Failure of Preventive Treatments in Migraine: An Observational Retrospective Study in a Tertiary Headache Center

CURRENT STATUS: UNDER REVIEW

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DOI: 10.21203/rs.3.rs-25315/v1

SUBJECT AREAS
  - Neurology
  - Neurosurgery

KEYWORDS
  - migraine, preventive treatment, observational study, tertiary headache center
Abstract

BACKGROUND

Despite the criteria of acute migraine treatment and prevention have been well described, there are still unmet needs, for a general underuse and low benefit of preventive treatments.

The aim of the present study was to observe retrospectively the short term effect of preventive treatment in a cohort of migraine patients come at a tertiary headache center, using data from an electronic medical record.

METHODS

This was an observational retrospective cohort study on data collected in a tertiary headache center. Data were extracted from an electronic dataset collected between January 2009 to December 2019. Main selection criteria were age 18-75, diagnosis of migraine without aura (MO), with aura (MA) and chronic migraine (CM), a control visit after three months from the first access, prescription of preventive treatment with level of evidence 1 as reported by Italian guidelines. As primary outcome measure we considered the change of frequency of headache at follow up, as second outcomes disability scores, intensity of headache, allodynia; as predictive factors age, migraine duration, sex and headache frequency, allodynia, anxiety and depression at baseline; comorbidity with fibromyalgia.

RESULTS

Among 6430 patients screened, 2800 met the selection, 1800 returned to follow up, 550 withdrawn for adverse events, 1100 were introduced into analysis. One hundred thirty four had a frequency reduction of 50% or more. Flunarizine was used in less severe migraine, with a better effect as compared to other drugs (odds ratio 1.48; p 0.022). Low headache frequency and absent or mild allodynia predicted a better outcome.

CONCLUSIONS

The mild effect of preventive drugs on migraine features and the number of patients lost to follow up or dropped out for adverse events confirm that in severely and chronic sufferers the first line preventive approach could delay a more focused therapeutic approach.
Background
Migraine is a diffuse and disabling disease, affecting roughly 12-14% percent of occidental population [1]. Despite the criteria of acute episodes treatment and prevention have been well described [2], there are still a large proportion of patients with unmet needs, for a general underuse and low benefit of preventive treatments [3]. National guidelines indicated the conditions for the prescription of preventive treatment, the drugs with evidence of action and consequent recommendation for their use [2]. Real world studies reported the modality of preventive treatment prescription for general practitioners and neurologists. An observational study in the US included 43660 migraine patients under preventive treatment, receiving different drugs in addiction to acute treatment [4]. The study identified main comorbidities associated to the preventive drugs prescription, such as sleep disorders or female gender, but no data on specific treatments and their effect. The French SMILE study, assessed the determinants of prescription of migraine preventive therapy among GPs and neurologists and factors determining eligibility, as frequency and severity of headache and scarce efficacy of acute treatment [5]. In an Italian study evaluating the use of triptans, only the 21.3% of patients using triptans were under oral preventive treatments or botulin toxin. In the same population, amitriptyline was the most prescribed drug, followed by topiramate (6.3%), propranolol (3.3%) and atenolol (2.7%). The rate of improvement was estimated on the triptans use reduction, and was even significantly lower among subjects treated with oral preventive therapies in comparison with those without these drugs, though a mild improvement was present in the group with chronic migraine [3]. The study just underlined that the current use of preventive therapies is scarce and with negligible benefits, and that the most of migraine patients have currently unmet needs.

Few data are available about preventive treatment prescription and their efficacy in patients observed at a third level headache center. This could be of potential interest in understanding the utility of available preventive drugs and the real need for the new drugs recently developed for migraine prevention [6].

The aim of the present study was to observe retrospectively the short term effect of preventive treatment in a cohort of migraine patients come at a tertiary headache center, using data from an
electronic medical record.

Methods

**Study design** This was an observational retrospective cohort study on data collected in a tertiary headache center.

**Setting** The Applied Neurophysiology and Pain Unit (ANPlab) includes 3 neurologists, 2 psychologists and 1 nurse. All patients are requested to fill an headache diary at the time of visit booking (which precede the first access for about three months), and to return after three months from the first visit, independently from the prescription of preventive treatment.

