Antiepileptic drugs prescription utilization behavior and direct costs of treatment in a national hospital of India

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Abstract

Background and Objectives: The present study evaluated the direct costs of active epilepsy and looked at the pattern of drug prescription and utilization in epileptic patients visiting the neuroscience centre of a national hospital of India. **Materials and Methods:** A total of 134 epileptic patients were studied over a period of 4 months. Patients demography, commonly prescribed antiepileptic drugs (AEDs), socioeconomic status, direct costs, response ratio (RR) for newer drugs, and quality of life (QOLIE-10) was evaluated. **Results and Discussion:** We found a higher percentage of male patients (67.9%) as compared with females. Most of the patients were in the age group 11–30 years and majority of them (39.6%) belonged to lower middle group. A higher percentage (68.7) of drugs was prescribed as polytherapy. Higher monthly cost was observed for some of the newer AEDs including the lamotrigine, levetiracetam, and lacosamide as compared with older drugs. Among the newer drugs, clobazam had the lowest cost. RR was calculated for 12 patients out of which 8 had a RR < −0.50. The QOL domains, following conventional or newer drugs, were not much affected. **Conclusion:** The study indicates an increasing trend toward clinical usage of newer AEDs, increasing trend of poly-therapy with significant escalations in the cost of therapy.

Key Words

Antiepileptic drugs, direct cost, prescription pattern, response ratio, quality of life

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Introduction

Epilepsy is the second most common chronic neurological condition. It is estimated that there are 55,00,000 persons with epilepsy in India, that is, one-eighth of the total epilepsy patients in the world.[1] Though monotherapy is usually recommended in epilepsy but polytherapy is often required for patients with multiple seizure types or refractory disease.[2] Epilepsy can be treated effectively in approximately 60% of patients who become seizure free with the first or second antiepileptic drug (AED) that they are prescribed.[3] The drawback of polypharmacy is higher incidence of adverse effects, drug interactions and added costs. The latter constitutes an economical burden on the patients in addition to the existing psychological medical and social burden.[4]

Pharmacoeconomics is a branch of economics that measures and compares the cost, risks, and benefit of programs, services or therapies and determines which alternative produces the best health outcome for the resource invested. Outcome of Pharmacoeconomics are 'humanistic' and 'economic'.[5] Economic consequences are analyzed as direct or indirect costs and antiepileptic drugs are known to be contributing majority to the direct costs.[6] Humanistic evaluation is done by analyzing quality of life (QOL).[7]

Since there is a paucity of Indian studies who have examined the economic aspects of epileptic patients and the financial impact of newer AEDs prescription, the present study is designed to evaluate the direct costs of active epilepsy in patients visiting the neuroscience center of a reputed national hospital of India. In addition to this, the study also analyzed the pattern of drug prescription and utilization in different types of epilepsies. A better understanding of the economic aspects of epilepsy and utilization behavior would hopefully help identifying the most common cost effective treatment especially in patients with refractory epilepsy.

Study Methods

The study was carried out between January and April 2011 in the Neurosciences Centre OPD at All India Institute of Medical Sciences (AIIMS), New Delhi. The study aim was prospective analysis of AEDs prescription and utilization behavior as well as analysis of QOL data. For determining direct costs, the cost

of investigations (eelectroencephalography (EEG), magnetic resonance imaging (MRI), and AEDs concentration in blood) were taken retrospective from 2010 to 2011. All patients diagnosed with epilepsy (irrespective of age and sex) were included in the study. Patients were classified according to gender, age, sex, seizure type, and socioeconomic status (SEC). For determining the SEC, Kuppuswamy's socioeconomic status scale was used.[8] Most commonly prescribed conventional and newer AEDs were determined. The direct costs (cost of AEDs + investigations), response ratio (RR), and QOL were also determined. RR was determined for patients prescribed with newer AEDs and was calculated by the difference between seizures at baseline (patient visited OPD last time) and after treatment (till 12 weeks) of add-on or *per se* therapy divided by the total number of seizures. A negative value for RR indicated reduction in seizures.[9] A value above −0.5 indicated at least 50% or more reduction in seizures. The patient's Quality of life was assessed by using a 10-item questionnaire QOLIE-10.[10] The QOLIE-10 covered general and epilepsy-specific domains and an overall quality of life. The statistical correlation between different domains of QOL was performed using Pearson correlation coefficien*t test*. The results were analyzed using statistical program SPSS version 17, internal consistency measure (Cronbach's Alpha), item–item, and item total correlation measure.

