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Original

Migraine preventive treatment failure: A cross-sectional study in a tertiary center in Brazil

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Background
In Brazil, there is a scarcity of evidence on migraine burden in patients who have experienced previous preventive treatment failure (PPTF).

Objective
To evaluate the associations between ≥ 3 PPTF and clinical, psychiatric, and medical history data.

Methods
In a retrospective, cross-sectional study, the medical records of migraine patients who first visited a tertiary specialized clinic were examined. We selected adults of both sexes aged ≥18 years who attended their first appointment between March and July 2017. Ordinal logistic regression models estimated the associations between number of PPTF (no previous treatment, 1 PPTF, 2, and ≥3 PPTF) and chronic migraine, the number of diagnosis exams performed, abortive drugs classes used, and non-pharmacological treatments tried (all categorized as none, 1-3, and ≥4), and severe depression (PHQ-9 ≥15) and anxiety (GAD-7 ≥15), adjusted for sex, age, and years with disease.

Results
Data from 440 patients (72.1% female) with a mean (SD) age of 37.3 (13.0) years were analyzed. The frequency of no previous treatment was 37.7% (166/440), while 31.8% (140/440) showed ≥3 PPTF. In patients with ≥3 PPTF, 35.7% (50/140) had episodic, and 64.3% (90/140) had chronic migraine. Compared to no previous treatment, patients with ≥ 3PPTF showed higher odds (95% confidence interval) for chronic migraine [2.10 (1.47, 2.98)], ≥ 4 diagnosis exams [6.59 (3.38, 12.84)], ≥4 abortive drug classes [16.03 (9.53, 26.94)], ≥4 non-pharmacological treatments [5.91 (3.07, 11.35)], and severe depression [1.75 (1.07, 2.88)] and anxiety [1.73 (1.05, 2.85)].

Conclusion
Patients first visiting a headache specialist had a high frequency of non-response treatment associated with higher migraine burden in terms of chronification, psychiatric comorbidity, acute medication and non-pharmacological treatment inefficacy, and unnecessary exams.

Keywords:
Migraine
Preventive Therapy
Treatment Failure
Healthcare Resources
Disease Burden

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Introduction

Migraine is characterized by a headache lasting from 4 to 72 hours, featuring debilitating pain and symptoms. This headache is typically pulsating, one-sided, exacerbated by physical activity, and often accompanied by nausea, vomiting, photophobia, and phonophobia.[1] Globally, it affects approximately one billion individuals,[2] and 15.2 % of Brazilian adults,[3] mostly being part of the economically active population. During episodes of pain, individuals may be compelled to take time off work or, if they continue working, their productivity is significantly diminished. This not only results in financial losses for both the affected individuals and their respective institutions but also poses a risk of job insecurity.[4,5] Beyond the economic ramifications, there is a notable social impact. Those experiencing migraine attacks miss out on crucial moments of social interaction with friends and family,[6] further adding to the multifaceted challenges associated with this condition.

Migraine can be divided into episodic, when headaches occur less than 15 days per month, and chronic, when they occur ≥15 days per month for ≥3 months, with ≥8 of these days featuring typical migraine pain.1 Prophylactic treatment is recommended for individuals who experience ≥3 days of pain for a period of ≥3 months or for those who, despite having less frequent pain, are profoundly impacted in their quality of life.[7]

The goals of prophylactic treatment extend beyond enhancing the patient's quality of life to also encompass reducing the socioeconomic impact, thus promoting cost-effectiveness for both the individual and society at large.[7,8]

Like many medical conditions, there are individuals who do not respond to treatment and experience failures with one or more therapies.[9] In planning a population-based health care policy for headache management, it is key to understand patients' response to therapies delivered by different levels of care. Public policies for headache care in Brazil has been a topic of interest and several initiatives established.[10] Despite the amount of information available on new treatments, medications, and the impact of migraine on an individual's life, there is a notable dearth of evidence regarding the burden raised by previous preventive treatment failure (PPTF) and the underlying reasons for these failures. In Brazil, no study has evaluated the clinical factors associated with PPTF.