An example of headache diary used by patients is reported in the supplementary Fig. 1. The diary includes the alldynia scale with scores from 0 to 12, according to previous studies [7].

Only a limited number of clinical features are converted in the electronic codes useful for the retrospective analysis, which included the variables reported below. The local Ethic Committee of Policlinico General Hospital approved the use of electronic database, and patients signed an informed consent about the inclusion of their data and use for scientific purposes.

**Participants.** The present data were extracted from the electronic dataset collected between January 2009 to December 2019 (Fig. 1)

For the present analysis, we selected patients aged 18–75, who received a diagnosis of migraine without aura (MO), with aura (MA) and chronic migraine (CM) [8, 9], who were free from previous and current preventive treatments and use of central nervous system acting drugs, who had at least a control visit after three months from the first access and were prescribed preventive treatment with level of evidence 1 as reported by italian guidelines [2]. We did not select patients with severe general medical comorbidities as hepatic, renal and cardiovascular insufficiency, previous or current neurologic diseases other than migraine, diagnosis of current or previous psychiatric diseases.

**Exposure** All the preventive drugs with level of evidence 1, that are antidepressants (amitriptyline), beta blockers (propranolol and atenolol), calcium channel blockers (flunarizine), antiepileptic drugs (topiramate) were firstly considered as a whole, than single analyses were conducted in the
subgroups treated with the different drugs. During the analysis of data, we noted that in a subgroup of patients specifically refusing in a first attempt the use of drugs, magnesium was prescribed. In another subgroup, clinicians decided for the use of candesartan, for the presence of hypertension and contraindication to the use of beta blockers. In the final analysis, we thus decided to include also these patients, though both treatments were not in the list of drugs with level of evidence A (see details below). Considering that valproate is not indicated in Italy for the treatment of migraine, clinicians prescribed topiramate as first preventive drug.

**Variables** As primary outcome measure for the effect of preventive treatment we considered the change of frequency of headache at follow up, as second outcomes the MIDAS score [10], the intensity of headache on a 0-10 scale, allodynia [7] and general quality of life [11]. For headache frequency, we considered the average number of headache days in a month, computed in the last three months. As predictive factors for headache frequency reduction we considered age, gender, duration of headache, frequency and intensity of headache, allodynia, anxiety and depression scores, as observed at the first access [12, 13]. Comorbidity with fibromyalgia was also considered, as the center has specific experience about this condition [14]. Potential confounder for the evaluation of outcome could be the lack of distinction between headache and migraine days, which was introduced as an option of the electronic database in the course of clinical activity. Potential bias could be the unpredictable number of patients lost at follow up, the scarce reliability of headache diaries, and the choice of other treatments then those recommended as first line drugs, which could be possible in clinical practice. Other bias could be the lack of data about the number of migraine days and analgesics assumed. In fact, data on symptomatic drugs and their effect were not available for a problem in the electronic database occurring in the time between 2009–2016.

Patients with missing data in the variables considered as primary and secondary outcome measures, were not considered in the present analysis.

**STATISTICAL ANALYSIS**
Considering that a mean reduction of migraine frequency around 50% is generally indicated as a good outcome, and that a reduction lower than 30% could be interpreted as a treatment failure, we stated
a minimum sample size of 459 patients to explore the general effect of preventive treatments. (π 0.05; α 95%). This was valid for the whole migraine group.

Preliminarily, an univariate ANOVA was conducted for the primary variable, comparing the percent rate of change of headache frequency among single migraine types and drugs subgroups. The number of cases with 50% change of migraine frequency, was computed in the whole group and in those treated with the different drugs, thus computing the odd ratio to establish the superiority of a drug in the whole of migraine group. A multivariate ANOVA analysis was also performed, to compare the change of secondary outcome variables among migraine types and preventive treatments. A multivariate linear regression analysis between the percent rate of change of primary outcome measure and predictive factors was thus calculated. We also computed the odd ratio for the primary outcome, considering gender, presence of allodynia and comorbidity for fibromyalgia.

