

# Association of escitalopram prophylaxis with pain intensity in tension-type headache: A retrospective, comparative cohort study

## Gerilim tipi baş ağrısında esitalopram profilaksisi ile ağrı şiddeti arasındaki ilişki: Retrospektif, karşılaştırmalı kohort çalışma

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### ABSTRACT

**Background:** This study aims to evaluate the association between escitalopram prophylaxis and pain intensity in patients with tension-type headache.

**Patients and Methods:** This retrospective, comparative cohort study included a total of 503 patients between July 1<sup>st</sup>, 2022 and October 1<sup>st</sup>, 2022. The patients were divided into two groups according to their treatment approach. The first group (Group 1, n = 300) consisted of patients who initiated escitalopram prophylaxis. The second group (Group 2, n = 203) consisted of patients who did not receive prophylactic treatment and were monitored with symptomatic treatment. Pain intensity was assessed using the Visual Analog Scale (VAS) at baseline and after approximately three months. Between-group changes were compared, and follow-up VAS scores were evaluated using regression models adjusted for baseline VAS, age and sex. The Headache Screening Questionnaire (HSQ) findings were considered exploratory.

**Results:** Of a total of 503 patients, 159 were male and 344 were female with a mean age of  $33.00 \pm 3.44$  (range, 22 to 46) years. The groups were similar in age and sex distribution, although baseline VAS scores were higher in the escitalopram group. The mean VAS scores decreased from  $5.06 \pm 1.23$  to  $4.55 \pm 1.17$  in the escitalopram group and increased from  $4.68 \pm 1.40$  to  $4.92 \pm 1.41$  in the symptomatic treatment group. The difference in change between groups was significant. Escitalopram use remained associated with lower follow-up VAS scores after adjustment for baseline VAS, age and sex. The HSQ findings were exploratory and were not interpreted as confirmatory evidence of treatment efficacy.

**Conclusion:** Escitalopram prophylaxis was associated with lower pain intensity after approximately three months. As treatment allocation was non-randomized and baseline pain severity differed between groups, the findings should be interpreted cautiously. Escitalopram warrants further investigation in patients who cannot tolerate or are unsuitable for first-line prophylactic treatments.

**Keywords:** Escitalopram, pain measurement, Tension-type headache.

### ÖZ

**Amaç:** Bu çalışmada, gerilim tipi baş ağrısı olan hastalarda esitalopram profilaksisi ile ağrı şiddeti arasındaki ilişki değerlendirildi.

**Hastalar ve Yöntemler:** Bu retrospektif, karşılaştırmalı kohort çalışmasına 01.07.2022 ile 01.10.2022 tarihleri arasında toplam 503 hasta dahil edildi. Hastalar, uygulanan tedavi yaklaşımına göre iki gruba ayrıldı. İlk grup (Grup 1, n = 300), esitalopram profilaksisine başlanan hastalardan oluştu. İkinci grup (Grup 2, n = 203), profilaktik tedavi almayan ve semptomatik tedavi ile izlenen hastalardan oluştu. Ağrı şiddeti, başlangıçta ve yaklaşık üç ay sonra Görsel Analog Ölçeği (VAS) kullanılarak değerlendirildi. Gruplar arasındaki değişimler karşılaştırıldı ve takip VAS skorları; başlangıç VAS skoru, yaş ve cinsiyete göre düzeltilmiş regresyon modelleri kullanılarak değerlendirildi. Baş Ağrısı Tarama Anketi (HSQ) bulguları keşifsel olarak değerlendirildi.

**Bulgular:** Toplam 503 hastanın 159'u erkek ve 344'ü kadın olup, ortalama yaş  $33.00 \pm 3.44$  yıl (aralık, 22-46) idi. Gruplar yaş ve cinsiyet dağılımı açısından benzerdi; ancak başlangıç VAS skorları esitalopram grubunda daha yüksekti. Ortalama VAS skorları esitalopram grubunda  $5.06 \pm 1.23$ 'ten  $4.55 \pm 1.17$ 'ye düşerken, semptomatik tedavi grubunda  $4.68 \pm 1.40$ 'tan  $4.92 \pm 1.41$ 'e yükseldi. Gruplar arasındaki değişim farkı istatistiksel olarak anlamlıydı. Başlangıç VAS skoru, yaş ve cinsiyet için yapılan düzeltmenin ardından da esitalopram kullanımı, daha düşük takip VAS skorları ile ilişkili bulunmaya devam etti. Baş Ağrısı Tarama Anketi bulguları keşifsel nitelikte olup, tedavinin etkinliğine ilişkin doğrulayıcı kanıt olarak yorumlanmadı.

