

Underuse of Prophylactic Treatment Among Portuguese Patients with Primary Headache: A Retrospective Observational Study

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Aims: To evaluate prescription of prophylactic treatment before and after consultation in a neurology headache clinic and to determine predictors for prophylactic treatment and clinical improvement. **Methods:** Clinical records of consecutive patients assessed in a neurologic headache clinic in Portugal and diagnosed with acute or chronic migraine and/or tension-type headache were assessed. Prescription of prophylaxis before and after the first visit to the clinic were compared. Logistic regression was used to evaluate predictors of the need for therapeutic intervention and clinical improvement. **Results:** Among 409 patients (86.8% women; mean age 41.6 years), 315 (77%) had indication for prophylaxis, and 70 (22%) of these patients were already on prophylactic treatment. Among the 265 patients with information for follow-up, prophylactic treatment was added in 178 (67.2%), and there was a significant change in the number of treated patients between the first and second visits. Ongoing treatment was switched or the dose increased in 21 patients. Multivariate logistic regression revealed that women (odds ratio [OR] = 2.09, 95% confidence interval [CI] 1.1 to 3.97) and patients with medication overuse headache (MOH) (OR = 6.97, 95% CI 1.60 to 30.39) were more likely to need therapeutic intervention, whereas patients referred from the emergency room were less likely to need it (OR = 0.44, 95% CI 0.22 to 0.89). Of the 265 patients, 185 (69.8%) had improved at a follow-up. Having prophylactic treatment at the time of the second visit was associated with improvement (OR = 2.39, 95% CI 1.23 to 4.63; $P = .01$). **Conclusion:** Women and medication overuse headache patients were more likely to need therapeutic intervention. However, only a minority of patients with treatment indication were treated before their first visit to the headache clinic. Prophylaxis prescription was associated with clinical improvement at follow-up. *J Oral Facial Pain Headache* 2019;33:331–336. doi: 10.11607/ofph.2122

Keywords: chronic headache, headache, migraine, outpatient clinic, prophylaxis, referrals

According to the latest Global Burden of Disease studies of 2015, headaches contribute more to disability-adjusted life years (DALYs) than any other neurologic disorder.¹ Migraine, the most disabling of the primary headaches, is responsible for 13.1% of DALYs lost and is surpassed only by cerebrovascular disorders.² Of the 10 leading causes of years lived with disability (YLDs), migraine is ranked 7, and is 3 in the age group between 25 and 39 years.^{1,3} Given the high prevalence and the many effective treatment options available today for patients with primary headaches, why does the burden remain so high?

Migraine undertreatment has been suspected as a culprit.⁴ Several epidemiologic studies have examined the issue of undertreatment of migraine patients in different countries—proportions of treated patients have ranged from 12% to 30%, which seems low given the wide availability of treatment options.^{5–11} Although there is some discrepancy regarding the proportion of treated patients, there seems to be a widespread issue related to the (under)prescription of prophylaxis, particularly in patients with migraine, which could be partly responsible for the consistently high disease burden.¹⁰

Portugal is a western European country where all residents have access to health care provided by the National Health Service (NHS),

financed through taxation. Primary care physicians are the gatekeepers for patients being referred to specialized care.¹² Despite the high impact of headaches,¹³ there is a lack of information regarding Portuguese patients with headaches and clinical outcomes after the introduction of prophylaxis.

The primary objective of this study was to evaluate the frequency of prophylaxis prescription before and after consultation in a newly created headache outpatient clinic among patients with primary headaches. The secondary objectives were to determine predictors of the need for therapeutic change and of clinical improvement at the first follow-up visit.

Materials and Methods

Patients

A retrospective cohort study was designed. The authors reviewed all electronic clinical records of adult patients evaluated in the headache outpatient clinic of Hospital de Egas Moniz from its inception (May 2013) up to June 30, 2016. Inclusion criteria were: patients older than 18 years and with a diagnosis of migraine with or without aura (MWA and MWOA, respectively), chronic migraine (CM), and/or tension-type headache (TTH) according to the International Classification of Headache Disorders (ICHD)-3 beta.¹⁴ Information regarding the presence of medication overuse headache (MOH) was also collected. Only those with at least one follow-up visit were included in the follow-up analysis.

