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Cost-Effective and Cost-Minimisation Analysis of Anti-Epileptic Drugs in Migraine Patients at a Tertiary Care Hospital in Bhubaneswar

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Abstract

Migraine is an enigmatic neurological condition impacting 1 billion individuals globally, including over 213 million people in India. The present study is undertaken to study the drug utilization pattern and to find the most cost-effective drug in migraine management. In this study 42.1% patients were diagnosed with migraine without aura and the significant burden of migraine was on women. The mean age of the migraine patients was 36.78±10.02 (mean ±SD). Anti-epileptic drugs were used as first line drugs. The three most commonly used anti-epileptic drugs in our study were Topiramate, Gabapentin and Divalproex sodium. The cost effectiveness of these three drugs were analysed by cost effectiveness analysis and cost minimisation analysis. The most expensive drug prescribed was Gabapentin. Gabapentin has higher cost-equivalent number. Divalproex sodium is the least expensive and cost- effective drug than Topiramate and Gabapentin. The findings of this study can aid healthcare professionals in choosing the most cost-effective antiepileptic drugs (AEDs) for migraine prevention in clinical practice. The insights from the cost-effectiveness and cost-minimization analyses can be used to improve treatment protocols, leading to better patient outcomes while lowering healthcare expenses. Future research should focus on larger, multicentre studies with extended follow-up periods to confirm and expand upon these results.

Keywords: Antiepileptic Drugs, Cost-Effectiveness, Cost Minimization, Migraine, Pharmacoeconomics.

Introduction

Pharmaco-economics plays a critical role in evaluating pharmaceutical products and treatment strategies through various analyses, including cost-benefit, cost-effectiveness, cost minimization, and cost-utility methodologies (1). It profoundly influences decisions surrounding the clinical development and market access of innovative medicines, as well as health outcomes research, particularly in assessing patient-reported outcomes and their impact on health-related quality of life (2). The pharmaceutical industry, already facing challenges such as the loss of patent protection for blockbuster drugs, intensifying generic competition, and escalating drug development costs, increasingly relies on pharmacoeconomic principles to guide formulation decisions. These include incorporating clinical data, designing disease management programs, and evaluating the cost-effectiveness of interventions (3, 4). Migraine, a complex neurological disorder, affects approximately 1 billion people globally, including over 213 million in India, and ranks as the second most common cause of disability (5). Women are disproportionately affected, experiencing migraines three times more frequently than men. Managing chronic migraine often necessitates long-term use of medication to reduce the frequency, severity, and duration of attacks. Among the various prophylactic options, anti-epileptic drugs (AEDs), including topiramate, divalproex sodium, levetiracetam, and gabapentin, are widely recognized for their efficacy (6). Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, aspirin, acetaminophen, naproxen, and diclofenac are commonly employed to avert migraine headaches (7). Effective prophylaxis not only

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improves patients' quality of life but also significantly reduces the costs associated with acute treatments and mitigates disability (8, 9). However, the economic burden associated with the long-term use of AEDs is a significant concern, particularly in resource-limited settings like India. The cost of these medications, combined with the need for sustained treatment, underscores the importance of evaluating their cost-effectiveness and cost-minimization. Tertiary care hospitals, which serve as referral centres for complex cases, are essential in providing specialized care to chronic migraine patients. In these settings, clinicians must navigate the challenging balance between therapeutic efficacy and the financial constraints faced by patients. Achieving this balance is crucial, as while effective migraine prophylaxis can substantially enhance patients' quality of life, the associated financial burden can be prohibitive for many (4). This study aims to analyse drug utilization patterns and identify the most cost-effective medication for migraine management at a tertiary care hospital in Bhubaneswar, employing pharmacoeconomic analyses such as cost-effectiveness and cost-minimization assessments.

Methodology

The study was conducted at a tertiary care hospital in Bhubaneswar, India, from July 2022 to December 2022, utilizing a cross-sectional study design.

Inclusion Criteria

- Patients visiting the selected tertiary care hospital from July 2022 to December 2022
- Patients who were diagnosed with migraine as per the International Classification of Headache Disorders 2 (ICHD 2) criteria during the study duration regardless of age, and sex
- Patients with prophylactic migraine therapy
- Patients who were prescribed anti-epileptic drugs

Exclusion Criteria

- Patients who are recommended to undergo solely clinical laboratory testing and not prescribed with any drugs.
- Patients prescribed with drugs other than anti-epileptics
- Patients with co-morbidities such as severe hepatic impairment, renal dysfunction, or a history of substance abuse
- Patients with concurrent neurological disorders, such as active seizures or other types of headaches.