Results

Demographic data of selected patients - The flow chart for patients selection is reported in Fig. 1. Two hundreds and fifty five patients used triptans as symptomatic treatment, the remaining used NSAIDS. All patients were suggested to take triptans and/or NSAIDs (ibuprofen 400–600 mg) for migraine attacks. Patients with medication overuse, were requested to change the drug of abuse, and to take the symptomatic therapy only in case of severe headache.

Demographic and main clinical data are reported in Table 1. Among 296 patients with chronic migraine, 202 reported use of more than 10 monthly doses of NSAIDs, so received the diagnosis of Medication Overuse Headache (MOH) (9). CM patients presented with older age and higher anxiety and depression scores. (Table 1).
Table 1
Demographic and clinical data of migraine patients: MO: migraine without aura; MA: Migraine with aura; CM: Chronic Migraine. Frequency: average number of days with headache in a month, computed in the three months preceding the first visit. SAS: Zung anxiety score. SDS: Zung depression score. The results of ANOVA test (DF 3) and post hoc Bonferroni are reported.

|                    | Mean   | Error  | DS    | 95% CI Lower | 95% CI Upper | Post hoc bonferroni |
|--------------------|--------|--------|-------|--------------|--------------|---------------------|
| age ANOVA F 9.08 P < 0.0001 cases | MO 176 M; 471 F | 37.49  | 0.52  | 36.46        | 38.51        | Vs CM p < 0.001     |
|                    | MA 3 M; 9 F | 28.55  | 3.91  | 20.86        | 36.23        | Vs CM p 0.005       |
|                    | MO + MA 17 M; 39 F | 35.91  | 1.89  | 32.20        | 39.63        | Vs CM p 0.009       |
|                    | CM 78 M; 218 F | 40.94  | 0.79  | 39.40        | 42.49        |                     |
| migraine duration ANOVA F 1.44 P 0.22 | MO 176 M; 471 F | 15.53  | 0.47  | 14.62        | 16.45        | n.s.                |
|                    | MA 3 M; 9 F | 11.27  | 3.49  | 4.42         | 18.12        |                     |
|                    | MO + MA 17 M; 39 F | 16.74  | 1.69  | 13.43        | 20.06        |                     |
|                    | CM 78 M; 218 F | 16.70  | 0.70  | 15.32        | 18.08        |                     |
| headache frequency ANOVA F 238.39 P < 0.0001 | MO 176 M; 471 F | 9.61   | 0.27  | 9.08         | 10.13        | Vs CM p < 0.001     |
|                    | MA 3 M; 9 F | 6.82   | 2.00  | 2.90         | 10.74        | Vs CM p < 0.001     |
|                    | MO + MA 17 M; 39 F | 9.24   | 0.97  | 7.35         | 11.14        | Vs CM p < 0.001     |
|                    | CM 78 M; 218 F | 11.27  | 1.90  | 8.73         | 13.80        |                     |
| MIDAS ANOVA F 27.93 P < 0.0001 | MO 176 M; 471 F | 25.62  | 1.70  | 22.29        | 28.95        | Vs CM p < 0.001     |
|                    | MA 3 M; 9 F | 18.82  | 12.68 | -6.06        | 43.70        | Vs CM p < 0.001     |
|                    | MO + MA 17 M; 39 F | 20.77  | 6.13  | 8.73         | 32.80        | Vs CM p < 0.001     |
|                    | CM 78 M; 218 F | 22.26  | 0.40  | 21.47        | 23.05        |                     |
| headache intensity (0-100 VAS) ANOVA F 4.67 P 0.005 | MO 176 M; 471 F | 8.74   | 0.05  | 8.65         | 8.83         | Vs CM p 0.007       |
|                    | MA 3 M; 9 F | 8.82   | 0.34  | 8.14         | 9.49         |                     |
|                    | MO + MA 17 M; 39 F | 9.09   | 0.17  | 8.76         | 9.41         |                     |
|                    | CM 78 M; 218 F | 9.04   | 0.07  | 8.90         | 9.17         |                     |
| Alloodynia F: 0.80 p 0.01 | MO 176 M; 471 F | 2.67   | 0.08  | 2.51         | 2.82         | n.s.                |
|                    | MA 3 M; 9 F | 1.82   | 0.60  | 0.64         | 3.00         |                     |
|                    | MO + MA 17 M; 39 F | 3.15   | 0.29  | 2.58         | 3.72         |                     |
|                    | CM 78 M; 218 F | 3.01   | 0.12  | 2.78         | 3.25         |                     |
| SAS F: 8.57 p < 0.001 | MO 176 M; 471 F | 36.68  | 0.37  | 35.97        | 37.40        | Vs CM p < 0.001     |
|                    | MA 3 M; 9 F | 35.64  | 2.75  | 30.24        | 41.04        |                     |
|                    | MO + MA 17 M; 39 F | 36.04  | 1.28  | 33.53        | 38.55        | Vs CM p 0.035       |
|                    | CM 78 M; 218 F | 39.88  | 0.55  | 38.81        | 40.95        |                     |
| SDS F: 11.2 p < 0.001 | MO 176 M; 471 F | 35.28  | 0.38  | 34.52        | 36.03        | Vs CM p < 0.001     |
|                    | MA 3 M; 9 F | 30.36  | 2.90  | 24.68        | 36.05        | Vs CM p 0.023       |
|                    | MO + MA 17 M; 39 F | 34.82  | 1.35  | 32.18        | 37.47        | Vs CM p 0.03       |
|                    | CM 78 M; 218 F | 38.94  | 0.57  | 37.82        | 40.07        |                     |

