PROFILE OF PHARMACOTHERAPY AND PHARMACOECONOMICS OF EPILEPSY TREATMENT AT A TERTIARY CARE HOSPITAL

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Abstract

Background : Pharmacotherapy and pharmacoeconomic study involving treatment of epilepsy was carried out at a tertiary care hospital. The aim of this study was to investigate the cost-effectiveness of treatment for epilepsy.

Methods : This was a prospective, non-interventional, observational study. The demographic, disease and treatment data were collected for one year from patients with epilepsy.

Results : The number of male patients were significantly more than females ($p < 0.05$). The mean ± SD (standard deviation) of the patients' age was 28.8 ± 15.6 years. Primary generalized epilepsy (58.5%) and seizures secondary to neurocysticercosis (73.5%) were frequent causes. Monotherapy was seen among 72% with maximum number of patients receiving phenytoin, followed by oxcarbazepine, carbamazepine-CR, sodium valproate-CR and others. Pharmacoeconomic evaluation using parametric, non-parametric and multivariate analysis showed direct and indirect annual treatment cost of INR (Indian Rupees) 8,518.74 per patient. Extrapolation of costs to 5 million population with epilepsy in India, was hence assumed to have economic burden of INR 42.6 billion, constituting 0.2% of GNP. Cost minimisation analysis showed a higher absolute annual cost of new vs old AEDs (anti-epileptic drugs) ($p < 0.05$). Multivariate analysis of patient sample model fit the data well ($R^2 = 0.71$, $F=43.036$, $p = < 0.001$).

Conclusions : Significant increase in direct and indirect treatment costs observed in the present study, suggests the need to design comprehensive treatment plan to encourage cost effective AED use, to reduce economic burden of epilepsy.

Key words : Epilepsy, Pharmacotherapy, Pharmacoeconomics, Direct costs, Indirect Costs

Introduction

The International League Against Epilepsy (ILAE) and International Commission on Economic aspects of Epilepsy (ICEE) at the 20th International Epilepsy Congress as well as the report of the workshop published in 1996, addressed the socioeconomic and methodological issues related to epilepsy from various nations to highlight the importance of economic impacts of epilepsy and future research into this area (1-3).

While, economic studies in India are limited, the economic burden of epilepsy is much more. India has about 5 million patients. It is identified as a public health problem but the only data on incidence available is from Yelandur, Bangalore, with 49.3 per 1,00,0000 per year (4, 5) A study, sponsored by the UK government for International development, states that India spends US $ 1·7 billion, per year toward the care for epilepsy (6).

The fact that the results of economic studies cannot be generalized across different geographical regions is recently demonstrated in a cost comparison study of epilepsy in eight western European countries that share similar economic and health care systems (7). Such differences are attributed to variations in the charges levied to health services in different regions thus emphasizing the need to conduct separate economic studies for each centre.

Recent interest to conduct drug utilization studies involving economic aspects is due to an increase in the number of newer antiepileptic drugs (AEDs), which have escalated costs of epilepsy treatment (8, 9). Therefore, the use of newer agents is debated in developing nations like India (10). Although, socioeconomic impacts of treatment options have been studied in a tertiary care centre in South India, data from our center are lacking (11,12). Although, previous studies designed to evaluate the pattern and the extent of the use of AEDs along with the extent of their co-administration with xanthenes (potential seizurogenic agents), these studies were not designed to examine the costs of epilepsy treatment from the patients' perspective (13-15).

The present pharmacoeconomic study was an attempt to collect information that would be necessary for allocating resources for AED treatment regimens. It is anticipated to help as a basic model to formulate appropriate and suitable cost-effective guidelines not for treatment of epilepsy as well as for other chronic conditions.

Materials And Methods

The study was carried out at St. Johns Medical College & Hospital, a tertiary health care center, with super speciality services in collaboration with the department of Neurology. The hospital is equipped with modern, state of the art, diagnostic and treatment facilities. All departments of the hospital run an outpatient department (OPD) service from Monday to Saturday.

Patients reporting at the neurology outpatient, diagnosed to have epilepsy were sent to the investigator by consulting neurologists. Patients with a history of recurrent seizures and receiving at least one agent in recommended antiepileptic dose who have given an informed consent to go through their records were registered.

Patients who presented with seizures not classified as epilepsy, as per the existing guidelines (ILAE), those who did not give consent and those with a history of chronic non-compliance to treatment were excluded. The data from every patient was collected, entered in a specially designed form and transferred into an Microsoft Office Excel worksheet, by the investigator.

