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Original

Should anti-CGRP monoclonal antibodies always be the drug of first choice for migraine prophylaxis in Brazil? - a pharmacoeconomic study

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Abstract

Efficacy (success of therapy under ideal conditions), efficiency (the relationship between the costs and outcomes of a specific intervention), and effectiveness (the balance between efficacy and efficiency in clinical practice) are measures used to evaluate health interventions. Thus, in private practice and the public health system, the knowledge of these pharmacoeconomic data should influence the appropriate treatment choice. Migraine prophylaxis falls within this context. Traditional medications are available in the public health system, while galcanezumab is not routinely available. The present study aims to analyze the efficacy and effectiveness of galcanezumab and traditional therapeutic alternatives (amitriptyline, divalproex sodium, and topiramate). Efficacy data were obtained from the relevant literature (PubMed) and cost values from the ABCFarma magazine. The economic impact analysis considered the cost of living for an economically active adult in Brazil based on the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE) and the Institute for Applied Economic Research (Instituto de Pesquisa Econômica Aplicada, IPEA). Efficacy: amitriptyline: 40%; divalproex sodium: 30%; topiramate: 31%; galcanezumab: 50%. Their annual costs were: amitriptyline R$ 240.00; sodium divalproate R$ 876.00; topiramate R$ 600.00; galcanezumab R$ 13,992.00. Efficiency: amitriptyline 200%; divalproex sodium 41.1%; topiramate 62%; galcanezumab 4%. Ultimately, effectiveness is amitriptyline 120%; divalproex sodium 35.7%; topiramate 46.5%; galcanezumab 27%. Galcanezumab is the most effective; however, in a broader analysis, where payers, availability, and patient conditions are considered, evaluating efficacy alone may not be feasible in practical contexts and, therefore, anti-CGRP antibodies will not always be the first-line medications in migraine prophylaxis.

Keywords:
Migraine Disorders
Calcitonin gene-related peptide receptor antagonists
Pharmacology

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Introduction

The efficacy of a health intervention is defined as the ability to achieve the proposed objectives under ideal conditions, not involving costs and other variables (1). It refers to an intervention's maximum potential for action, often assessed in controlled studies. Efficiency is the ability to obtain the best possible results, taking into account the materials used, always focusing on optimizing the use of available resources to achieve a specific objective (1); effectiveness is an assessment of an intervention's ability to achieve goals in a real scenario (1), taking into account the various variables present in the scenario. It considers efficacy and efficiency, i.e., how well the intervention achieves the objectives (efficacy) and the resources used (efficiency).

Migraine is the most prevalent and debilitating neurological disorder worldwide, affecting approximately 15% of the global population (2). Calcitonin Gene-Related Peptide (CGRP) has been identified as a critical pathophysiological mediator in migraine processes, playing a crucial role in the modulation of headaches and associated inflammatory responses (3).

Advances in understanding the involvement of CGRP in migraine in recent decades have led to the development of innovative therapies, such as CGRP antagonists (mAbs), which lead to a significant reduction in the frequency and severity of seizures compared to traditional treatments such as amitriptyline, divalproex sodium and Topiramate (4). Despite their superior efficacy (4), mAbs are more expensive drugs. Therefore, despite their greater efficacy, data on the efficiency and effectiveness of this group of drugs is still being determined (5,6).

It is worth noting that the drugs mentioned as traditional or conventional (Amitriptyline, Topiramate, and Divalproex Sodium) for migraine are classified as essential. At the same time, Galcanezumab is considered an ideal medication, as established by the International Headache Society Global Practice Recommendations for Preventive Pharmacological Treatment of Migraine (7).

This motivated them to carry out this study, which sought to analyze efficacy, efficiency, and effectiveness in the Brazilian context to encourage research into the cost-effectiveness of mAbs in migraine prophylaxis.

Objective

To analyze the efficacy, efficiency, and effectiveness of galcanezumab and traditional therapeutic alternatives (amitriptyline, divalproex sodium, and topiramate) in treating migraine. Based on these data, to answer whether mAbs should always be the first choice for migraine prevention.e, interventions, results and conclusions were analyzed.