Table 2 reports the preventive treatments used in the total of patients. Fifty patients treated with antidepressants, 66 with antiepileptics, 2 with beta blockers, 5 with calcium channel blockers and 1 with sartans, reported slight side effects, which did not request drug suspension. Eight hundred and twenty patients used triptans with good effect, 220 continued to use NSAIDs, in the remaining both were not efficacious.
### Table 2
Preventive drugs used in migraine patients

| Drugs               | Daily Dosages                              | Migraine diagnosis | Total |
|---------------------|--------------------------------------------|--------------------|-------|
| Beta blockers       | Propranolol: 80–160 mg; atenolol 50–100 mg | MO                 |       |
|                     |                                            | MA                 |       |
|                     |                                            | MA + MO            |       |
|                     |                                            | CM                 |       |
| Calcium channel     | Flunarizine 5 mg                           | 139                |       |
| blockers            |                                            | 2                  |       |
| Antidepressants     | Amitriptyline 10–25 mg                     | 245                |       |
| Integrators         | Magnesium 300–400 mg                       | 57                 |       |
| Antiepileptics      | Topiramate 50–100 mg                       | 149                |       |
| Sartans             | Candesartan 8–16 mg                        | 21                 |       |
| **Total**           |                                            | 647                | 1011  |

The mean frequency of migraine was different at baseline for the different drugs prescribed, as it was higher in the groups treated with antiepileptics and antidepressants, as compared to other groups, excluding sartans (Table 3). In 154 females, presenting with FM comorbidity, neurologists suggested amitriptyline in 104 cases, topiramate in 25 cases, flunarizine in 5 cases, propranolol in 2, magnesium in 2 and sartans in 3 cases.

### Table 3
Frequency of headache at baseline in the different drugs groups: ANOVA with drugs as factor: F 20.54 p < 0.0001. Bonferroni: Antiepileptics and antidepressants vs beta blockers, calcium channel blockers and integrators: p < 0.001. Sartans vs integrators p < 0.05.