Cost data were collected through self-reporting by the patients and from other hospital departments such as the pharmacy, medical billing section and the outpatient registration counter. Each of the subsequent visits made by a patient during the study period was also recorded, for refill information on AEDs.

Data collected from patients with epilepsy :

Socio-demographic Data : Age, sex, the place of residence, marital status of the patient, level of education and occupational status were recorded.

Epilepsy Data : Patients of all age groups, with either active or inactive epilepsy receiving AEDs, were included. A simple classification of seizures as suggested by the International League Against Epilepsy (ILAE) for epidemiological studies was considered for analysis of the data (16) . This consisted of the primary and secondary types. In patients with secondary epilepsy, if the cause of seizure is known, it was entered. Patients having generalised tonic-clonic and absence seizures were grouped as generalised seizures, simple partial and complex partial seizures. Complex partial seizures with secondary generalization, were grouped as partial seizures. Further classification as fresh cases and known cases was defined as patients receiving AEDs for less than 12 months duration and those on treatment with AEDs for more than 12 months duration respectively.

Antiepileptic Drug (AED) treatment data: The drug treatment data included the number of AEDs (monotherapy/polytherapy), generic/brand name, dose and duration of treatment for each patient. These details were obtained from the prescription orders. Details of the dose administered (prescribed daily dose (PDD) was also collected along with the number of times each AED prescribed to the patients.

Data on costs : Definition of costs : Total cost of epilepsy treatment was a sum of direct and indirect costs.

Direct costs: This included cost of AEDs, hospital resources used and cost of travel. The hospital resources used comprised of out patient consultation charges and the cost of the investigations. Only investigations done in the last 12 months for purpose of diagnosis or follow up of epileptic seizures were recorded in addition to the distance travelled for visiting the hospital by every patient.

AED acquisition costs were collected from the hospital pharmacy. The local price, in Indian Rupee (INR) was assigned for each AED. The cost of hospital consultation was assigned as INR 20.00 and the cost of investigations was assigned its local price prevailing at the time of study. The St. Johns Hospital price list issued for the year 2002-2003 was the source for obtaining the costs of various hospital resources. Travel cost was arbitrarily fixed as INR 5.00 for every kilometre of distance, travelled by the patient.

Indirect costs: This included the cost of travel for accompanying attendees and lost wages. On an average, two attendees accompanied every patient. The daily wages for the patient were fixed arbitrarily at INR 150.00 per day. This was assumed for all patients, irrespective of the age or their employment status (17).

Statistical methods :

Variables: The data were statistically analysed for continuous and categorical variables. The data for medication were converted into continuous variables by taking the number of times each AED was refilled in one year.

Descriptive statistics: Descriptive statistics included means and relative frequencies for continuous and categorical data, respectively. Parametric and non-parametric tests were applied as necessary to compare differences in continuous and categorical variables respectively.

Cost of illness analysis: The direct and indirect costs of illness, as incurred by the patient were included. The approach for analysis was bottom up. All costs were derived from individual patients with epilepsy, through an observational study. A human capital method was adopted. All costs were calculated for the entire sample in INR and were converted into USD for the sake of comparison. The conversion applied was 1 USD = INR 48 (using the value of the dollar at that time). Average cost per patient was calculated by dividing the total cost by the sample number. The absolute and relative costs of old and new AEDs were also calculated for comparison.

Economic burden of epilepsy assessed as percentage of the per capita gross national product (GNP), was assumed as USD 456.09. The total expenditure on health, for India in 2000 was assumed as USD 71 (18). We calculated the extent of money, which each patient with epilepsy would spend in comparison to the total expenditure on health by Government of India. This was done to estimate the difference in health expenditure between patients with epilepsy and normal population.

Multivariate analyses: A multiple linear regression analysis was carried out while controlling for co-linearity to evaluate association between demographic, clinical and pharmaceutical characteristics of epilepsy and the total direct annual cost of epilepsy treatment. For this analysis the total direct cost (sum of annual cost of drugs, cost of travel for the patient, cost of consultation and cost of investigations) was made the dependent variable. The independent variables were patient demographics age, gender (with male as the reference), patient status (with known cases as reference), seizure type (with generalized seizures as reference), aetiology (with idiopathic as reference), medications (with phenytoin, carbamazepine, phenobarbitone, sodium valproate, oxcarbazepine, topiramate, lamotrigine, gabapentin, clobazam and clonazepam) and hospital based variables (costs of consultation, travel to the hospital and investigations as reference). AEDs were entered as continuous variable i.e. the number of times they were prescribed to the study population, in one year.