**Sonuç:** Esitalopram profilaksisi, yaklaşık üç ay sonra daha düşük ağrı şiddeti ile ilişkili bulundu. Tedavi atamasının randomize olmaması ve başlangıç ağrı şiddetinin gruplar arasında farklılık göstermesi nedeniyle, bulgular dikkatle yorumlanmalıdır. Birinci basamak profilaktik tedavileri tolere edemeyen veya bu tedaviler için uygun olmayan hastalarda esitalopram başka çalışmalarda araştırılmalıdır.

**Anahtar sözcükler:** Esitalopram; ağrı ölçümü, gerilim tipi baş ağrısı.

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Tension-type headache is one of the most commonly encountered conditions among primary headaches in clinical practice. In cases characterized by frequent attacks or a tendency to become chronic, patients' daily functioning, work performance and quality of life may be significantly affected. Therefore, tension-type headache is a condition that must be addressed not only in terms of pain intensity, but also in terms of its recurrent nature and long-term burden on the patient.<sup>[1]</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics used during the acute phase may provide temporary relief in many patients. However, in patients experiencing frequent headaches, it is not always possible to achieve lasting control through symptomatic treatment alone. In this patient group, prophylactic treatment options come to the fore. Amitriptyline is one of the most commonly used prophylactic agents for tension-type headaches; however, it may not be suitable for every patient due to side effects such as sedation, dry mouth, weight gain and other effects that may hinder treatment adherence.<sup>[1-4]</sup>

Selective serotonin reuptake inhibitors (SSRIs) are being considered as an alternative option in some patients, particularly due to their tolerability profiles. Although escitalopram is primarily used in the treatment of psychiatric disorders, the role of the serotonergic system in central pain modulation has led to research into the potential use of this drug in headache management. However, evidence regarding the use of escitalopram in tension-type headaches is limited, and the results of existing studies are inconsistent. It is, therefore, important to evaluate escitalopram's role in this patient group more cautiously, based on real-world data.<sup>[5-12]</sup>

Current literature fails to support the use of SSRIs as viable preventive strategies for tension-type headaches. In a study by Bendtsen et al.,<sup>[5]</sup> citalopram showed no therapeutic benefit in chronic cases, while a Cochrane systematic review confirmed that clinical evidence remained inadequate for both SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in this patient group.<sup>[6]</sup> Despite these limitations, the present study sought to evaluate escitalopram, given its continued use in real-world clinical practice among specific patient subgroups and its comparatively favorable tolerability profile relative to traditional tricyclic agents. In Türkiye, escitalopram is included among the drugs listed for off-label use in tension-type

headache following applications to the Turkish Medicines and Medical Devices Agency (TİTCK).<sup>[13]</sup>

In the present study, we hypothesized that patients receiving escitalopram prophylaxis would show a greater reduction in Visual Analog Scale (VAS) scores at approximately three months than patients managed with symptomatic treatment alone. We, therefore, aimed to assess the effect of escitalopram prophylaxis on pain intensity in patients diagnosed with tension-type headache following approximately three months of follow-up.

## PATIENTS AND METHODS

This single-center, retrospective, comparative cohort study was conducted at Adıyaman University Faculty of Medicine, Department of Neurology between July 1<sup>st</sup>, 2022 and October 1<sup>st</sup>, 2022. The medical records of patients followed between October 1<sup>st</sup>, 2019 and April 1<sup>st</sup>, 2022 were reviewed. As the study was conducted in the Department of Neurology which does not exclusively focus on headache disorders, the analyzed patient population was evaluated by a pool of eight different neurologists working within the same department.