| Drugs               | Mean  | Error  | DS   | 95% CI       |
|---------------------|-------|--------|------|--------------|
| Beta blockers       | 9.46  | 1.25   | 7.01 | 11.90        |
| Calcium channel     | 9.45  | 0.65   | 8.17 | 10.73        |
| blockers            |       |        |      |              |
| Antidepressants     | 14.64 | 0.41   | 13.84| 15.43        |
| Integrators         | 7.30  | 1.05   | 5.25 | 9.36         |
| Antiepileptics      | 15.24 | 0.50   | 14.25| 16.23        |
| Sartans             | 12.94 | 1.40   | 10.21| 15.68        |
The mean reduction of headache frequency and confidence intervals are reported in Table 3 and Table 1S. The most of patients had a reduction of headache frequency less than 50%, with a slight increase of patients with favorable outcome in the group treated by flunarizine. (Table 4; Fig. 2). One hundred and eighty CM patients with associated MOH discontinued the previous symptomatic drug, using the suggested therapy (triptans). One hundred fifty five persisted chronic, the remaining shifted to a diagnosis of episodic migraine, in all of them the diagnosis of MOH was not confirmed. The remaining 40 patients continued to use NSAIDs in excess and the diagnosis of CM with MOH was confirmed.
Table 4

|                | beta blockers | calcium channel blockers | antidepressants | Integrators | antiepileptics | Sartans |
|----------------|---------------|--------------------------|-----------------|-------------|----------------|---------|
| < 50%          | 28            | 98                       | 288             | 40          | 196            | 27      | 677     |
| > 50%          | 17            | 67                       | 137             | 24          | 80             | 9       | 334     |
| Odds ratio     | 1.23          | 1.48                     | 0.93            | 1.23        | 0.77           | 0.66    |
| 95% CI         | 0.67 to 2.30  | 1.05 to 2.08             | 0.71 to 1.2     | 0.71 to 2.08 | 0.57 to 1.046 | 0.3 to 1.4 |
| z statistic    | 0.69          | 2.25                     | 0.461           | 0.78        | 1.67           | 1.037   |
| Sig. level     | P = 0.48      | P = 0.02                 | P = 0.64        | P = 0.43    | P = 0.09       | P = 0.29 |

The MANOVA analysis comparing secondary outcome variables among different treatments and migraine subtypes, showed a general improvement at 3 months follow up, which was not different for the preventive treatments and migraine diagnosis. The within subjects analysis, showed a significant reduction of headache intensity and allodynia in the whole of treated patients (Table 5).

Table 5

Mean (M) and Standard Deviation (SD) of secondary outcome variables in 1011 migraine patients in baseline condition and after 3 months under preventive treatment (demographic data are reported in Table 1)

| Condition          | MIDAS         | VAS          | ALLODYNIA    | PH SF36  | MH SF36 |
|--------------------|---------------|--------------|--------------|----------|---------|
| Baseline           | M 33.30       | 8.82         | 2.81         | 36.59    | 38.67   |
|                    | SD 43.97      | 1.16         | 2.00         | 8.93     | 8.75    |
| follow up          | M 21.74       | 8.30         | 2.40         | 38.10    | 39.48   |
|                    | SD 31.22      | 1.46         | 1.98         | 8.74     | 8.99    |
| Within subjects    |               |              |              |          |         |
| ANOVA              | F 2.93        | 9.39         | 3.39         | 1.14     | 1.37    |
|                    | DF 2          | 2            | 2            | 2        | 2       |
|                    | P 0.053       | < 0.001      | 0.034        | 0.31     | 0.25    |
| MANOVA: condition  | (baseline vs  | F (Roy square): 5.12, DF 5, p < 0.0001; conditions vs drugs: F 0.64, DF 5, P 0.69; condition vs migraine type: F 1.83, DF 5 p 0.1 ; condition vs drugs vs migraine type F 0.55; DF 12; p 0.88. The within subjects ANOVA results are reported |
| (baseline vs follow up): F (Roy square): 5.12, DF 5, p < 0.0001; conditions vs drugs: F 0.64, DF 5, P 0.69; condition vs migraine type: F 1.83, DF 5 p 0.1 ; condition vs drugs vs migraine type F 0.55; DF 12; p 0.88. The within subjects ANOVA results are reported |
| PH Physical Health score SF36; MH: Mental Health SCORE SF36.