Transformation of the total direct cost into its logarithmic values was done to normalize the data for analysis.

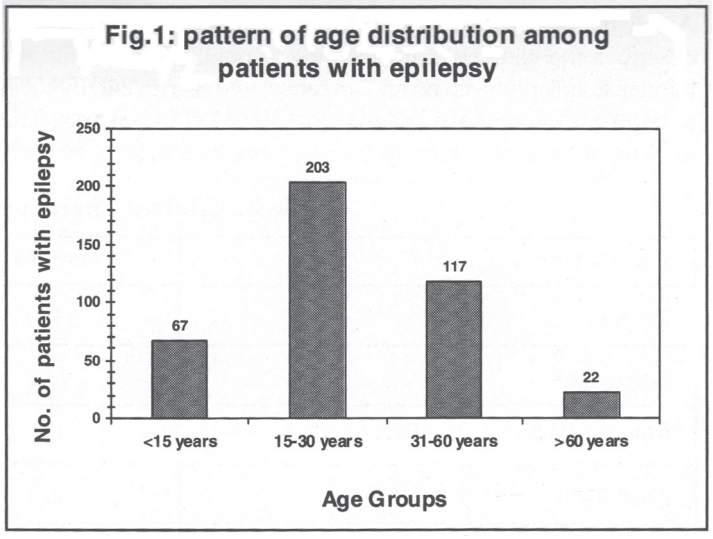
Multiple regression analysis was used for the total number of patients, where variables were entered into the regression models simultaneously. For all analysis a two tailed $p < 0.05$ was considered statistically significant.

The rule of thumb was applied to have 10-30 subjects per independent variable (Gupta, 1999) (19). With present sample size of 410, the ratio of subjects to independent variables was 18 to 1. All statistical analyses were carried out using SPSS version 7.51 (SPSS Inc., Chicago, IL).

Results

Analysis of demographic data: Table 1 shows the demographic characteristics of 410 epilepsy patients from the neurology out patient department over a period of 12 months. There were more number of males (223; 54.4%) compared to females (187; 45.6%).

The mean ± SD (standard deviation) for age was 28.80 ± 15.60 years with a range of 1 to 80 years. Figure 1 shows the age distribution of patients. Maximum number of patients was between 15 and 30 years of age followed by those between 31 and 60 years. More patients were from an urban background (380; 92.7%) than from a rural area (30; 7.3%). More males (107; 39.7%) were married than females (with 65; 19.8%) with overall mean age of 40.80 ± 14.18 years. A chi square test showed statistically significant difference ($p < 0.05$) between the genders.



More than 90% of patients had minimum primary education and 70% of patients were employed. The gender distribution for educational status did not show significant difference. The various levels of education and occupation have been described in the Table 1.

Table 1 : Demographic Characteristics of Patients with Epilepsy

Characteristic	Female	Male	Total	P Value
Gender	187	223	410	
Age (mean ± SD) in years	25.52 ± 12.0	31. 54 ± 17.68	28.80 ± 15.60	0.000
Urban	169	211	380	
Rural	18	12	30	
Place of Residence				0.127
Un-married	122	116	238	
Married	65	107	172	
Marital Status				0.009
Pre-School	3	10	13	
1 - 10th Standard	43			
Upto 12th Standard	59			
Graduate	82			
Educational Status				0.121
Student	102	102	204	
Employed	74	106	180	
Un-employed	8	5	13	
Occupational Status				0.006*

$p < 0.05$ for differences between females and males

Analysis of clinical data for type of epilepsy: Table 2, describes the clinical characteristics of patients with epilepsy. Idiopathic epilepsy (with no known cause) was seen in 240 (58.5%) patients and secondary epilepsy in 170 (41.5%) patients. The analysis of causes of secondary epilepsy were neurocysticercosis (55 females and 70 males: 73.5%), followed by stroke (CVA), infections of the central nervous system and alcohol/drug abuse. The age of patients with a history of primary epilepsy was 24.77 ± 12.95 years and those with a history of a known cause was 34.47 ± 17.28 years.