We performed the preliminary patient screening using the International Classification of Diseases (ICD)-10-CM/ICD-10 diagnosis codes within the G44 category. Rather than relying solely on this administrative classification, we cross-referenced outpatient history files and electronic prescribing records to verify that the recorded clinical presentations aligned with actual tension-type headache criteria. Any individuals who carried a co-existing diagnosis of migraine, specifically indicated by any G43-series ICD-10 code, were excluded from the study. The study included adult patients diagnosed with tension-type headache according to the criteria of the International Classification of Headache Disorders, third edition (ICHD-3).<sup>[14]</sup> To be included in the study, patients were required to have VAS records at baseline and at the approximately third-month follow-up, to have completed at least three months of outpatient follow-up, and to have complete follow-up data. Inclusion criteria were as follows: a diagnosis of tension-type headache in clinical records, no prior use of antidepressants, sedatives or antipsychotic medication, completion of a follow-up period of at least three months, and availability of pain intensity records at baseline and follow-up assessments. Exclusion criteria were as follows: a diagnosis of depression or an anxiety disorder, a

concurrent diagnosis of migraine, use of analgesics for more than 10 days per month, incomplete clinical records, and absence of baseline or follow-up VAS data. Depression and anxiety disorders were identified from previously documented psychiatric diagnoses and psychiatric clinic or consultation records. Analgesic-use frequency was determined from outpatient history notes and prescription records. Patients with documented use on more than 10 days per month were excluded. A total of 1,131 patients with an ICD-10 code of G44.2 were initially identified. As some patients met more than one exclusion criterion, the criteria were applied sequentially to avoid duplicate counting. A total of 628 patients were excluded: 413 due to incomplete clinical records or missing required data, 121 due to follow-up shorter than three months, 67 due to analgesic use on more than 10 days per month, 16 due to having a previous psychiatric diagnosis, and 11 due to having a concurrent migraine diagnosis. The final study cohort consisted of 503 patients. The patients were divided into two groups according to their treatment approach. The first group (Group 1,  $n = 300$ ) consisted of patients who initiated escitalopram prophylaxis. The second group (Group 2,  $n = 203$ ) consisted of patients who did not receive prophylactic treatment and were monitored with symptomatic treatment. The study flowchart is shown in Figure 1.

A written informed consent was obtained from each patient. The study protocol was approved by the Adiyaman University Ethics Committee for Non-Interventional Clinical Research (Date: 20.04.2022, No: 2022/4-4). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinicians considered prophylactic intervention for individuals presenting with frequent or highly disruptive tension-type headaches, provided that routine daily prevention was deemed clinically suitable. The choice to start escitalopram rested entirely with the managing neurologist following a shared decision-making process with the patient. This specific agent was favored owing to its tolerability profile and a lower risk of anticholinergic or sedative adverse effects compared to tricyclic options. As several eligible candidates opted against a daily preventive regimen, choosing instead to manage their symptoms on an as-needed basis, treatment selection was driven by pragmatic clinical judgments and individual patient choices rather than formal randomization.

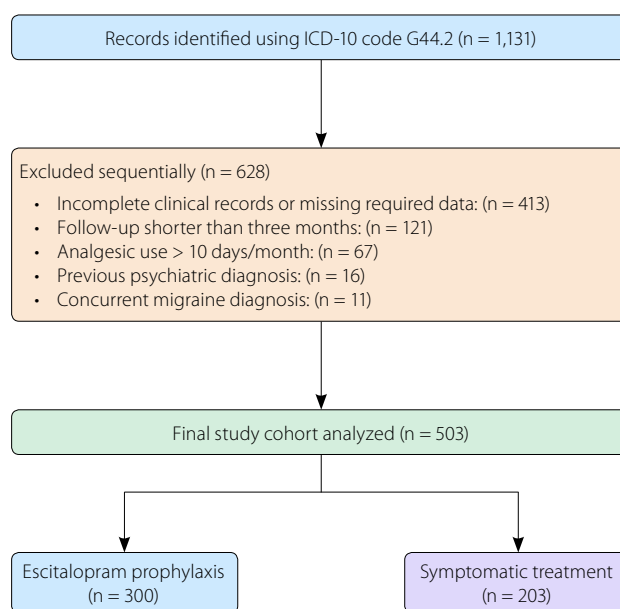
## Treatment protocol and follow-up

Escitalopram treatment was initiated at a dose of 5 mg/day for the first seven days, after which the dose was increased to 10 mg/day. Patients were reassessed approximately one month after the start of treatment. Only patients who completed at least three months' follow-up and had complete baseline and follow-up assessments were included in the analysis. Patients in the control group were monitored without prophylactic treatment, receiving symptomatic treatment recommendations and routine outpatient follow-up. The VAS scores were recorded at baseline and at approximately the third month in both groups.