At baseline (first headache outpatient visit), the following variables were collected: demographic data (age, gender); diagnosis (MWA, MWOA, CM, TTH, or MOH) according to the ICHD-3 beta¹⁴; referring doctor (primary care, other referral clinics [such as neurosurgery, nonheadache neurology, otolaryngology, or internal medicine], emergency room (ER), or other hospitals); current use of prophylactic treatment; and proposed changes to treatment. The variables current prophylactic treatment and proposed changes to treatment were both reported as dichotomous variables (yes/no) and as categorical variables with the following categories:

- Current prophylactic treatment: valproic acid; topiramate; tricyclic antidepressant; propranolol; calcium channel blocker; or other
- Proposed changes of treatment: no change; switch drug; increase dose; add drug; or stop drug.

Indication for prophylactic treatment was considered by the authors according to published guidelines.¹⁵

At the patients' first follow-up visit, information regarding current use of prophylactic treatment and clinical improvement (set as a reduction of at least 50% of headache days per month) was collected, and these variables were coded as dichotomous variables (yes/no).

Informed consent was obtained from all patients as per local practice guidelines, and the study was approved by the ethics committee of Centro Hospitalar de Lisboa Ocidental, to which Hospital de Egas Moniz (where the work was performed) belongs.

Statistical Analyses

Comparisons between groups were performed using *t* test or Mann-Whitney *U* test (depending on the distribution of the variables) for continuous variables and chi-square or Fisher exact test for categorical variables. McNemar test was performed to compare the frequency of prophylactic prescription before and after evaluation by the neurologist.

Both a univariate and a multivariate logistic regression analysis were conducted to ascertain the effects of gender, age, diagnosis, the origin of referral, previous prophylactic treatment, and class of prophylaxis on the likelihood of the need for a therapeutic intervention (positive = add, switch, or increase dose; negative = none) and on the likelihood of clinical improvement at follow-up. Potential confounders were considered according to the assumption of a causal relation between a given variable and the outcome of interest. Cases with missing data were excluded from the analyses.

Significance level was set at $\alpha = .05$. The analysis was performed using IBM SPSS version 23.0.

Results

Patient Selection

A total of 551 patients were seen in the outpatient clinic during the 39 months considered, and 409 were included in the primary analysis evaluating the frequency of prophylaxis prescription and in the analysis of predictors of the need for therapeutic change. Of these patients, 265 had at least one follow-up consultation and were included in the analysis of predictors of clinical improvement.

Of the excluded patients, 142 were excluded for the following reasons: 3 for being under 18 years old; 39 for nonheadache diagnosis; and an additional 100 due to a headache diagnosis not fulfilling the inclusion criteria (further information can be found in Fig 1). Of the 409 patients included for initial analysis, 355 (86.8%) were women, the mean age was 41.6 years (range 18 to 88), and the main referrals were from another clinic in the same hospital (27.6%), ER

(26.9%), and primary care (25.4%). The most common diagnosis was episodic migraine (76.3%). Full information on patient characteristics can be found in Table 1.

Impact of Outpatient Clinic Observation on Prescribed Prophylactic Therapy

At the time of the first observation in the clinic, 71 patients (17.4%) were on prophylactic therapy, which was considered as not indicated in a single patient, in whom it was stopped. Among the 315 patients (77%) for whom prophylactic therapy was considered indicated, 245 (77.8%) were not taking any prophylactic drug and 70 (22%) were already on prophylactic treatment. Of the followed-up 265 patients, in 174 (65.7%), one prophylactic drug was added; in 4 (1.5%), two prophylactic drugs were added; in 16 (6%), the dose was increased; in 5 (1.9%), the treatment was switched; and in 1 (1.5%), it was stopped. In 65 (24.5%) patients, no change was made. Table 2 reflects the treatment changes among the 265 patients with a follow-up visit according to previous treatment status. Regardless of other treatment changes, all patients with MOH diagnosis were instructed to stop taking acute medication. There was a significant increase in the proportion of patients treated with prophylactics after evaluation in the headache outpatient clinic (71/409 to 214/265, $P < .05$; McNemar test for related samples).