Table 2 : Clinical Characteristics of Patients with Epilepsy

Characteristics	Female	Male	Total	P Value
Primary	114	126	240	-
Secondary	73	96	170	-
Epilepsy type	-	-	-	0.120
Neurocysticercosis	55	70	125	-
CVA	6	19	25	-
Alcohol & Drug Abuse	2	6	8	-
Head Trauma & CNS Infection	10	2	12	-
Generalized Tonic - Clonic Seizures	91	101	192	-
Simple Partial Seizures	29	20	49	-
Complex Partial Seizures	31	40	71	-
Complex Partial Seizures with Secondary Generalization	30	60	90	-
Seizure Type	-	-		0.132

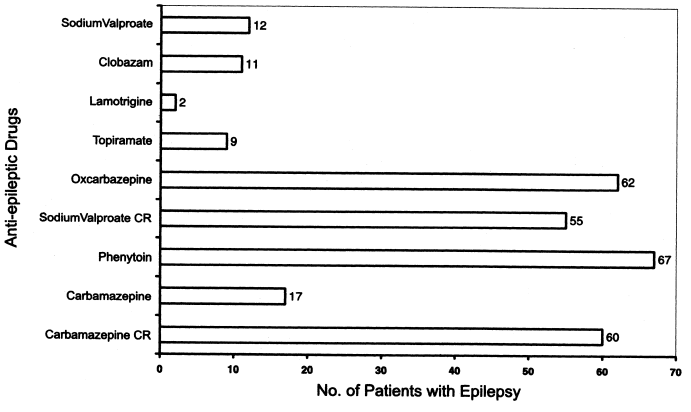
$p < 0.05$ was significant for differences between males & females

Analysis for the type of seizures showed 210 (51.22%) (90 females and 110 males) with partial seizures and 200 (48.78%) (97 females and 103 males) with generalized seizures. The gender distribution for etiology and type of seizures did not show statistically significant differences ($p > 0.05$).

Analysis of data for AED treatment: 295(72%) patients received monotherapy (a single AED) while, 115 (28%) patients received polytherapy (combination of AEDs) with 110 (95.66%) on two-drug combination and 5 (4.3%), on three-drug regimen. Figure 2, shows pattern of use of AEDs used in monotherapy. Among the newer agents maximum number of prescriptions were for oxcarbazepine (62, 22.04%), followed by clobazam (11, 3.72%), topiramate (9, 3.05%) and lamotrigine (2, 0.67%).

Figure 3 shows the pattern of AED prescription. The most frequently prescribed drugs were carbamazepine-CR and clobazam. Newer AEDs were used as add-ons in patients with polytherapy (104, 90.5%). The choice of AEDs for different types of epilepsy revealed use of CBZ (CR) for generalised seizures, phenytoin for patients with GTCS and sodium valproate for absence seizures. Patients with partial seizures received monotherapy with oxcarbazepine followed by sodium valproate and carbamazepine (CR).

Fig. 2 : Pattern of AEDs in patients with Epilepsy Receiving Monotherapy



A combination of phenytoin and clobazam was used in 16(14.6%) patients with GTCS; phenytoin and topiramate in 4(44.4%) patients with complex partial seizures and CBZ-CR and clobazam in 5(21.7%) patients with complex seizures with secondary generalization.

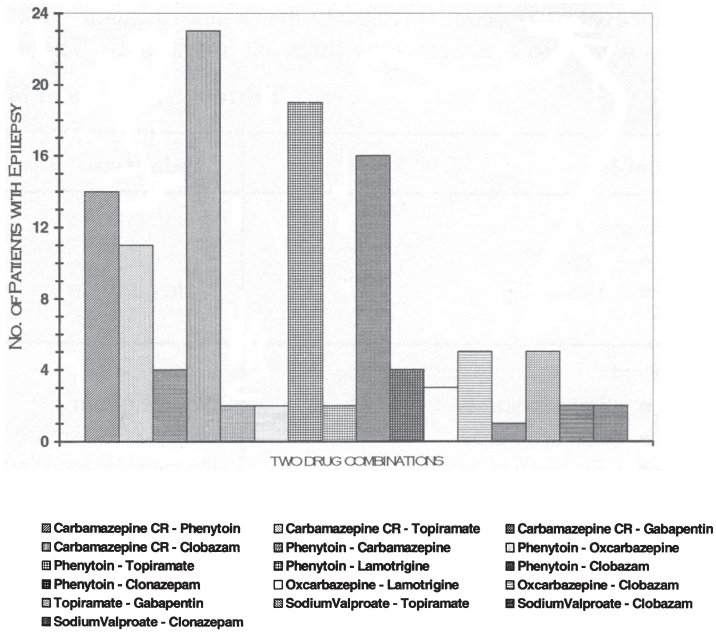
Pharmacoeconomic evaluation of drug treatment :

The direct & indirect costs: In this study, the total annual cost per patient amounted to INR 8,518.74 (USD 177.47) with total direct costs of INR 6209.13(USD129.36) and the indirect costs per patient of INR 2,309.61 (USD 48.12) respectively.