Regarding acute symptom management, both cohorts received identical clinical recommendations. Clinicians prescribed NSAIDs, primarily ibuprofen or diclofenac, based on individual clinical suitability, advising patients to limit analgesic intake to a maximum of 10 days per month. To maintain data integrity, we excluded individuals who failed to complete the three-month evaluation period or those missing baseline or follow-up VAS scores. Since a substantial portion of non-returning patients left no subsequent medical records, we could not systematically verify whether they had ceased escitalopram therapy or establish the precise reasons behind their loss to follow-up.

## Assessment tools

Pain intensity was assessed using the VAS. The VAS was used as a measurement tool in which



**Figure 1.** Study flowchart.

ICD-10, International Classification of Diseases-10.

patients rated their pain intensity on a scale of 0 to 10; 0 represented the absence of pain, while 10 represented the most severe pain.<sup>[15]</sup>

The Headache Screening Questionnaire (HSQ) data were analyzed to identify clinical characteristics associated with tension-type headache. In this study, the HSQ items were not used as a valid total score or continuous domain score indicating treatment response, as the HSQ is primarily a diagnostic and screening tool designed to distinguish between headache types; furthermore, some items contain categorical clinical features rather than ordinal measures of severity. Therefore, the HSQ data were evaluated in a supportive and exploratory manner.<sup>[16]</sup>

### Outcome measures

The primary outcome measure of the study was the change in VAS scores between baseline and approximately the third month. The escitalopram prophylaxis group was compared with the control group in terms of both within-group and between-group changes in VAS scores. As baseline VAS scores differed between groups, the treatment effect was also assessed using analyses adjusted for baseline VAS scores.

### Statistical analysis

Statistical analysis was performed using the SPSS version 30.0.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean  $\pm$  standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. To evaluate baseline demographics, we employed the independent-samples t-test for age comparisons and the chi-square test to examine the distribution of sex. Given that the changes in VAS scores deviated from a normal distribution, we applied non-parametric approaches: the Wilcoxon signed-rank test for within-group longitudinal changes and the Mann-Whitney U test to compare change scores between the two cohorts.

We also verified baseline VAS comparability via an independent-samples t-test. To analyze follow-up VAS outcomes, we constructed two linear regression models. The first model (Model 1) adjusted for treatment allocation and baseline VAS, whereas the second model (Model 2) further incorporated age and sex as covariates. From these models, we extracted unstandardized regression coefficients (B) accompanied by robust standard errors, 95% confidence intervals (CIs), and corresponding *p* values. There were no missing values for the variables included in the primary analyses among the final cohort of 503 patients. A *p* value of  $< 0.05$  was considered statistically significant.

## RESULTS

Of a total of 503 patients, 159 were male and 344 were female with a mean age of  $33.00 \pm 3.44$  (range, 22 to 46) years. Both groups were comparable in terms of age and sex distribution. However, baseline VAS scores were higher in the escitalopram group than in the control group ( $p = 0.002$ ). Therefore, treatment effects were interpreted in conjunction with analyses adjusted for baseline values. The baseline characteristics of the study groups are shown in Table 1.

At three months, the mean VAS score decreased in the escitalopram group, while it showed a slight increase in the control group. The change within each group was statistically significant in both groups ( $p < 0.001$ ); however, the directions of change were opposite. Baseline and third-month VAS scores are presented in Table 2.

The between-group difference in VAS change was in favor of the escitalopram group. As baseline pain intensity differed between groups, the interpretation should take into account both the raw change scores and the regression model adjusted for baseline values. The regression model adjusted for baseline values is shown in Table 3.

**Table 1.** Baseline demographic characteristics

| Variable   | Escitalopram (n = 300) |      |                  | Symptomatic treatment (n = 203) |      |                  | <i>p</i> |
|------------|------------------------|------|------------------|---------------------------------|------|------------------|----------|
|            | n                      | %    | Mean $\pm$ SD    | n                               | %    | Mean $\pm$ SD    |          |
| Age (year) |                        |      | 32.98 $\pm$ 3.46 |                                 |      | 33.03 $\pm$ 3.43 | 0.854    |
| Sex        |                        |      |                  |                                 |      |                  |          |
| Female     | 208                    | 69.3 |                  | 136                             | 67.0 |                  | 0.649    |
| Male       | 92                     | 30.7 |                  | 67                              | 33.0 |                  |          |

SD, standard deviation. Age was compared using the independent-samples t-test; sex was compared using the chi-square test.