A multivariate logistic regression analysis showed that women (OR = 2.09; 95% CI 1.1 to 3.97) and patients with diagnosis of MOH (OR = 6.97; 95% CI 1.60 to 30.39) were more likely to need therapeutic intervention, whereas patients referred from the ER were less likely to need it (OR = 0.44; 95% CI 0.22 to 0.89) (Table 3).

Follow-up

The first follow-up visit was performed at a mean of 4.8 ± 2.8 months (range 1 to 18) following the baseline visit. In terms of follow-up, of the 409 patients, 16 (3.9%) were discharged

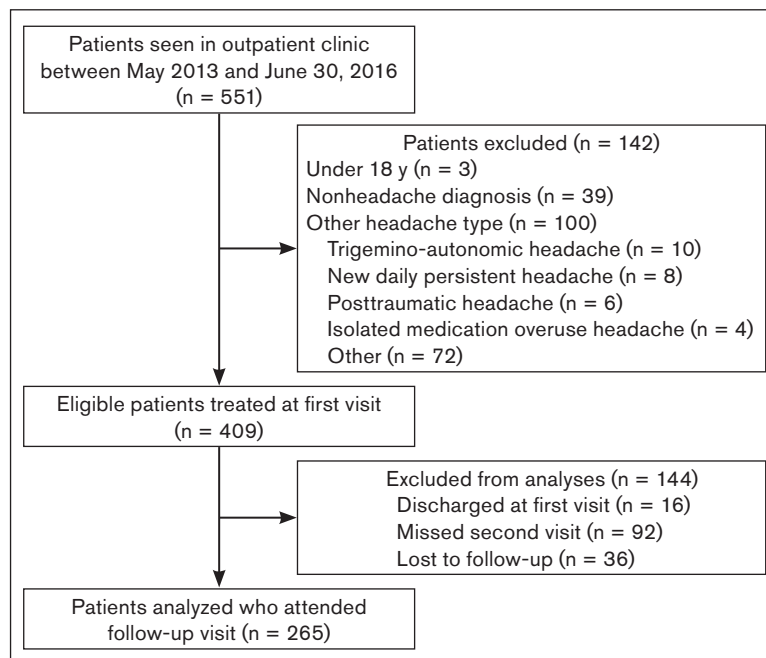


Fig 1 Sample selection according to inclusion and exclusion criteria.

immediately at first consultation, 36 (8.8%) were lost to follow-up, and 92 (22.7%) missed their second appointment (a secondary analysis revealed there was no difference between these patients and the remaining). Among the remaining 265 who had data available regarding the follow-up visit, 185 (69.8%) registered a qualitative improvement (reduction of at least 50% headache days per month), 48 (18.1%) remained the same, and 32 (12.1%) actually worsened or did not tolerate the prophylactic treatment that was initiated. Considering improvement according to diagnosis, 75% with MWA, 77% each with CM and TTH, and 64.8% of patients with MWOA improved.

A univariate logistic regression analysis showed that the use of prophylactic treatment was associated with a 2.5-fold increase in the likelihood of clinical improvement at follow-up (odds ratio [OR] = 2.49; 95% confidence interval [CI] 1.33 to 4.67; $P = .004$). The remaining variables were not determinant of the clinical outcome. A multivariate analysis showed that patients who were treated with prophylaxis were more likely to improve by the time of the second consultation regardless of demographic characteristics, diagnosis, or origin of referral (OR = 2.39; 95% CI 1.23 to 4.63; $P = .01$).