The direct and indirect costs represented 72.9% and 27.1% of the total cost of epilepsy treatment. The annual direct medical expenses included costs of outpatient consultation (INR 57.90), cost of AEDs (INR 3406.43) and costs of investigations (INR 2241.40). The annual direct non-medical expenses included cost of travel (INR 503.40) for an average distance of 28 km, per patient. The annual indirect expenses included the lost wages due hospital visits (INR 1302.80) and the cost of travel for the attendants (an average of two per patient, INR 1006.80) (Fig. 4).

Economic Burden: This was calculated based on the following considerations. There are about 5 million epilepsy patients in India. Extrapolating the figures to the population of India, economic burden due to epilepsy to the nation is to the tune of INR 42.6 billion (0.90 billion USD). The GNP of India for the year 2002 was 471 billion USD and the per capita GNP was 456.09 USD. Therefore, annual cost of epilepsy per person constituted 39% of the per capita GNP. The economic burden of epilepsy would be 0.2% of GNP of India.

FIG 3: PATTERN OF USE OF AEDS IN PATIENTS WITH EPILEPSY RECEIVING POLYTHERAPY



Cost Minimisation Analysis : The absolute cost of AEDs, if prescribed in dosages equivalent to DDD, is shown in Table 3. The average, absolute annual cost, of old AEDs was INR 1033.37 (21.53 USD) and the new AEDs was INR 2363.24 (49.23 USD). This difference in the cost was significant ($p < 0.05$).

Table 3 : ATC Codes Defined Daily Dose (DDD) of Antiepileptic Drugs (AEDs) with Absolute Acquisition costs

Antiepileptic Drug	ATC Code	DDD in mg	Absolute Cost (INR)
Phenytoin	N 03 AB 02	300	3.60
Phenobarbitone	N 03 AA 02	100	2.40
Carbamazepine (CR)	N 03 AF 01	1000	9.60
Carbamazepine	N 03 AF 01	1000	8.15
Sodium Valproate	N 03 AG 01	1500	19.89
Oxcarbazepine	N 03 AF 02	1000	16.50
Topiramate	N 03 AX 11	300	52.50
Gabapentin	N 03 AX 12	1800	29.40
Lamotrigine	N 03 AX 09	300	34.50
Clobazam	N 05 BA 09	20	14.74
Clonazepam	N 03 AE 01	8	17.08

*WHO collaborating Center for drug statistics methodology, 1999. "Anatomical Therapeutic Chemical (ATC) classification index" Oslo.

**St. John's Medical College Hospital Pharmacy Drug Acquisition costs for the year 2002 - 2003.

Multivariate Analysis: The Beta regression coefficients and their respective 95% confidence intervals (CI) along with predictors that entered the linear regression model are shown in Table 4. All tolerance values exceeded 0.1; likewise the variance inflation factor values were also well below the threshold mark of 10. These results indicate that the interpretation of regression coefficients are not affected by multi-co-linearity. The multivariate analysis included the entire sample of patients and the model fitted the data well (R2 = 0.71, F = 43.036, P = < 0.001).

Table 4 : Results of Multiple Linear Regression

Variable	Modalities	Beta Coefficients (95% CI)
Demographic·		
• Age·		0.138 (0.01, 0.021)*
• Sex	Male / female	0.023 (-0.020, 0.047)
Clinical ·		
• Patient status·	New / Known	0.026 (-0.075, 0.370)
• Epilepsy type·	Partial / Generalized	0.043 (-0.016, 0.067)
• Epilepsy aetiology	Primary / Secondary	- 0.011 (-0.082, 0.068)
Type of AED	New, Old·	
	• Carbamazepine (CR)·	- 4.402 (-.209, -.080) ***
	• Carbamazepine·	5.400 (0.032, 0.068) ***
	• Phenytoin·	1.855 (-0.002, 0.066)
	• Sodium valproate·	0.564 (-0.014, 0.024)
	• Sodium valproate (CR)·	6.957 (0.058, 0.104)
	• Oxcarbazepine·	1.742 (-0.004, 0.060) ***
	• Topiramate·	4.685 (0.033, 0.081) ***
	• Lamotrigine·	6.766 (0.058, 0.106) ***
	• Gabapentin·	4.943 (0.065, 0.150) ***
	• Clobazam·	0.286 (-0.047, 0.62)
	• Clonazepam	3.759 (0.024, 0.078) ***
		3.385 (0.036, 0.136) ***
Hospital Resources	• OPD VISITS	- 0.126 (-0.069, -0.016) **
	• EEG	8.656 (0.089, 0.141) ***
	• MRI	3.091 (0.053, 0.240) ***
	• CT	6.101 (0.208, 0.406) **
	• TDM	3.330 (0.029, 0.114) **
Model fit	R^2 = 0.719, F = 43.036***	
* p = < 0.05, ** p = < 0.01, *** p = < 0.001		

The predictor that weighed most highly on total cost among hospital resources was outpatient consultations followed by EEG and MRI utilization. As the number of outpatient consultations and diagnostic tests increased, the total cost for patients also increased.