**Table 2.** VAS scores at baseline and follow-up

| Measure                     | Escitalopram (n=300) | Symptomatic treatment (n=203) | Between-group |
|-----------------------------|----------------------|-------------------------------|---------------|
|                             | Mean $\pm$ SD        | Mean $\pm$ SD                 | <i>p</i>      |
| Baseline VAS                | 5.06 $\pm$ 1.23      | 4.68 $\pm$ 1.40               | 0.002         |
| Follow-up VAS               | 4.55 $\pm$ 1.17      | 4.92 $\pm$ 1.41               | -             |
| Change in VAS               | -0.51 $\pm$ 0.67     | +0.24 $\pm$ 0.51              | < 0.001       |
| Within-group <i>p</i> value | < 0.001              | < 0.001                       |               |

SD, standard deviation. Within-group changes were tested using the Wilcoxon signed-rank test; change scores were compared between groups using the Mann-Whitney U test. Baseline VAS was compared using the independent-samples t-test. Follow-up VAS was evaluated using the regression models presented in Table 3.

**Table 3.** Linear regression models for follow-up VAS

| Model/predictor           | B       | Robust SE | 95% CI           | <i>p</i> |
|---------------------------|---------|-----------|------------------|----------|
| Model 1: Escitalopram use | -0.700  | 0.049     | -0.797 to -0.604 | < 0.001  |
| Model 1: Baseline VAS     | 0.869   | 0.020     | 0.830 to 0.909   | < 0.001  |
| Model 2: Escitalopram use | -0.700  | 0.050     | -0.798 to -0.603 | < 0.001  |
| Model 2: Baseline VAS     | 0.869   | 0.020     | 0.830 to 0.909   | < 0.001  |
| Model 2: Age              | -0.0001 | 0.008     | -0.015 to 0.015  | 0.988    |
| Model 2: Male sex         | 0.001   | 0.055     | -0.108 to 0.110  | 0.979    |

VAS, Visual Analog Scale; B, unstandardized coefficient; SE, standard error; CI, confidence interval. Model 1 included treatment group and baseline VAS. Model 2 additionally included age and sex.

**Table 4.** Descriptive changes in selected HSQ items during follow-up

| HSQ item                        | Escitalopram (n = 300) |      | Symptomatic treatment (n = 203) |      |
|---------------------------------|------------------------|------|---------------------------------|------|
|                                 | n                      | %    | n                               | %    |
| Monthly headache frequency (Q3) | 102                    | 34.0 | 9                               | 4.4  |
|                                 | 198                    | 66.0 | 194                             | 95.6 |
|                                 | 0                      | 0.0  | 0                               | 0.0  |
| Headache duration (Q4)          | 37                     | 12.3 | 11                              | 5.4  |
|                                 | 262                    | 87.3 | 191                             | 94.1 |
|                                 | 1                      | 0.3  | 1                               | 0.5  |
| Activity aggravation (Q7)       | 3                      | 1.0  | 2                               | 1.0  |
|                                 | 297                    | 99.0 | 201                             | 99.0 |
|                                 | 0                      | 0.0  | 0                               | 0.0  |
| Activity avoidance (Q8)         | 6                      | 2.0  | 0                               | 0.0  |
|                                 | 294                    | 98.0 | 199                             | 98.0 |
|                                 | 0                      | 0.0  | 4                               | 2.0  |
| Headache severity (Q10)         | 50                     | 16.7 | 0                               | 0.0  |
|                                 | 247                    | 82.3 | 180                             | 88.7 |
|                                 | 3                      | 1.0  | 23                              | 11.3 |

HSQ, Headache Screening Questionnaire. Values are presented as improved / unchanged / worsened, n (%). HSQ findings were evaluated descriptively; no composite treatment-response score was calculated, and no inferential comparison was performed because the HSQ was not used as a validated longitudinal treatment-response scale.

Inter-group comparisons of VAS change scores revealed a statistically significant advantage in favor of patients receiving escitalopram ( $p < 0.001$ ). When adjusting for baseline VAS in our primary regression model, introducing escitalopram corresponded to

an average reduction of 0.70 points in the final VAS assessment ( $B = -0.700$ ; 95% CI: -0.797 to -0.604;  $p < 0.001$ ). This association remained essentially unchanged after age and sex were added to the model ( $B = -0.700$ ; 95% CI: -0.798 to -0.603;  $p < 0.001$ ).