Discussion

In the present sample, although the majority (77%) of patients had an indication for prophylactic treatment, only 22% started treatment before evaluation in a tertiary center. Predictors of the need for prophylactic treatment included female gender and diagnosis of MOH. After the first consultation in the headache outpatient clinic, there was a significant increase in the proportion of patients under prophylactic treatment. At follow-up, the use of prophylactic treatment was associated with clinical improvement regardless of patient clinical or demographic characteristics.

Table 1 Patient Demographics, Diagnosis, and Referral Origins upon First Visit

| | All patients (n = 409) | Prophylactic treatment at first visit | |
|----------------------------|------------------------|---------------------------------------|-------------------|
| | | No (n = 338) | Yes (n = 71) |
| Demographics | | | |
| Age (y), mean ± SD (range) | 41.6 ± 14.6 (18–88) | 40.6 ± 14.2 (18–84) | 46 ± 15.9 (19–88) |
| Female, n (%) | 355 (86.8) | 289 (85.5) | 66 (93) |
| Diagnosis, n (%) | | | |
| TTH | 76 (18.6) | 61 (18) | 15 (21.1) |
| MWOA | 184 (45) | 158 (46.7) | 26 (36.6) |
| MWA | 83 (20.3) | 69 (20.4) | 14 (19.7) |
| CM | 7 (1.7) | 5 (1.5) | 2 (2.8) |
| TTH + MWOA | 15 (3.7) | 12 (3.6) | 3 (4.2) |
| TTH + MWA | 3 (0.7) | 2 (0.6) | 1 (1.4) |
| MWOA + MWA | 3 (0.7) | 2 (0.6) | 1 (1.4) |
| TTH + MOH | 7 (1.7) | 6 (1.8) | 1 (1.4) |
| MWOA + MOH | 15 (3.7) | 11 (3.2) | 4 (5.6) |
| MWA + MOH | 7 (1.7) | 5 (1.5) | 2 (2.8) |
| CM + MOH | 7 (1.7) | 6 (1.8) | 1 (1.4) |
| TTH + MWOA + MOH | 2 (0.5) | 1 (0.3) | 1 (1.4) |
| Origin, n (%) | | | |
| Primary care | 104 (25.4) | 91 (26.9) | 13 (18.3) |
| Outpatient | 113 (27.6) | 90 (26.6) | 23 (32.4) |
| ER | 110 (26.9) | 91 (26.9) | 19 (26.8) |
| Other | 82 (20) | 66 (19.5) | 16 (22.5) |

CM = chronic migraine; ER = emergency room; MOH = medication overuse headache; MWA = migraine with aura; MWOA = migraine without aura; TTH = tension-type headache.

Table 2 Treatment Changes in the 265 Patients with a Follow-up Visit According to Previous Treatment

| Previous treatment status | Treatment change | | | | | | Total |
|---------------------------|------------------|----------|-----------|---------------|----------|----------|------------|
| | Add one | Add two | No change | Increase dose | Switch | Stop | |
| No prophylactic | 156 | 3 | 50 | 0 | 0 | 0 | 209 |
| Tricyclic antidepressant | 4 | 0 | 1 | 3 | 2 | 0 | 10 |
| Propranolol | 7 | 0 | 6 | 3 | 0 | 0 | 16 |
| Valproic acid | 2 | 0 | 6 | 2 | 1 | 0 | 11 |
| Topiramate | 0 | 1 | 0 | 3 | 2 | 0 | 6 |
| Calcium channel blocker | 2 | 0 | 1 | 0 | 0 | 1 | 4 |
| Other | 2 | 0 | 1 | 3 | 0 | 0 | 6 |
| Two prophylactics | 1 | 0 | 0 | 2 | 0 | 0 | 3 |
| Total | 174 | 4 | 65 | 16 | 5 | 1 | 265 |

All data reported as number of patients.