We aimed in this study to assess the amount of PPTF and the associated clinical factors in patient's journey until reaching a tertiary headache center.

Methods

This retrospective, single-center observational study aimed to characterize the clinical history with focus on PPTF, procedures, mental health burden, and follow-up strategies undertaken by migraine patients in Brazil before their initial consultation with a headache specialist at a tertiary center. Data were extracted from patient medical records after they participated in an interview during their first clinic visit. The study adhered to all applicable local regulations. Given its cross-sectional nature and reliance on medical chart reviews without the identification of specific subjects, the study did not require signed informed consent.

Eligibility criteria

We included medical records of adult patients of both sexes, aged 18 years or older, who attended their initial consultation at the Sao Paulo Headache Center, a tertiary care facility, during the period from March to July 2017.

Exclusion criteria

Comprised patients with concurrent dementia, or those exhibiting substantial neurological impairments.

Study procedures

In this clinical setting, patients typically undergo an interview as part of their initial routine visit. The interview comprises a structured questionnaire designed to collect data on various aspects, including sociodemographic details, characteristics of their headaches, prior diagnostic approaches employed, clinical history, family medical history, and previous treatments received. Additionally, patients were assessed for comorbid mental disorders using the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) questionnaires to screen for symptoms of depression and anxiety, respectively.[11,12]

Study variables

Previous preventive treatment failure (PPTF) - Outcome Variable

The number of PPTF was categorized as no previous treatment, 1 PPTF, 2 PPTF, and ≥3 PPTF.

Medical History, Clinical, and Mental Disorders - Explanatory Variables

The number of diagnosis exams performed, abortive drugs classes used, and non-pharmacological treatments tried were categorized as none, 1-3, and ≥4. Severe depression and severe anxiety were defined as PHQ-9 and GAD-7 scores ≥15.

Covariates
We included in the adjusted analyses the variables, sex (female or male, assigned at birth), age (continuous, years) and disease duration (continuous) as years living with migraine.

Statistics
Descriptive statistics for sociodemographic, clinical, and mental disorders variables are reported as count and percentage or mean with standard deviation (SD). Pearson X^2 tests was adopted to estimate asymmetry of proportions for sociodemographic, clinical, and mental disorders variables between PPTF groups. Post hoc Bonferroni´s correction test was performed for multiple comparisons of significant associations. One-way ANOVA with pairwise comparisons employing Bonferroni corrections were used to compare continuous variables (age, years living with migraine) between PPTF groups.

Because the ordered feature of categorical variables, ordinal logistic regression models were performed. These models estimated the crude and adjusted odds ratios and 95% confidence interval [OR (95% CI)] for the number of PPTF (outcome variable) according to each clinical and mental disorder (explanatory variables). Adjusted models controlled for the effects of sex, age, and years with migraine. Severe depression and anxiety were categorized as "no" (set as reference category), or "yes".

To eliminate the expected effects of underdiagnosis and undertreatment in the analysis from patients with no previous treatment and having undergone no diagnostic exams, used no abortive medications, or tried no non-pharmacological treatments, we compared the same associations between patients with 1 PPTF (reference) and ≥3 PPTF.

The assumption of proportional odds for the effects of the explanatory and covariates in the ordinal regression models were tested. No models violated this assumption ($p > 0.05$). The statistical analyses were computed with a SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY). A two-tailed p-value <0.05 was considered statistically significant.

Results

Data from 440 patients (72.5% female) with a mean (SD) age of 37.2 (12.8) years were analyzed. The frequency of patients with no previous treatment was 37.7% (166/440), while 31.9% (140/440) showed ≥3 PPTF. In patients with ≥3 PPTF, 35.7% (50/140) had episodic migraine and 64.3% (90/140) had chronic migraine (Figure 1).