The HSQ items were not treated as a valid total score or a treatment response score. As the questionnaire contained both ordinal and categorical clinical characteristics, HSQ data were used to define the headache phenotype and to provide exploratory support for VAS-based findings.

Descriptive changes in selected HSQ items are presented in Table 4. Improvement in monthly headache frequency was observed in 102 of 300 patients (34.0%) in the escitalopram group and nine of 203 patients (4.4%) in the symptomatic-treatment group. Improvement in headache severity was observed in 50 patients (16.7%) in the escitalopram group, whereas no improvement in this item was observed in the symptomatic-treatment group. Most patients showed no change in headache duration or activity-related items. Of note, these findings were considered descriptive and exploratory.

Given that the questionnaire was not processed as a validated tool for monitoring longitudinal responses, we treated these HSQ outcomes as strictly exploratory rather than utilizing them to deduce therapeutic efficacy.

## DISCUSSION

In the present study, we evaluated the association between escitalopram prophylaxis and pain intensity in patients with tension-type headache. Our study results showed a reduction in VAS scores at the end of approximately three months of follow-up in patients with tension-type headache receiving escitalopram prophylaxis. In the control group, however, a slight increase in VAS scores was observed over the same period. As baseline pain severity was higher in the escitalopram group, the treatment effect was assessed not only using raw change scores, but also via a model adjusted for baseline VAS values. These findings suggest that escitalopram use may be associated with a lower VAS score at three months.

The need for prophylactic treatment in tension-type headaches is becoming increasingly important, particularly in patients who experience frequent attacks or who are at risk of the condition becoming chronic. Amitriptyline is one of the most widely supported options in this field and is included among first-line prophylactic treatments in many guidelines.<sup>[1-3]</sup> However, its use may be challenging in some patients due to side effects such as sedation, dry mouth, weight gain and other effects that may affect treatment adherence. Therefore, the evaluation of

alternative medicines that may be better tolerated, using real-world data, is clinically important.

The role of SSRIs in tension-type headaches is more controversial than that of tricyclic antidepressants. Findings regarding the efficacy of SSRIs in the literature are inconsistent; some studies have failed to demonstrate a significant advantage, while others have reported limited benefits in selected patient groups.<sup>[4-7]</sup> Therefore, in the light of the current evidence, escitalopram should not be considered as a first-line prophylactic treatment. The findings of our study also suggest that, rather than demonstrating that escitalopram is a strong or superior prophylactic option, it may be associated with a reduction in pain intensity in selected patients.

When contextualizing our outcomes, it is essential to consider them alongside the negative randomized trial data for citalopram and the inconclusive evidence highlighted in the Cochrane review.<sup>[5,6]</sup> Indeed, the data presented here do not refute those established conclusions. Several variables likely underlie these divergent clinical observations, including differences in drug selectivity, trial design, patient demographics, the distribution of headache subtypes, dosing regimens, follow-up durations, and the non-randomized nature of treatment allocation. More intriguingly, the retrospective framework of our investigation inherently leaves room for the influence of residual confounding.

Although they do not definitively confirm therapeutic efficacy for tension-type headaches, certain clinical observations in allied pain and headache disorders justify evaluating escitalopram independently from its racemic counterpart. For instance, a comparative study involving migraine patients free of comorbid depression or anxiety demonstrated that both escitalopram and venlafaxine yielded significant improvements in headache metrics over a three-month course.<sup>[10]</sup> Mechanistically, escitalopram represents the pharmacologically active S-enantiomer of citalopram, possessing greater selectivity and higher potency for the serotonin transporter than the racemic formulation.<sup>[11]</sup> This characteristic is corroborated by human neuroimaging studies, which confirm substantial serotonin-transporter occupancy when escitalopram is administered at standard therapeutic doses.<sup>[12]</sup> While these data provide a rationale for further investigation of escitalopram, they neither resolve the conflicting literature surrounding SSRIs in tension-type headache nor do they substitute

for dedicated randomized trials in this specific population.

Although the change in VAS observed in this study was statistically significant, the magnitude of the effect should be interpreted with caution from a clinical perspective. While a reduction of approximately half a point in the mean VAS score was observed in the escitalopram group, a slight increase was seen in the control group. The difference in change between groups and the model adjusted for baseline VAS values favored escitalopram. However, due to baseline differences in pain intensity between groups, the retrospective design and the non-randomized nature of treatment selection, these results should not be interpreted as indicating a causal effect. In this study, the HSQ findings were interpreted only as descriptive and exploratory, as the questionnaire was not used as a validated longitudinal treatment-response scale.