Table 3 Predictors of Need for Therapeutic Intervention According to Logistic Regression

| | Multivariate analysis | | |
|---------------------|-----------------------|------------|------------|
| | OR | 95% CI | P value |
| Demographics | | | |
| Age (y) | 1.01 | 0.99–1.03 | .38 |
| Female gender | 2.09 | 1.10–3.97 | .02 |
| Diagnosis | | | |
| TTH | 1.28 | 0.49–3.32 | .61 |
| MWOA | 0.52 | 0.19–1.42 | .20 |
| MWA | 0.57 | 0.20–1.66 | .30 |
| MOH | 6.97 | 1.60–30.39 | .01 |
| Referral | | | |
| Primary care | 1.27 | 0.59–2.71 | .54 |
| Outpatient | 0.55 | 0.27–1.10 | .09 |
| ER | 0.44 | 0.22–0.89 | .02 |
| Other | 1.63 | 0.74–3.60 | .22 |

OR = odds ratio; CI = confidence interval; ER = emergency room; TTH = tension-type headache; MWOA = migraine without aura; MWA = migraine with aura; MOH = medication overuse headache. Significant values are in bold.

The proportion of patients on prophylactic treatment before the first consultation reflects a significant underuse of medication in diverse contexts such as primary care, other outpatient clinics, and the ER, which might relate to unfamiliarity with headache preventive treatment guidelines or to little experience with the treatments used, as previously reported.¹⁶ Women and patients with MOH tend to have a high frequency of headache episodes, and that could be a possible reason why the institution of prophylactic treatment in these groups was more likely.¹⁷ Similarly—although this issue was not addressed in this study—it seems reasonable to assume patients in the ER have already been evaluated by the on-call neurologist, and thus the need for therapeutic change could be lower.

At follow-up, the main predictor of clinical improvement was the institution of prophylactic treatment irrespective of timing (before or at first consultation), which reinforces the role of prophylactic treatment in the management of patients with primary headaches. The proportion of patients already prescribed prophylactic treatment (22%) is similar to reports from other countries, such as the USA, where of the 38% of migraine sufferers meeting criteria for preventive treatment, only 12% are using it.⁵ Interestingly, in Spanish cohorts, a similarly low number of patients referred to specialty clinics are already on prophylactic treatment (30% to 40%); however, this number more than doubles after specialist consultation to 70.4%.^{6,7} Similar data were published by Ferrari et al regarding the Italian practice, where initially only 16.8% of patients were under prophylactic treatment, a number that increased to 58.2% after assessment by a neurologist.⁹ Data from a Hungarian headache clinic reveals similar proportions of prophylaxis prescription; however, no information regarding follow-up was given.¹⁸ However, Swiss studies reveal higher proportions of patients on prophylactic treatment.^{19,20}

This study consists of a robust analysis of a large sample size of patients with primary headache; however, it does have its limitations. The retrospective nature of the study means the authors only had access to existing clinician-reported data. A precise quantification of headache days per month was not collected, since their reports were not universal. Also, this study was performed in a tertiary reference center, and thus the investigated sample may represent more severe cases and might not be representative of the general population. However, with this in mind, a high rate of prophylactic use would be expected by these “severe” patients—which is not the case. Lastly, gender analysis should be interpreted with caution, given the overrepresentation of women in headache (and especially migraine) cohorts.

In summary, given the high incidence/prevalence of primary headaches in clinical practice and the relatively simple management strategies required in a large proportion of patients in order to obtain a positive result, there seems to be a missed opportunity regarding the trial of at least one prophylactic treatment before referring to a specialized clinic in cases of refractory or atypical headaches. This might represent an opportunity to sensitize primary care doctors to the indications and benefits of prophylactic treatments, and future studies should evaluate whether such interventions translate into higher rates of prophylactic prescription before a neurology visit and more selective referral of more severe patients.

Conclusions

Most patients with primary headaches can be successfully managed with a single prophylactic drug. As such, the present authors believe there is an important underlying message regarding the need for improving the management of patients with primary headaches prior to referral to a specialized outpatient clinic, and they also highlight the importance of educational measures for treatment strategies and to minimize misdiagnosis.

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