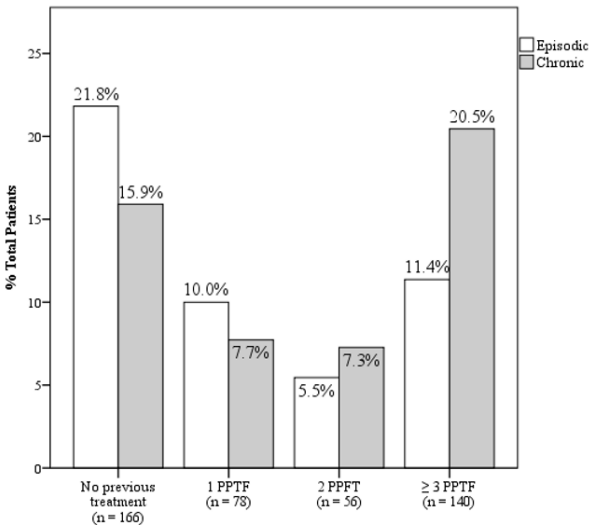

Figure 1 – Frequency of migraine type according to PPTF in 440 patients first visiting a headache specialist clinic.

PPTF: Previous Preventive Treatment Failure;

Table 1 summarizes the sociodemographic and clinical characteristics of groups. Compared to the no previous treatment group, patients reporting ≥3 PPTF were predominantly female, had higher frequency of chronic migraine, severe depression but not anxiety, as well as performed more diagnosis exams, used more classes of abortive medications, and tried more non-pharmacological treatments (Table 1).

Both crude and adjusted ordinal logistic regression models featured a similar pattern of association. Compared to the group with no previous treatment, there was a gradual increase in the odds of chronic migraine, for undergoing more diagnostic exams, using a greater number of abortive medications, trying more non-pharmacological treatments, and exhibiting severe depression and anxiety as the number of PPTF increased (Table 2). This trend persisted regardless of sex, age and years lived with migraine. Compared to the group without previous treatment, patients with ≥3 PPTF showed higher odds for chronic migraine [2.10 (1.47, 2.98), $p < 0.001$], ≥4 diagnosis exams [6.59 (3.38, 12.84), $p < 0.001$], ≥4 abortive drug classes [16.03 (9.53, 26.94), $p < 0.001$], ≥4 non-pharmacological treatments [5.91 (3.07, 11.35), $p < 0.001$], severe depression, [1.75 (1.07, 2.88), $p = 0.025$], and severe anxiety [1.73 (1.05, 2.85), $p = 0.031$)] (Figure 2).

Compared to patients with 1 PPTF and , the adjusted ordinal models showed that patients with ≥3 PPTF had

Table 1. Sociodemographic characteristics of 440 patients first visiting a headache specialist clinic.

	No previous treatment (n =166)	1 PPTF (n = 78)	2 PPTF (n = 56)	≥ 3 PPTF (n = 140)
Mean (SD) Age, years	35.8 (13.3)	37.8 (12.3)	38.8 (13.0)	37.9 (12.4)
Mean (SD) years with migraine	14.9 (10.8)	16.1 (9.2)	19.5 (12.1) a	19.3 (11.9) b
Female, n (%)	116 (69.9)	51 (65.4)	37 (66.1)	115 (82.1) *#†
Chronic Migraine, n (%)	70 (42.2)	34 (43.6)	32 (57.1)	90 (64.3) *#
Diagnosis Exams, n (%)				
None	29 (17.5)	8 (10.3)	2 (3.6) *	7 (5.0) *#
1-3	91 (54.8)	44 (56.4)	27 (48.2)	46 (32.9) *#†
≥ 4	46 (27.7)	26 (33.3)	27 (48.2) *	87 (62.1) *#
Abortive Drug Classes, n (%)				
None	105 (63.3)	21 (26.9) *	13 (23.2) *	14 (10.0) *#†
1-3	51 (30.7)	38 (48.7) *	23 (41.1)	54 (38.6)
≥ 4	10 (6.0)	19 (24.4) *	20 (35.7) *	72 (51.4) *#†
Non-pharmachological treatments, n (%)				
None	58 (34.9)	22 (28.2)	7 (12.5) *#	13 (9.3) *#
1-3	96 (57.8)	52 (66.7)	39 (69.6)	96 (68.6)
≥ 4	12 (7.2)	4 (5.1)	10 (17.9) *#	31 (22.1) *#
Severe Depression, n (%)	20 (12.0)	6 (7.7)	11 (19.6) #	29 (20.7) *#
Severe Anxiety, n (%)	24 (14.5)	8 (10.3)	5 (8.9)	32 (22.9) #†

PPTF: Previous Preventive Treatment Failure; [a]: $p < 0.05$; [b] $p < 0.01$ vs No previous treatment, One-way ANOVA, Bonferroni-adjusted; *: $p < 0.05$ vs No previous treatment; #: $p < 0.05$ vs 1 PPTF; †: $p < 0.05$ vs 2 PPTF, chi-square's test, Bonferroni-adjusted.

