHICAL DECLARATIONS

Ethics Committee Approval

Institutional approval was obtained. Ethics committee approval is not required for this study since it is produced from a thesis before 2020.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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