This study used drug utilization patterns followed by cost-effectiveness analysis and cost-minimization analysis methods for the pharmacoeconomic analysis. Pharmacoeconomic assessments contain studies that assess alternative treatments' costs (resources consumed) and consequences (clinical, humanistic).

Drug Utilization Study

A concurrent drug utilisation review was done in the present study (10). Both acute and prophylactic migraine therapies used in the study were noted. As per the inclusion criteria, we included only anti-epileptic drugs used prophylactically for the Pharmacoeconomic analysis.

Cost Effective Analysis (CEA)

For this method cost and efficacy was compared. Cost includes direct cost and indirect cost. Direct cost includes drug acquisition cost, doctor's appointment charges and indirect cost includes travel cost. Efficacy of drugs used in the migraine treatment was calculated by dividing the mean reduction in headache with the baseline migraine per month before treatment and multiplied with 100. Here to evaluate efficacy of drugs Migraine Disability Assessment Scale (MIDAS) Score before treatment and after treatment was noted. The reduction in migraine days experienced by the patients was also tracked. Then we compared the mean reduction in MIDAS Score with the base line MIDAS score before treatment (9).

Cost-Equivalent Number (CEN) was also measured to determine the cost-effectiveness. It can be calculated by the following formula.

CEN= Pp/(Ep*A)

Where Pp = cost per month of preventive therapy

Ep=efficacy of preventive drugs

A=cost of acute care treatment per headache

In this study sumatriptan (85mg) + naproxen(500mg) was used as the acute care treatment. The cost of acute care treatment was ₹139.4.

Cost-Minimization Analysis (CMA)

Cost minimization analysis (CMA) is an economic evaluation method used when comparing two or more interventions that have already been proven to have equivalent outcomes. The primary focus

of CMA is on identifying which intervention incurs the least cost while achieving the same effectiveness (11). For this method the total number of tablets per treatment was calculated. Then the acquisition price of each tablet and price per course was calculated and compared to know which drug has lower cost than others.

Collection of Data

Patients were enrolled in the study based on specific inclusion and exclusion criteria. Demographic information (such as age, gender, location, contact details, etc.) and clinical data (including diagnosis, prescribed medication, co-prescribed drugs, and treatment regimen) were gathered from patient prescriptions. To evaluate efficacy, data on the number of pre-treatment headaches per month, headache frequency during treatment, and reduction in headaches per month were collected. The MIDAS score was also included in the analysis. Anti-epileptic drugs (AEDs) listed in the prescriptions were considered for this study. The cost of AED treatment, frequency of migraines, average reduction in the number of migraines per month, and cost per migraine reduced were examined. Data computations were performed using Microsoft Excel 2019, and descriptive statistics were employed to analyse the results.

Results

Demographic Profile

A total of 162 patients with complaints of migraines or headaches visited the hospital, out of which 133 patients met the study's inclusion criteria. They include 56 patients suffering from migraine without aura, 50 patients suffering from chronic migraine, 18 patients suffering from vestibular migraine, 5 patients suffering from chronic tension type headache, and 4 patients suffering from tension type headache. More prevalent episodes observed were three to four times by 68(51.12%) patients. Patient ages ranged from 10 to 80 years, with the highest number of AED prescriptions occurring in the 31-40 age groups. The median age of patients was 39 years (Table 1).

Table1: Demographic Data of Migraine Patients at a Tertiary Care Hospital (n=133)

Variables		Number of patients (Percentage)
Age (years)	0-10	2 (1.50%)
	10-20	9 (6.76%)
	21-30	20 (10.00%)
	31-40	51 (38.34%)
	41-50	36 (27.06%)
	51-60	10 (7.51%)
	61-70	4 (3.01%)
	70-80	1 (0.75%)
Gender	Male	30 (22.55%)
	Female	103 (77.44%)
Indications		
	Migraine	56 (42.10%)
	Chronic migraine	50 (37.59%)
	Vestibular migraine	18 (13.53%)
	Chronic tension type headache	5 (3.76%)
	Tension type headache	4 (3.01%)

Clinical Profile

Out of the 162 patients, 133 were prescribed anti-epileptics. The average MIDAS score for these patients was 26.24. All AEDs were administered orally. The most frequently prescribed AEDs were Divalproex sodium, Topiramate, and Gabapentin. In our study, 51.12% of patients observed three-four episodes of migraine pain per month. Only 6.01% patients experienced migraine pain up to 13-15 episodes per month (Table 2).