Table 2. Medical history factors and mental health burden associated with having PPTF in 440 patients first visiting a headache specialist.

	Crude Model		Adjusted Model	
	OR (95% CI)	*p*	OR (95% CI)	*P*
Chronic Migraine				
Yes	2.04 (1.44-2.88)	< 0.001	2.10 (1.47-2.98)	< 0.001
No	Ref.	Ref.	Ref.	Ref.
Diagnosis Exams				
≥ 4	5.72 (2.98-10.95)	< 0.001	6.59 (3.38-12.84)	< 0.001
1-3	2.13 (1.13-4.02)	0.019	2.28 (1.19-4.34)	0.012
None	Ref.	Ref.	Ref.	Ref.
Abortive Drug Classes				
≥ 4	16.89 (10.11-28.24)	< 0.001	16.03 (9.53-26.94)	< 0.001
1-3	5.10 (3.25-7.98)	< 0.001	4.83 (3.07-7.59)	< 0.001
None	Ref.	Ref.	Ref.	Ref.
Non-pharmacological Treatments				
≥ 4	6.94 (3.65-13.19)	< 0.001	5.91 (3.07-11.35)	< 0.001
1-3	2.94 (1.90-4.56)	< 0.001	2.69 (1.73-4.20)	< 0.001
None	Ref.	Ref.	Ref.	Ref.
Severe Depression				
Yes	1.84 (1.13-3.01)	0.014	1.75 (1.07-2.88)	0.025
No	Ref.	Ref.	Ref.	Ref.
Severe Anxiety				
Yes	1.64 (1.00-2.68)	0.049	1.73 (1.05-2.85)	0.031
No	Ref.	Ref.	Ref.	Ref.

Reference group: No previous treatment (n = 166). The adjusted models controlled for the effects of age, sex, and years living with migraine.

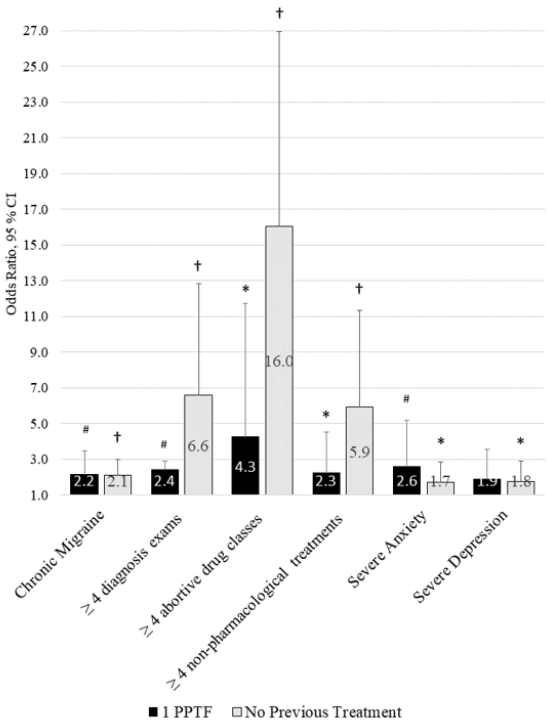

Figure 1 – Association of ≥ 3 PPTF with clinical, medical history, and mental health comorbidities. Data are expressed as odd ratio with 95 % confidence interval (CI).