The multiple regression analysis, showed that a lower allodynia score and frequency of headache at baseline predicted a favorable outcome with at least 50% frequency reduction (Table 6, Table 2S; Fig. 3). The relationship with allodynia score and headache frequency are confirmed for antiepileptics, while in the group treated with antidepressants, lower allodynia score and headache intensity were associated with a better outcome (Table 3S). The multiple regression analysis did not show relevant results in the groups treated with the other drugs.
Table 6

Multiple regression analysis for change of frequency at follow up in 1011 migraine patients.

|                  | not standardized coefficients | standardized coefficient | t     | sig.  |
|------------------|-------------------------------|--------------------------|-------|-------|
|                  | B                | standard deviation (error) | Beta |       |       |
| (Constant)       | 49.46            | 12.72                    | 3.89  | 0.0001|
| SAS              | -0.37            | 0.23                      | -0.08 | -1.58 | 0.11  |
| SDS              | 0.03             | 0.23                      | 0.01  | 0.14  | 0.89  |
| VAS              | -0.47            | 1.27                      | -0.01 | -0.27 | 0.71  |
| frequency at baseline | 0.65          | 0.17                      | -0.13 | -3.83 | 0.001 |
| allodynia        | -3.02            | 0.79                      | -0.13 | -3.81 | 0.001 |
| AGE              | -0.13            | 0.13                      | -0.04 | -1.02 | 0.31  |
| Illness duration | 0.00             | 0.15                      | 0.00  | 0.01  | 0.99  |
| SAS: Zung anxiety score |                   |                           |       |       |       |
| SDS: Zung depression score |                   |                           |       |       |       |

The comorbidity with FM and the presence of allodynia were associated with a lower number of patients with a good outcome, while gender had no effect on drugs efficacy. (Table 7).

Table 7

Effect of fibromyalgia (FM) comorbidity, gender and allodynia on primary outcome (50% headache frequency reduction).

|                  | Outcome | Odds ratio | 95% CI:   | z statistic | Significance level |
|------------------|---------|------------|-----------|-------------|--------------------|
| FM comorbidity   | no      | 571        | 299       | 1.58        | 1.05 to 2.38       | 2.2  | P = 0.02 |
|                  | yes     | 106        | 35        | 1.08        | 0.8 to 1.44        | 0.523| P = 0.6  |
| Gender           | M       | 180        | 94        | 1.08        | 0.8 to 1.44        | 0.523| P = 0.6  |
|                  | F       | 497        | 240       | 0.5         | 0.35 to 0.72       | 3.67 | P = 0.0002 |
| Allodynia        | No      | 73         | 67        | 0.5         | 0.35 to 0.72       | 3.67 | P = 0.0002 |
|                  | Yes     | 594        | 277       |             |                    |      |         |

Discussion

This observational retrospective cohort study tested the effects of preventive treatments in a population of migraine patients come to a tertiary headache center.

Main results consist of a mild effect of treatments on headache frequency, with less than 50% of reduction in most cases, as well as on migraine related disability and general quality of life.

Flunarizine was prescribed in patients with lower headache frequency as compared to antiepileptics and antidepressants, and showed a slight superiority in the therapeutic efficacy. Moreover, absent or less severe allodynia predicted a better outcome, while comorbidity with fibromyalgia was associated with reduced therapeutic effect.

General considerations on headache populations These real life data showed that in our south Italy tertiary headache center, the most of patients suffered from medium-high frequency migraine, not previously treated with preventive drugs, and only a minority of them used triptans. An Italian study
[3] showed that only a minority of patients using triptans and worthy of prophylaxis, assumed preventive drugs, that means that they did not have access to headache specialist or center, or that they had scarce compliance to the prescribed treatment, or they withdraw for adverse events. Our impression is that the most of patients were addressed to our center for a medium-high frequency migraine that was previously underestimated, though worthy of preventive treatment and triptans prescription. This is in line with results of a study conducted 10 years ago in 10 Italian headache centers, which demonstrated that only 26.8% out off 2675 patients attending the Centers had previously received a diagnosis of migraine [15].

In the total number of patients free from other CNS drugs or relevant comorbidities, about 1000 were lost to follow up, in accord to previous studies (16,17). More than 500 patients withdrawn for adverse events, that confirms that reasons for scarce compliance may be side effects and low efficacy of prescribed drugs.