The relationship for AED use was negative, as more patients received old AEDs. Among the old AEDs the predictor that weighed most was sodium valproate-CR, followed by carbamazepine-CR and for the new AEDs, topiramate, lamotrigine, oxcarbazepine and clobazam. As more patients received newer AEDs the total cost also increased. The remaining AEDs had a less significant predictor value.

Discussion

Pharmacoeconomics is defined as the study of health economics, that aims at quantifying the cost and benefit of drugs used therapeutically. It is a tool to measure therapeutic benefits in monetary terms. Thus, it helps allocate the necessary resources for health care (20). Epilepsy, a public health problem in India has an incidence of 4.9 per 1000 population (4, 5). Treatment of epilepsy in India suffers from a huge treatment gap or lack of treatment (percentage of people not receiving treatment at any given time, 73.7% of 40 million), as most patients do not get even the cheapest drug like phenobabarbital for control of seizures (21, 22). There is an increase in the economic burden of epilepsy, due to the loss of productivity and efficiency as a result of chronic absenteeism from school or work(9). Though cost utility analysis is considered the gold standard, while the cost minimization analysis is most widely preferred (1).

The present study on pharmacotherapy profile and the pharmacoeconomics, of epilepsy treatment at a tertiary care hospital was undertaken as there is a lack of sufficient information on this aspect in India. It was found that direct medical and non-medical costs, were most significant predictors of the total cost of epilepsy treatment. The target study population was similar to economic studies conducted in other centres in India and elsewhere (12, 23) Unlike other developed countries patients with epilepsy in this country receive treatment frequently from tertiary care centres (24). Hence, patients of all age groups with active and inactive epilepsy receiving AEDs at the neurology out patient department were included.

The age of the patients in this study was 28.80 ± 15.60 years, which is different from studies reported from developed nations that showed higher incidence in the higher age groups (25) The Commission of Epidemiology and Prognosis of Epilepsy, has offered a simplified version of classification for epidemiological studies related to epilepsy (16). In most Indian studies the occurrence of primary generalised seizures seems to account for more than 50% of the cases of epilepsy. In our study the results were similar. There were 183 (44.6%) cases with history of primary generalised seizures. In contrast, the studies from developed countries show that partial seizures account for more than 50% of the cases (22). The incidence of generalised absence seizures was only 1.7%. Patients with absence seizures are better detected in developed countries probably due to the better understanding of the disorder, compared to developing countries (25). The observation that we have reported only eight patients with absence seizures, may explain the possibility of gross under detection of absence seizures.

The number of secondary epilepsy was higher among patients who had partial seizures. Neurocysticercosis has been identified recently as the main etiology of secondary epilepsy, which may be attributed to a higher prevalence of taeniasis in developing countries along with wide spread availability of CT/MRI facilities in many centres to identify single ring enhancing lesions (SSEL)(26, 27). Similar findings have been reported in the study conducted at a tertiary care centre in Kerala, India These various factors can increase the direct and indirect costs of epilepsy treatment as shown in the multicentric study conducted in six tertiary level hospitals across three southern states of India (12, 28).

Profile of Antiepileptic Drug (AED) Use: Preference for monotherapy seen in the present study(72% patients) reported during the last three decades is supported by clinical evidence that shows clear advantages of monotherapy over polytherapy. Some of the main advantages of monotherapy as mentioned in such studies was that patients enjoyed effective seizure control, had fewer side effects and incurred lower cost of therapy(12). In addition, monotherapy improves compliance due to fewer neurotoxic side effects and medication convenience (29).

The pharmacotherapy of epilepsy was evaluated in a tertiary referral centre in Kerala, India and a multicenter study in six tertiary level hospitals in three different states of South India (Karnataka, Tamilnadu & Kerala) (12, 28). These studies examined, pattern of AED use and cost of epilepsy treatment. Monotherapy with carbamazepine and sodium valproate were found to be most preferred treatment options for epilepsy, in these centres.