Methods

Data from original publications were used to evaluate the efficacy, efficiency, and effectiveness of galcanezumab, amitriptyline, divalproex sodium, and topiramate. The articles for galcanezumab were found in the Neurology Journals and The Lancet Neurology (8). For amitriptyline, the article found in the Journal of Neurology, Neurosurgery & Psychiatry(9) was used for divalproex sodium, the publication Princeps (Neurology Journals)(10), and for topiramate, the article in the journal Cephalalgia(11) was used.

Efficacy is the ability to achieve defined objectives under ideal and controlled conditions(12); in this study, the parameter used was the percentage of responding patients according to IHS standards (13). Efficiency is defined as the ratio between efficacy and annual drug costs(14), expressed as a percentage:

$$\textbf{Efficiency} = \left(\frac{\textbf{efficacy}}{\textbf{annual drug cost}}\right) \textbf{x 100}$$

Effectiveness is defined as the combination of efficacy and efficiency in a real clinical scenario (15), with values expressed as a percentage (3):

$$\textbf{Effectiveness} = \left(\frac{\textbf{Efficacy} + \textbf{Efficiency}}{\textbf{2}}\right) \textbf{x 100}$$

The actual average income in 2024 was taken from the PNAD (16). The costs of the medicine galcanezumab 120 mg, amitriptyline 25 mg, divalproex sodium 500 mg, and topiramate 100 mg were obtained from ABCFarma magazine (17).The Brazilian public system spent 14 billion reais on medicines in 2022 (18).

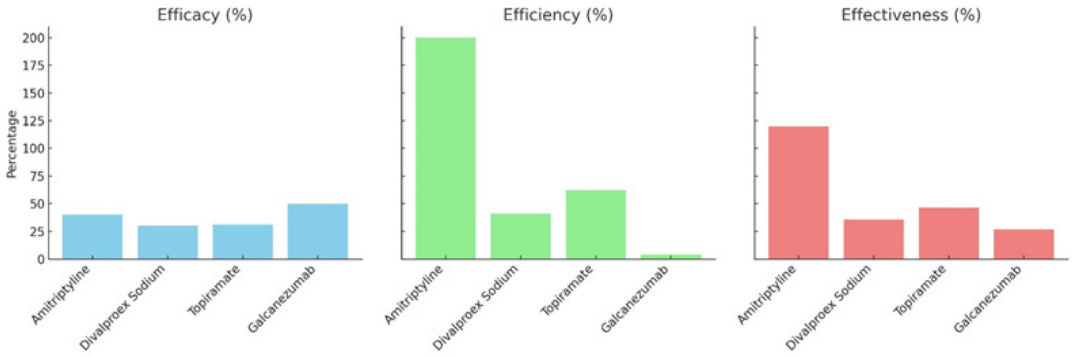
Results

The efficacy of galcanezumab is 50% (8), the efficacy of amitriptyline is 40% (9), the efficacy of divalproex sodium is 30% (10), and the efficacy of topiramate is 31% (11). The annual costs in Reais in 2024 were: galcanezumab R$14,000, amitriptyline R$240, divalproex sodium R$876, and topiramate R$600 (17). The efficiency of galcanezumab is 4%, that of amitriptyline is 200%, that of divalproex sodium is 41.1%, and that of topiramate is 62%. The effectiveness of galcanezumab is 27%, that of amitriptyline is 120%, that of divalproex sodium is 35.7%, and that of topiramate is 46.5%. Table 1 and figure 1 summarize the data found.

Table 1. Costs, efficacy, efficiency, and effectiveness of amitriptyline, divalproex sodium, topiramate, and galcanezumab for migraine prophylaxis in Brazil in 2024

Medicines	Costs BRL (monthly)	Efficacy	Efficiency	Effectiveness
Amitriptyline	R$ 20	40%	200%	120%
Sodium Divalproate	R$ 73	30%	41,1%	35,7%
Topiramate	R$ 50	31%	62%	46,5%
Galcanezumab	R$ 1166	50%	4%	27%

Source: own authors



Source: own authors
Figure 1. Efficacy, efficiency and effectiveness of amitriptyline, divalproex sodium, topiramate, and galcanezumab for migraine prophylaxis in Brazil in 2024.