PPTF: Previous Preventive Treatment Failure; *: p-value < 0.05; #: p-value < 0.01; †: p-value < 0.001

higher odds for chronic migraine [2.17 (1.35, 3.48), p = 0.001], ≥4 diagnosis exams [4.25 (1.54, 11.75), p = 0.005], ≥ 3 abortive drug classes [1.98 (1.16, 3.38), p = 0.011], ≥3 non-pharmacological treatments [2.25 (1.12, 4.53), p = 0.022], severe anxiety, [2.58 (1.28, 5.18), p = 0.008], but not severe depression [1.87 (0.98, 3.54), p = 0.055)] (Figure 2).

Discussion

Our study found a high proportion of patients with multiple PPTF before visiting specialized headache center, which were more likely to have chronic migraine, undergo more diagnostic exams, use a variety of abortive medications, try more non-pharmacological treatments, and experience severe depression and anxiety.

The findings of this study indicate that migraine is undertreated and mistreated, leading to a prolonged

and exhaustive journey for patients before finding a headache specialist.[13,14] Also, this study underscores the substantial increase in healthcare utilization and burden associated with PPTF and the importance of early

specialized headache care to avoid socioeconomic and personal burden.

Our findings have similarities and discrepancies with data from the BECOME study, a prospective, multicentric study in Europe/Israel involving 163 headache specialist centers from 18 countries, with 20,837 patients screened.[15] Among 2,419 patients analyzed cross-sectionally in the part 2 of the study, 28.7% had ≥3 PPTF, while higher PPTF was accompanied by higher healthcare utilization and higher prevalence of chronic migraine,[15] Depression was not associated with higher PPTF, as observed in our comparison with the 1 PPTF group, however, contrary to our results, anxiety showed a trend to decrease. This partly discrepant data may be related to patients' characteristics in the BECOME study, which was composed of patients already visiting headache specialist, and the criteria for severe anxiety used in our study.

Although we did not conduct a pharmacoeconomic analysis in the present study, our findings concur with data from a study that investigated healthcare utilization costs from an US health insurance database with 24,282 patients with incident migraine who had at least 1 PPTF.16 16 Compared to patients with 1 PPTF, patients with ≥3 PPTF showed up to 4-fold higher all-cause and migraine-specific health care costs, with an average annual cost of US$8,912 (95% CI: $7,141–$10,822).[16]

To address the complex challenges posed by migraine, policymakers should consider implementing a

comprehensive set of public policies aimed at improving access to migraine treatments and reducing its societal impact.[17] For instance, raising awareness and education about migraine among healthcare providers, employers, and the public to facilitate early diagnosis and appropriate treatment is crucial. Ensuring equitable access to healthcare services, including affordable medications and specialized care at headache centers, is a pivotal aspect of this strategy. Additionally, promoting policies that support mental health services and provide access to behavioral health specialists for helping individuals cope with comorbid conditions like depression and anxiety, which often accompany migraine,[18,19] is essential. Implementing workplace accommodations, such as flexible schedules and telecommuting options, can assist individuals in managing their migraines and maintaining productivity.[20,21] Lastly, fostering research and innovation in migraine treatments and therapies is an indispensable component for developing more effective and accessible solutions.[22,23] By implementing these policies, governments would significantly improve the lives of those affected by migraine while reducing the economic burden on healthcare systems and society.

New prophylactic migraine medications have been granted access by health insurance in other countries and region (e.g., US, Europe, Australia). This new drug class has been shown effective for patients with PPTF.[6, 9,24,25] The implementation of novel, albeit expensive medications, such as monoclonal antibodies for migraine prevention, within public healthcare systems and health insurance programs necessitates a well-considered and systematic approach. The core challenge lies in achieving the dual objectives of ensuring widespread accessibility to these treatments while effectively managing the associated costs. A multifaceted strategy encompasses several key elements to facilitate successful implementation.

Importantly, the development of clear and evidence-based clinical guidelines for the use of monoclonal antibodies in migraine prevention is crucial.[7 7, 26] These guidelines serve as a compass for healthcare practitioners, offering guidance on appropriate patient selection and treatment administration. Specific eligibility criteria, rooted in factors such as a history of treatment failures or the severity of migraine attacks, are essential to ensure that these medications are targeted to those who will benefit most.[7 7]

The implementation of a prior authorization process acts as a safeguard, ensuring that monoclonal antibodies are prescribed only when deemed medically necessary. Simultaneously, a step therapy approach encourages patients to explore less expensive treatment alternatives before accessing monoclonal antibodies, aligning treatment decisions with cost-effectiveness considerations.[7, 8 7]

Incorporating these new medications into the healthcare system's formulary, potentially within a distinct, restricted tier, helps manage costs without sacrificing accessibility. Regular review and updates of the formulary, informed by emerging evidence and cost-effectiveness data, ensure that the approach remains dynamic and responsive to evolving circumstances.