In our selected migraine sample, only a minority suffered from medium-high frequency migraine with aura, which is in accord with data on general population (18,19).

Duration of migraine was very long in our sample, though patients were free from previous preventive treatments. Patients with CM were naïve to treatment, despite their clinical picture was obviously more severe than episodic migraine groups, with more severe disability and higher anxiety and depression scores. It is so conceivable that transformation into chronic migraine was almost recent, though the most of them were drug abusers, according to current knowledge (20).

The neurologists treated patients in accord with Italian guidelines (2). Sodium valproate was reserved as second line approach, as its use is off-label in Italy. The choice of antidepressants and antiepileptics as first line therapy was reserved to patients with more severe and chronic migraine, according to previous studies (20). The use of magnesium in 64 patients as preventive treatment deserves discussion. Nutraceutics have low efficacy in migraine prophylaxis, and their level of evidence is very low (21,22). Moreover, migraine patients are not confident with CNS acting drugs (23), and sometimes they do not agree with this approach. The use of magnesium and other nutracetics is frequent in clinical practice (21). This was the reason why we decided to introduce also
patients with magnesium treatment in the final analysis. According to current national guidelines (2),
candesartan has a level III of recommendation, but clinicians used it in a small number of patients.
The revision of clinical records, showed that patients had a mild but underestimated and not
controlled hypertension and contraindications to the use of beta blockers. Considering that this
situation may occur in clinical practice, we introduced also this group in the final analysis.

*Effects of preventive treatments on migraine frequency.* There was only a mild effect on headache
frequency in the three months following preventive drugs prescription, in accord to previous studies
based on indirect evidence (3,16,20). This could suggest that there is a bias between Randomized
Controlled Trials (RCTs) and real life. Moreover, RCTs are few and conducted many years ago in small
patients series (2). It is thus not surprising that magnesium was not inferior as efficacy when
compared to recommended drugs, as its mild effect confirmed results of RCTs (22). Also candesartan
exerted a slight effect on headache frequency, not inferior to other drugs (24). The comparison
among groups with different cases number, is quite unreliable under a statistic point of view (view the
paragraph below), but it could support a general impression of a weak action of all the prescribed
drugs on headache frequency.

Flunarizine at 5 mg dosage was more efficacious than the other drugs on headache frequency (25).
Moreover, clinicians prescribed flunarizine to patients with lower frequency of migraine, a factor
predisposing to a better outcome.

Patients reported the use of triptans in the majority of cases, which could be partly responsible for
reduction of headache intensity. Chronic patients with medication NSAIDs overuse, were also invited
to shift to triptans, a recommendation followed by the most of them. In any case, the majority of
patients remained chronic with overuse of triptans, for the weak effect of preventive treatments.

*Effects of preventive treatments on other clinical variables* A general improvement of migraine
related disability, quality of life, headache intensity and allodynia was independent from the drug and
type of migraine. Considering the single variables, the intensity of headache and allodynia changed in
a relevant way, an effect attributable to the preventive treatments and probably to the use of
triptans. The effect of antiepileptics and antidepressants on allodynia was also reported in previous
studies (26). An Italian longitudinal study on migraine evolution over three months observation, reported an evident trend toward improvement in disability and social activity, independent from the use of preventive treatments (27). The slight improvement of the evaluated clinical features, would partly be a spontaneous evolution in patients during continuity of care, and partly an effect of preventive and acute treatment.

**Predicting variables**-Low frequency of migraine and reduced expression or absence of allodynia symptoms at baseline predicted a better effect of preventive treatments in the whole of patients. In studies on factors predicting the effects of acute treatments, alldynic patients had a worse response to triptans (28). A predictive role of allodynia, was present in antidepressants and antiepileptics groups, which included a reliable number of patients. Anxiety and depression at baseline, that were more expressed in CM group, were not associated with a worse efficacy of treatments on headache frequency. We excluded cases with previous documented psychiatric diseases. Considering that scores ≥ 50 for the depression scale and ≥ 45 for the anxiety scales (12,13) indicate relevant symptoms, our patients presented with scores within normal ranges, though they were higher in CM patients. Basal anxiety and depression scores seem not relevant for the final effects of drugs, at least in non psychiatric patients.