Table 2: Headache Frequency Per Month of Migraine Patients at A Tertiary Care Hospital (N=133)

Headache frequency Per month	No. of patients	Percentage
1-2 times	36	27.06%
3-4 times	68	51.12%
5-6 times	7	5.26%
7-8 times	7	5.26%
10-12 times	10	7.51%
13-15 times	8	6.01%

Drug Utilization Study

Both acute and prophylactic migraine therapies such as triptans, ergotamines, CGRP (Calcitonin gene-related peptide) inhibitors, beta-blockers, anti-epileptic drugs, etc and OTC (over the counter) drugs like NSAIDs (Nonsteroidal anti-inflammatory drugs) were used in the study. As per the inclusion criteria, we included only anti-epileptic drugs used prophylactically. The most commonly used drugs were Topiramate followed by Gabapentin followed by Divalproex sodium. These three drugs were used for pharmacoeconomic analysis.

Cost Effectiveness Analysis (CEA)

The drug Topiramate was prescribed with the frequency of 25mg once at bed time (HS) for 7days, followed by 25mg in the morning (M) and 25mg at bed time (HS) for 7days, followed by 25mg (M) and 50 mg HS for 7days, followed by 50mg (M) then 50mg (HS) for 7days. The MIDAS score before treatment was 26.3. The mean reduction in MIDAS score after treatment with topiramate was 7.9. So, the efficacy was 42.93%. Topiramate has a cost of ₹1115.4/- per month for the 25 mg and 50 mg tablet. Adding consultant fees (₹700/-) and travel cost (₹350/-), the total cost per treatment was ₹2165.4/-. Thus, the cost effectiveness was 50.44. The cost equivalent number for topiramate was 18.64 (Table-3). Gabapentin 300mg once in a day for 7 days, followed by twice in a day for 1 month dose was used with a cost of ₹1120/- per month. The MIDAS score before treatment was 27.08. The mean reduction in MIDAS score after treatment with Gabapentin was 6.4. So, the efficacy was 30.94%. Adding consultant fees (₹700/-) and travel cost (₹355/-), the total cost per treatment was ₹2175/- and the cost effectiveness was 70.29. The cost equivalent number for Gabapentin was 25.97 (Table-3). Divalproex sodium 250mg once in a day (OD) for 7days, followed by 500mg once in a day was used with a cost of ₹782/- per month. The MIDAS score before treatment was 25.35. The mean reduction in MIDAS score after treatment with Divalproex sodium was 7.22. So, the efficacy was 39.82%. Adding consultant fees (₹700/-) and travel cost (₹350/-), the total cost per treatment was ₹1832/- and the cost effectiveness was 46.00. The cost equivalent number for divalproex sodium was 14.09 (Table 3).

Table 3: Cost-Effectiveness Analysis of Anti-Epileptics Among Migraine Patients at a Tertiary Care Hospital (N=133)

Particulars	Topiramate	Gabapentin	Divalproex Sodium
Dose and Frequency	25mg OD HS 7days; 25mg (M), 25mg (HS) 7days; 25mg(M), 50 mg (HS) 7days; 50mg(M), 50mg (HS) 7days.	300mg OD 7days followed by 300mg BD 1 month	250mg OD 7days followed by500 mg OD 1month
Baseline MIDAS Score	26.3	27.08	25.35
Mean MIDAS Score after treatment	18.4	20.68	18.13
Mean reduction in MIDAS Score	7.9	6.4	7.22
Effectiveness = Mean reduction in MIDAS Score/ Baseline MIDAS	42.93%	30.94%	39.82%

Score X 100			
Cost for 1 month	₹1115.4	₹1120	₹782
Consultant fees	₹700	₹700	₹700
Travel cost	₹350	₹355	₹350
Total cost per treatment	₹2165.4	₹2175	₹1832
Cost effectiveness (cost/effectiveness)	50.44	70.29	46.00
CEN (cost equivalent number)	18.64	25.97	14.09

OD- once daily, M- morning, HS- at bed time, BD- twice daily

Cost-Minimization Analysis (CMA)

Topiramate was prescribed in two doses e.g. 25 mg and 50mg. 28 tablets of 25mg and 21 tablets of 50mg Topiramate were used. Thus, the total price per course for 25mg Topiramate was ₹358.4 and for 50mg Topiramate was ₹510.51. Thus, the total expenditure for Topiramate was ₹868.91 (Table-4). Gabapentin was prescribed with 300mg once in a day for 7days, followed by twice in a day for 1 month. 53 tablets of 300mg Gabapentin were used. Thus, the total price per course was ₹988.98 (Table-4). Divalproex sodium was prescribed with 250mg once in a day (OD) for 7days, followed by 500mg once in a day for 1month. 7 tablets of 250mg Divalproex and 23 tablets of 500mg Divalproex tablets were used. Thus, the total price per course for 250mg Divalproex was ₹79.31 and for 500mg Divalproex was ₹469.66. Thus, the total expenditure for Divalproex was ₹548.97(Table 4).