The present study examined the economic aspects of epilepsy treatment at our centre, which has an estimated prevalence of 9/1000 (13). Although, the use of phenytoin has declined because of more side effects compared to carbamazepine or valproate, we still found that phenytoin was used most frequently followed by oxcarbazepine, carbamazepine-CR and sodium valproate-CR(30). Studies in rural South India, have also shown similar preference as well as efficacy of phenytoin in controlling epileptic seizures (31).

The studies carried out in other tertiary care centres of South India, showed a similar pattern with the usage of carbamazepine-CR and oxcarbazepine in 21.2% for partial seizures in patients receiving monotherapy(12, 28). This may be due to fewer neurotoxic side effects and better pharmacokinetic profile (32) of this drug. The choice of AEDs for various seizure types showed a similar pattern as most other centres, with preference for carbamazepine and phenytoin in generalised tonic-clonic seizures; and sodium valproate and lamotrigine in absence seizures. Lamotrigine has been reported to be more effective for absence seizures and is becoming the alternate drug of choice for this condition next to sodium valproate (33). Ethosuximide was not found to be the first choice in these patients. Phenobarbitone or Primidone are not commonly used most likely due to the side effect of cognitive impairment, often with sedation in adults and hyperactivity in young children (31, 34).

Five new drugs for epilepsy such as lamotrigine, gabapentin, oxcarbazepine and topiramate have been licensed in India within the past 10 yrs as "add on" treatments. Recently, lamotrigine and oxcarbazepine have been licensed for monotherapy in partial seizures (33, 36). There are limited comparative trials with newer agents but there is little evidence to show that one is more effective

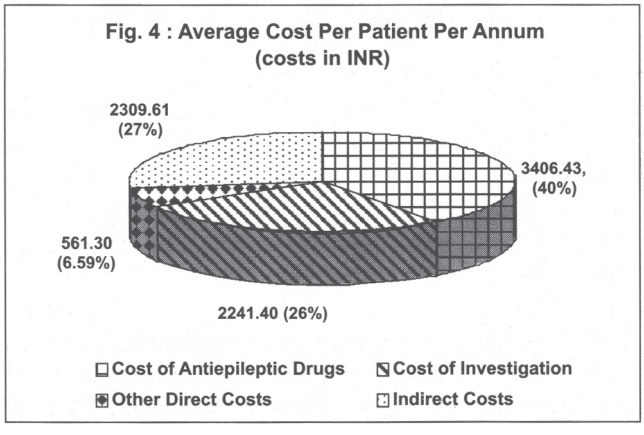


Fig. 4 : Average Cost Per Patient Per Annum (costs in INR)

than the other (35) The pattern of use in our study showed nearly 50% of the patients to be on one of the newer AEDs as monotherapy or as an add-on drug in polytherapy. This trend shows a significant influence of practice of evidence based medicine. Among newer AEDs, the use of carbamazepine-CR, clobazam and topiramate was maximum (Fig. 3).

The extent of newer AEDs among patients receiving polytherapy was 90.5%. This is similar to those reported from developed countries and this could be due to la lower potential of these drugs to produce drug-drug interactions (36), in addition to their increased efficacy in patients not responding to the old AEDs (33). The use of clobazam both as monotherapy and as an add-on drug was found to be high, similar to that reported by Feely 1999 (34). This may be due to the fact that it is a non-sedating benzodiazepine which is effective in treating various seizure types and generally well tolerated by all age groups (33).

Topiramate was used more as an add-on drug for generalised seizures and complex partial seizures. The use of polytherapy was highest in patients with this type of seizures as they do not usually respond to a single drug. Topiramate was initially licensed for use, in such difficult to treat seizures and evidence suggests that it is efficacious in controlling refractory epilepsy (37).

Pharmacoeconomics of Epilepsy Treatment: The recent globalization of the world economy has increased awareness on the economic aspects of pharmacotherapy in all areas of medicine. The introduction of new AEDs has escalated the costs of epilepsy treatment all over the world. The economic burden of epilepsy is high in India and not many studies have looked into the impact of new AEDs on the costs of epilepsy treatment (11). Previous studies from Chinese population in Hong Kong suggest a direct influence of severity of the illness on the increased costs incurred by patients with epilepsy (38).

A study of different populations in The Netherlands, also showed the influence of prognosis of seizures on the costs of treatment. The authors concluded that the costs of AEDs and hospital services were important contributing factors to the total cost (39). Yet another study in the U.K., compared the difference in utilization of health care facilities between normal individuals and people with epilepsy. This study showed that patients with epilepsy used many more health care facilities and incurred greater costs compared to the normal population (40). A study in the state of Oman has shown that the cost of hospitalization followed by the cost of new AED and radio imaging tests are important contributing factors of total direct cost (23). Population based economic surveys of patients with epilepsy done in various countries have been compared in Table 5.