Gender was also unrelated to the effect of preventive drugs. Males were the 27% of the total selected population, which is coherent with migraine representation in a sample of Italian population (29). Previous studies reported that males have a better compliance with treatments than females, though the effect of sex on treatment efficacy was not evaluated. (30)

The comorbidity for FM was also associated with reduced effect of preventive drugs on headache frequency. The most of patients assumed amitriptyline, which may be a good chance for migraine patients with FM comorbidity (14). In previous studies, we observed an association between FM and more severe migraine (14). Present results could also confirm a minor response to preventive treatments. FM patients have generally a scarce response to different treatments, indicating the need of an individualized therapeutic approach. In migraine patients with FM comorbidity, central sensitization is a predominant phenomenon, causing a diffusion of pain in somatic sites (14). In light
of present study, we could suggest that the clinical expression of central sensitization phenomena as alldynia and FM comorbidity, could predict a worse response to preventive treatment.

Study limitation—This observational retrospective study has several flaws

The sample size for the first outcome variable was reliable for the entire group and that treated with antidepressants, while the cases number was smaller for the other drugs. Moreover, In our opinion, results could shed light on real life situation.

Potential confounders and bias affected the final reliability of data. We found particularly important the lack of information about the efficacy of symptomatic treatments, giving that the reduction of alldynia and intensity of headache at follow up, cannot be assigned to triptans or preventive treatments.

We focused on fibromyalgia comorbidity, as our Center has specific experience in application of diagnostic criteria. Other comorbidities, as hypertension or obesity, life styles, as physical inactivity, habits, as smoking, or even professions, could affect the outcome of treatments, but we decided to focus on main clinical and demographic aspects in selected patients at their first preventive approach, reserving the global evaluation of these factors to further analyses.

The study is observational, and lacks of a control population, which would be useful to dissect the effect of drugs from a spontaneous evolution.

Conclusions

A mild effect of current preventive treatments on headache frequency and disability emerge from present data. The number of patients lost to follow up or dropped out for adverse events is impressive and confirms that the preventive approach to migraine seems currently inefficacious and unwelcome, even in tertiary headache centers. The low number of chronic patients reverting into episodic form after three months follow up confirms this impression. No drug demonstrated higher efficacy, except for flunarizine, which was prescribed to less affected patients. A potential useful indication for the use of current first line preventive drugs may be a low frequency of migraine and absence of alldynia and other central sensitization symptoms as fibromyalgia. These results indicate the early use of more recent treatments as botulinum toxin or CGRP antagonists in naïve patients with medium-severe
headache frequency and allodynia, in contrast to the general trend to offer these opportunities to first
line preventive drugs resistant patients.

List Of Abbreviations
MA
Migraine with aura
MO
Migraine without aura
CM
Chronic migraine
FM
Fibromyalgia
SDS
Self Rating Depression Scales
SAS
Self Rating Anxiety Scales

Declarations
Ethics approval and consent to participate
The local Ethic Committee of Policlinico General Hospital approved the use of electronic database, and
patients signed an informed consent about the inclusion of their data and use for scientific purposes.
Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding
author on reasonable request.
Consent to publish
Marina de Tommaso confirms that she had full access to all the data in the study and had final
responsibility for the decision to submit for publication
Competing interests:
Marina de Tommaso received remuneration for scientific contributions from: Allergan, Novartis, Teva
Authors contribution
Marianna Delussi: patients’ evaluation, database construction, data analysis
Eleonora Vecchio: patients evaluation and selection
Silvia Quitadamo: patients evaluation and selection
Giuseppe Libro: patients evaluation and selection
Marina de Tommaso: study design, data analysis, manuscript preparation and editing

Acknowledgements

not applicable

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Figures

Figure 1
Flow chart reporting migraine patients selection criteria.
Figure 2

Representation of percent rate of headache frequency change for single cases.
Figure 3

Linear regression analysis between rate of headache frequency change and allodynia at baseline.

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