Table 4: Cost-Minimisation Analysis of Anti-Epileptics among Migraine Patients at a tertiary Care Hospital (N=133)

Drug	Topiramate	Gabapentin	Divalproex Sodium
Dose	25mg OD HS 7days; 25mg (M), 25mg HS 7days; 25mg(M), 50 mg HS 7days; 50mg(M), 50mg (N) 7days.	300mg OD 7days followed by BD for 1 month	250mg OD 7days, followed by 500 mg OD 1month
No of tablets per treatment course	25mg-₹28 50mg-₹21	₹53	250mg-₹7 500mg-₹23
Acquisition price for each tablet	25mg-₹12.8 50mg-₹24.31	₹18.66	250mg-₹11.33 500mg-₹20.42
Price per course	25mg-₹358.4 50mg-₹510.51 Total = ₹ 868.91	Total =₹988.98	250mg-₹79.31 500mg-₹469.66 Total = ₹ 548.97

OD- once daily, M- morning, HS- at bed time, BD- twice daily

Discussion

Specific exclusion criteria related to comorbidities were implemented to ensure the appropriate selection of antiepileptic medications. Patients with significant comorbid conditions such as severe hepatic impairment, renal dysfunction, or a history of substance abuse were excluded, as these factors could impact the pharmacokinetics and safety profiles of the AEDs. Additionally, individuals with concurrent neurological disorders, such as active seizures or other types of headaches, were also excluded to isolate the effects of the AEDs on migraine specifically. By establishing these criteria, we aimed to create a more homogeneous study population, thereby enhancing the validity of the findings regarding the efficacy and safety of the selected AEDs in treating migraines. The International Classification of Headache Disorders (ICHD) is an algorithmic system used to define and categorize all recognized headache disorders. ICHD-II classifies headache disorders into three categories: primary headaches, secondary headaches, and cranial neuralgia, as well as central and primary facial pain and other headache types (12). Migraines, a primary headache disorder, are characterized by recurrent, moderate to severe headaches often

accompanied by nausea, sensitivity to light, sound, and movement. Mainly it is of two types; migraine with aura and migraine without aura (13). In this study 42.1% patients were diagnosed with migraine without aura which is less than other studies where 75% of patients were migraine without aura (14). In our study, the mean age of the migraine patients was 36.78±10.02 (mean ±SD) which is in agreement with other studies where range is within 30-40 years (15). In our study, 51.12% of patients observed three-four episodes of migraine pain per month. Only 6.01% patients experienced migraine pain up to 13-15 episodes per month which is in contrast to other studies where about 50% patients experienced migraine pain up to 14 episodes per month (16). So, the migraine pain is of moderate nature in patient population of our study. Drug utilization review (DUR) is categorized into three types: Prospective, which involves evaluating a patient's drug therapy before the medication is dispensed; Concurrent, which entails ongoing monitoring of drug therapy during the treatment process; and Retrospective, which is the review of drug therapy after the patient has already received the medication (10, 17). The present study is a concurrent drug utilisation study. According to the inclusion criteria, only antiepileptic drugs used for prophylactic treatment were included in the study. The most commonly used medications were Topiramate, followed by Gabapentin, and Divalproex sodium. Hence, these three drugs were selected for the pharmacoeconomic analysis. Anti-epileptic drugs are the standard prophylactic drugs used in the management of migraine. In our study, anti-epileptic drugs were used as first line drugs in contrast to other studies where less than 1% of migraine patients were prescribed with anti-epileptic drugs (18). This may be the reason behind success of anti-epileptic drugs in the management of migraine in our study. The three most commonly used anti-epileptic drugs in our study were Topiramate, Gabapentin and Divalproex sodium. The cost effectiveness of these three drugs were analysed by cost effectiveness analysis and cost minimisation analysis. The utilization of AEDs for migraines may vary significantly by region due to several factors, including local prescribing practices, availability of medications, and regional treatment guidelines. In our study region, AEDs have been frequently prescribed for migraine prophylaxis, likely due to established clinical guidelines and positive treatment outcomes reported in local healthcare settings. However, comparative studies suggest that the overall prevalence of AED use for migraines can be lower in some regions where alternative treatment options, such as traditional migraine therapies (e.g., triptans), are more commonly employed (19). Cost-effectiveness analysis (CEA) involves a series of analytical and mathematical procedures that aid in selecting a course of action from various alternatives. CEA assists decision-makers in identifying a preferred choice among possible alternatives by evaluating multiple drug treatments for the same condition. The costs of drug treatments, including acquisition costs, physician involvement, and nursing costs for medication administration, are weighed against the effectiveness of the drugs (9, 20). Cost minimization, a tool in Pharmacoeconomics, is applied when comparing multiple drugs of equal efficacy and tolerability. This approach is used when the outcomes of the two interventions are identical. Only the input costs are considered, and the option with the lowest cost is selected (11, 21). The data concerning drug pricing, hospitalization expenses, and related healthcare costs used multiple cross-reference sources, such as pharmacy records, hospital billing records, published drug price catalogues and insurance claims data. Drug prices were compared against the latest data from pharmaceutical pricing authorities in India, ensuring consistency across different healthcare providers. Data regarding travel costs were collected from the individuals during filling the MIDAS Questionnaire. Consultation fees were collected from official billing statements where the consultations took place. Cost data gathered from multiple sources ensured the accuracy and consistency of the financial data collected. Here the most expensive drug prescribed was Gabapentin. Gabapentin has higher cost-equivalent number than Topiramate and Divalproex Sodium. Divalproex sodium is the least expensive and cost-effective drug than Topiramate and Gabapentin. These results are in agreement with similar studies carried out in other parts of the world (22-28). Topiramate has demonstrated significant clinical efficacy in