The possible effect of escitalopram can be explained through several mechanisms. It is known that the serotonergic system plays a role in central pain modulation. Consequently, drugs that affect serotonergic transmission may exert indirect effects on pain perception. However, this mechanism alone is insufficient to explain escitalopram's clinical efficacy in tension-type headaches. Furthermore, as patients with psychiatric comorbidities were excluded from this study, it cannot be concluded that the observed change stemmed from an improvement in symptoms of anxiety or depression. Nevertheless, it should not be overlooked that unmeasured variables such as sleep, stress perception, muscle tension and pain threshold may have influenced the results. Serotonergic pathways are involved in descending pain modulation, although their effects vary according to receptor subtype and neural level.<sup>[8,9]</sup>

The study has a number of strengths. One of these is its relatively large sample size and the fact that it is based on real-world data. Furthermore, the presentation not only of within-group variation but also of between-group differences and a model adjusted for baseline VAS scores allows for a more cautious interpretation of the results. The fact that the HSQ data were not used as a total score, the validity of which for treatment response has not been established, also ensured a more cautious approach.

The higher baseline VAS scores in the escitalopram group may have been related to treatment-selection patterns in routine clinical practice. Patients with more severe or disruptive headaches may have been

more likely to receive or accept a daily preventive regimen, whereas patients with milder symptoms may have continued with symptomatic treatment alone. Although we adjusted for baseline VAS in our multivariate model, we cannot entirely rule out the influence of regression to the mean and residual confounding. Furthermore, key unmeasured variables, such as stress levels, sleep quality, and physical muscle tension, might have differed systematically between the two groups, and our study design did not allow us to evaluate these factors using standardized assessment tools.

However, certain limitations should be acknowledged. First, as the study is retrospective, causality cannot be established. Second, as treatment allocation was not randomized, there is a possibility of selection bias. Third, the baseline VAS score was higher in the escitalopram group; although baseline VAS values were taken into account in the analyses, confounding effects cannot be entirely ruled out. Fourth, certain variables that could influence the outcomes, such as the frequency of analgesic use, treatment adherence, side effects, sleep patterns, stress levels, muscle sensitivity and lifestyle, could not be assessed in detail. Fifth, as the HSQ was not used in this study as a valid scale for measuring treatment response, the HSQ findings should be regarded as entirely exploratory. Finally, the fact that the follow-up period was limited to approximately three months makes it difficult to draw conclusions regarding the long-term effect and sustainability of escitalopram. Furthermore, as our dataset was limited strictly to patients who completed the entire follow-up period and had complete documentation, the potential influence of attrition bias cannot be entirely discounted. Similarly, we could not evaluate the role of occupation-related variables, as employment histories were inconsistently recorded within the retrospective medical charts.

In conclusion, our study results showed that escitalopram prophylaxis in patients diagnosed with tension-type headache was associated with a reduction in VAS scores at the end of approximately three months of follow-up. As baseline VAS values differed between groups, the results were interpreted using analyses adjusted for baseline pain severity. Although some exploratory findings based on HSQ items showed descriptive changes in favor of the escitalopram group, the HSQ was not used as a valid treatment response scale in this study. Therefore, the main result of the study is based on VAS change and adjusted regression analysis. Taken

together, these findings suggest that escitalopram should be considered not as the standard first-line prophylactic treatment for tension-type headaches, but as an alternative option that may be evaluated in selected patients. Further multi-center, large-scale, randomized studies are warranted to confirm these findings.

#### Author Contributions

A.B.E., A.Z.A.T.: Idea/concept, design, analysis and/or interpretation, critical review; A.Z.A.T.: Control/supervision; A.B.E.: Data collection and/or processing, literature review, writing the article, references and fundings, materials.

#### Conflict of Interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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#### Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### AI Disclosure

The authors declare that artificial intelligence (AI) tools were not used, or were used solely for language editing, and had no role in data analysis, interpretation, or the formulation of conclusions. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors. The authors further confirm that AI tools were not used to generate, fabricate, or 'hallucinate' references, and that all references have been carefully verified for accuracy.

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