Effective negotiations with pharmaceutical manufacturers to secure favorable pricing and rebates for monoclonal antibodies are imperative. Exploring value-based agreements that link medication costs to real-world effectiveness can further enhance cost management efforts, aligning financial considerations with patient outcomes.

Patient education materials play a pivotal role in raising awareness about the availability and benefits of monoclonal antibodies. Concurrently, support programs are essential to assist patients in navigating the approval process and accessing financial assistance when needed, thereby addressing barriers to access.

Comprehensive training of healthcare providers on the proper use of monoclonal antibodies, patient selection, and ongoing monitoring is essential for optimal patient care.[27] Encouraging collaboration between specialists and primary care physicians enhances the efficiency of patient management, facilitating a holistic approach to treatment.

To ensure ongoing evaluation and refinement of the implementation strategy, the establishment of a robust data collection system is indispensable. This system tracks outcomes, cost-effectiveness, and patient satisfaction related to monoclonal antibody use, providing valuable insights for decision-makers.[15]

Strategic budget allocation, with a dedicated budget for these medications within the healthcare system, allows for financial planning and ensures the sustainability of the program. Regular assessments of the financial impact and necessary adjustments to budget allocations are integral to financial stewardship.

Public awareness campaigns play a pivotal role in informing patients about new migraine prevention options and guiding them on how to access these treatments. These campaigns empower patients to make informed decisions about their healthcare.

Investing in ongoing research to assess the safety and effectiveness of monoclonal antibodies remains paramount. Promoting innovation in migraine management helps identify more cost-effective treatments in the long term, aligning with the goal of sustainable cost management.

Collaboration with private health insurance companies to

align coverage policies and share best practices in cost management and patient access enhances the overall effectiveness of the strategy.[10]

Advocacy for legislative support and policies that facilitate the affordability and accessibility of new migraine treatments is a vital component of the strategy, addressing broader societal and political dimensions.[6,10,28,29]

Lastly, the implementation of a robust system for monitoring patient outcomes allows for timely adjustments to optimize results and cost-effectiveness, ensuring that the strategy remains responsive to the evolving healthcare landscape. In synthesizing these strategies, healthcare systems and insurers can strike a harmonious balance between providing access to innovative migraine prevention medications and effectively managing the associated costs, thereby enhancing the quality of care for migraine sufferers.

The main limitation of this study is its cross-sectional feature. Despite the plausibility of making causal assumptions between PPTF and higher personal and socioeconomic burden from a clinical practice' perspective, studies adopting prospective design and employing a pharmacoeconomic approach are needed to confirm this relationship. Besides, non-response to the new treatment's options can be observed even in patients in the highest level of headache care.15 Therefore, more study is needed to identify clinical, biological, and social factors associated with PPTF.

In conclusion, the implementation of new, more expensive monoclonal antibody medications for migraine prevention within the public healthcare system and health insurance programs demands a strategic and multifaceted approach.[15] While these innovative treatments offer significant benefits in improving the quality of life for individuals with migraine, their cost implications necessitate careful planning.[15,30,31] By developing clear clinical guidelines, employing cost-control measures such as prior authorization and step therapy, negotiating favorable pricing agreements, and prioritizing patient education and support, healthcare systems can strike a balance between accessibility and cost-effectiveness. Continuous data collection and evaluation, along with ongoing collaboration between healthcare providers, insurers, and pharmaceutical manufacturers, will be essential in optimizing the impact of these medications while ensuring their sustainability within the broader healthcare landscape. Ultimately, the successful integration of monoclonal antibodies for migraine prevention represents a significant stride toward enhancing patient care and addressing the substantial burden of migraine on individuals and society alike.

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