reducing migraine frequency, severity, and duration, making it a first-line treatment option for migraine prophylaxis, as supported by multiple randomized controlled trials (23, 24). Gabapentin shows modest efficacy in preventing migraines, though its results are less consistent across studies and it is typically used off-label for this purpose (25, 26). Divalproex sodium is also effective in reducing migraine frequency and is FDA-approved for migraine prophylaxis, with clinical trials indicating substantial improvements in patient outcomes (27, 28). This study provides a comprehensive analysis of the drug utilization patterns and the cost-effectiveness of anti-epileptic drugs (AEDs) in migraine management at a tertiary care hospital in Bhubaneswar. Our findings underscore the significant burden of migraine on patients, particularly women, and highlight the effectiveness of AEDs such as Divalproex sodium, Topiramate, and Gabapentin in reducing migraine frequency and severity. The insights gained from the cost-effectiveness and cost-minimization analyses can be utilized to optimize treatment protocols, ultimately enhancing patient outcomes while reducing healthcare costs. Additionally, the demographic and clinical profiles outlined in this study can aid clinicians in identifying patient groups that are most likely to benefit from specific AED treatments. Despite its valuable contributions, this study has several limitations. The sample size was relatively small and limited to a single tertiary care hospital, which may affect the generalizability of the findings. Additionally, the study relied on patient-reported outcomes and prescription data, which may be subject to reporting bias and inaccuracies. The study period was also relatively short, limiting the ability to observe long-term outcomes and cost implications of AED treatment. Future research should consider larger, multicentre studies with longer follow-up periods to validate and extend these findings. We recognize that socioeconomic disparities in healthcare access in India can significantly affect patients' ability to obtain necessary medications, including antiepileptic drugs for migraine treatment. Since we have used the top 3 AEDs prescribed for prophylaxis of migraine in our study, this important issue was missed. In our future study, we will include an analysis of the pricing of these medications and discuss how these costs may be prohibitive for low-income individuals. By addressing this aspect, we may provide a more comprehensive understanding of the barriers faced by low-income patients in accessing effective migraine treatment and highlight the need for potential policy interventions to improve affordability and access.

Conclusion

This study analyses drug utilization and cost-effectiveness of anti-epileptic drugs (AEDs) in migraine management at a tertiary care hospital in Bhubaneswar. It highlights the effectiveness of AEDs like Divalproex sodium, Topiramate, and Gabapentin in reducing migraine frequency, especially in women. Divalproex sodium is the least expensive and cost-effective drug than Topiramate and Gabapentin. Despite its valuable insights; the study has limitations, including a small sample size, reliance on patient-reported data, and a short study period.

Abbreviations

AED: Anti-Epileptic Drugs, ICHD 2: International Classification of Headache Disorders, 2nd edition., SD: Standard Deviation, MIDAS: Migraine Disability Assessment Scale, OD: once in a day, M: morning, HS: horasomni (at bedtime), BD: twice in a day.

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Author Contributions

All authors contributed equally to the study design, data collection, analysis, and manuscript preparation.

Conflict of Interest

No conflict of interest was declared by the authors.

Ethics Approval

The Ethical Committee of AMRI Hospital (REF. NO.: IEC/AMRI/BBSR/2020/0003) granted the study.

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