The average real usual income in April 2024 was R$3,222 (18). Thus, Brazilians receiving this average income would spend 36.2% of their monthly income on galcanezumab, 0.62% on amitriptyline, 2.3% on divalproex sodium, and 1.5% on topiramate. The relevant fact is that the country's median income is R$1,167 (16,19), so treatment with mAbs would consume one's entire income.

Discussion

Studies related to migraine prophylaxis often focus on drug efficacy. However, this analysis is partial; incorporating aspects of efficiency and effectiveness makes it possible to broaden the evaluation's scope significantly.

The findings of the present study indicate that the maximum efficiency and effectiveness were of amitriptyline, respectively 200, 120, followed by topiramate 62, 46.5; divalproex sodium 41.1, 35.7 and the lowest of galcanezumab 4, 27.

With this data, an investigation was carried out into the rules guiding the use of prophylactics, including mAbs, in various world regions.

The Brazilian consensus for migraine prophylaxis mentions that mAbs are effective but does not comment on when to use them, quoting Melhado EM et al.(20), "*and they are effective to treat EM.*"

The 2018 American Headache Society (AHS) consensus recommends starting treatment with mAbs in patients who have not tolerated or responded inadequately to at least two essential preventive treatments, have moderate to severe disability, and are at least 18 years old (21).

The 2019 European Headache Federation (EHF) consensus (22) followed the same line as the AHS, as did the Argentine consensus (23). Later, in 2022, the EHF committee stated, according to Sacco S. et al.(24), "*In individuals with migraine who require preventive treatment, we suggest monoclonal antibodies targeting the CGRP pathway to be included as a first-line treatment option*". Likewise, the AHS in 2024 according to Charles et al.(25), "*The CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without a requirement for the prior failure of other classes of migraine preventive treatment.*"

Therefore, the IHS and EHF consensus migrated from using mAbs as a third-choice medication to first-line medication. In the United States and Europe, mAbs are currently offered as the first line, alongside other essential drugs, which does not necessarily imply the first choice.

Considering the issue in Brazil, we have:

1) Brazilians with an average income would use 36.2% of their earnings to buy mAbs (galcanezumab).

2) Half of the Brazilian population would consume practically all their income for this purpose.

3) Thus, since neither the public system nor the most significant health organizations in Brazil bear the costs of mAbs for migraine, it is unfeasible even to consider this medication as a first choice

It is known that 15% of the Brazilian population suffers from migraine over a year (26), that around 38% of migrants are eligible for prophylaxis (27), and that only 25% of these (9.5% of all migrants) receive it (28). In Brazil, with 215 million inhabitants, there are 32.2 million migrants, 12.2 million of whom are eligible for migrant prophylaxis. If mAbs were offered to the 25% most severely ill, there would be 3.05 million migrants. The annual cost of mAbs is R$13992.00 per patient, and to care for this most severe population (3.05 million migrants) would be around R$42.6 billion, or three times the total public system expenditure on medicines, so this approach does not seem viable either. Even in economically developed countries, Diener HC, May A(6) states: "*The treatment costs for the monoclonal antibodies are currently still very high," and then concludes with "only a minimal fraction of all migraine patients who could benefit from these drugs receive modern migraine prophylaxis".*

Our study showed that mAbs are the most efficient but also the least efficient and effective group of drugs. In the United States and Europe, mAbs are currently offered as first-line alongside other essential drugs, which does not necessarily imply the first choice.

Conclusion

The answer to the question "Should monoclonal antibodies against CGRP (mAbs) always be the drugs of first choice for migraine in Brazil?" is no.

In patient-centered medicine, if the patient can afford to buy the mAbs, this should be a circumstance for their use. In difficult-to-treat patients, such as those who have previously failed two or more prophylactic treatments, the doctor and the patient can join forces so that the patient can receive the monoclonal antibodies.

Hence, despite galcanezumab having the highest efficacy in migraine prophylaxis, due to its high monetary cost and low efficiency, consideration should be given to choosing an economically viable treatment. National and international guidelines express caution when choosing mAbs, preserving their use for cases where essencial prophylaxis has been unsuccessful.

Therefore, although clinical practice is moving towards more specific and personalized treatments, the high cost of mAbs drastically limits their use. As a result, this major advance in migraine treatment is only accessible to a small fraction of migraineurs, highlighting the need for health policies to balance clinical effectiveness with economic efficiency, optimize the use of resources, and maximize patient results.

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