Table 5 : Prevalence Based Estimates of Annual Cost of Epilepsy

Reference**	country/ year	population	Cost measures & Data sources	Direct cost per person	Indirect cost per person
Banks et al., 1995	Australia1992	All epilepsy age 5 +	Direct medical, some indirect. Provider and population surveys	USD2751	USD3381
Cockerel et al., 1994	UK 1990	All active and inactive epilepsy	Direct medical & non-medical, some indirect. Administrative records	USD2600	USD5989
Murray et al	USA 1994	Refractory adult epilepsy	Direct medical and some indirect. Disease model	USD2971	USD9418
Radhakrishnan et al., 1999	India 1998	All epilepsies	Direct medical, non-medical and some indirect Population survey and provider	INR5070	INR 6000

** Modified from Thomas, 2001.

These studies provided us with important guidelines for designing the present study. The most common approach we followed was the human capital method in which costs are divided into direct and indirect. The total cost per patient with epilepsy was found to be approximately INR 6209.13 and 72% of this cost was related to the direct medical expenses. The direct costs included the cost of AEDs and the use of outpatient services. The use of in-patient hospital resources was not recorded in this economic evaluation; hence the indirect costs were lower as compared to a previous study (29). The preference of conventional AEDs at this centre conveys the confidence of doctors in using these drugs as these agents were found to be cheaper. Hence, by improving the availability of these basic AEDs, there is a possibility to design an effective comprehensive program to treat epilepsy in this country.

The absolute annual cost of newer AEDs was significantly higher than the older AEDs, in our study. These patients had to pay more towards their drug expenses compared to patients treated with conventional drugs. Higher costs of new AEDs have been compensated by better seizure control and lesser side effects as shown in various comparative clinical trials of newer versus older AEDs (10). A cost utility analysis, which considers quality of life in these patients would be an ideal way to compare the actual differences between the newer and older AED treatment approaches (1). This should be addressed in future studies.

Factors Contributing to the Cost of Epilepsy Treatment : Various factors predict the total annual cost of epilepsy treatment, which is a combination of both direct and indirect costs. The use of new AEDs had a significant influence on the direct costs of epilepsy treatment. The use of various diagnostic tests like the EEG, CT and MRI were also important predictors of total cost. The high prevalence of neurocysticercosis may be another reason why MRI utilization was high in the present study. Patients with epilepsy had to spend more money on drugs and hospital visits than normal population. This trend was also seen in population based surveys conducted in other countries.

Previous studies have shown that the cost of AEDs and the use of diagnostic investigations were important predictors of total direct costs (23) The multicentric study in south India, also reported a similar pattern (28). Another study that looked into the socioeconomic aspects of newly diagnosed epileptic patients also reported that the cost of diagnostic work up of the illness was an important contributing factor to the total cost. Our study showed that the consultation costs, cost of new AEDs and the cost of investigations like EEG and MRI were important predictors of the total direct cost of epilepsy treatment (11). A multicenter study conducted in six hospitals in various cities of south India examined the various costs but did not evaluate the predictors of the total cost. In contrast the present study examined the various costs in addition to determining the predictors of the total direct cost. Therefore, it is possible to examine the actual areas where health economists and policy makers need to intervene in order to cut down on economic burden of epilepsy in this country.

Future scope and conclusions:

Epilepsy is a chronic disorder that is associated with intercurrent medical illnesses, which in turn may complicate the treatment strategies. This may result in leading to polypharmacy and thus subject the patients to a greater risk of drug-drug interactions. Therefore, quality of life as well as drug-drug interactions may also have significant impact on costs of treatment. Our pharmacodynamic and pharmacokinetic drug interaction studies between xanthines and AEDs in animal models of seizures and normal human volunteers have found serious drug interactions (41-43). These issues may further influence costs of treatment significantly and thus need to be addressed in future. Further, the methodology employed in the present study may also serve as a basic model to study economic impact of other chronic disorders in different populations.

In conclusion, the cost of the treatment of patients with epilepsy appears substantial to the nation and it is probably underestimated. At present the services for epilepsy care are mostly confined to the urban areas while, there is a need to extend such services to the rural areas. Since the economic burden of epilepsy is found to be significant, the cost of epilepsy treatment on national economy can possibly be reduced by improving the health care facilities at the primary care level. To achieve this, more prospective economic studies are needed to plan and execute a comprehensive epilepsy management program that would incorporate efficient treatment strategies, with available resources.

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