Results

Demographic profile
During 4 months study, 134 patients were observed to receive AED therapy at AIIMS. The demographic profile of patients, classification according to seizure type and SEC and the most commonly prescribed AEDs are depicted in Table 1. The AEDs were used as either monotherapy (31.34%) or polytherapy (68.66%).

Direct costs
The cost of MRI at AIIMS was divided into three types: MRI (Rs 3000), MRI with film (Rs 3500), MRI with contrast (Rs 7000). Out of 134 patients, 19 patients got free MRI from AIIMS and employees' state insurance (ESI) while 74 patients got free EEG from AIIMS and ESI. The consultant fee of OPD (AIIMS) was nominal (Rs 10). The direct cost to patient increased linearly by adding AED to prescription [Figure 1].

Response ratio
The baseline seizure period was taken from 1st January to 15th January for calculation of RR. Out of 134 prescriptions,
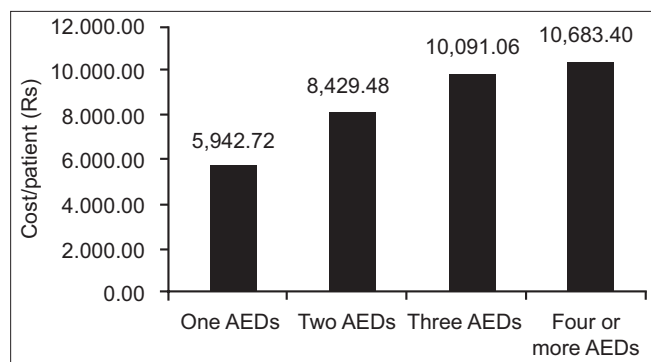
only 12 were found to be on the newer AEDs having baseline seizures during that period. The seizures were considered to be controlled if there was 50% reduction in the RR. Of 12 patients, 8 patients had RR < −0.50 while 4 had RR > −0.50 [Table 2].

Quality of life
Out of 134 patients, 19 patients were less than 12 years of age while 9 patients did not respond personally/telephonic calls and were rejected for assessing QOL. The Cronbach's alpha was found to be 0.94. A reliability coefficient of 0.7 or higher is considered acceptable in most social sciences research situations. Table 3 depicts the Pearson correlation coefficient for the various domains of QOLIE, which was correlated well ($P < 0.001$). The ratings of QOL were almost comparable for most AEDs on all the parameters of QOLIE-10. Comparing

Table 1: Patient demographics and characteristics

Total no. of patients	134(%)
Gender	
Male	91 (67.9)
Females	43 (32.1)
Age range	1–60 years
Age distribution	10–30 years (62.75)
Type of epilepsy	
Generalized tonic clonic	61 (45.5)
Complex partial	45 (33.6)
Tonic clonic	18 (13.4)
Myoclonic	06 (4.5)
Absence	02 (1.5)
Reflex	02 (1.5)
No. of AEDs prescribed	
One	42 (31.3)
Two	41 (30.6)
Three	37 (27.6)
Four	14 (9.1)
Most frequently prescribed conventional AEDs	
Valproic acid/Sodium valproate	51 (37.8)
Carbamazepine	42 (31.1)
Phenytoin	27 (20)
Divalproex	07 (5.3)
Clonazepam	04 (2.7)
Phenobarbitone	04 (2.7)
Most frequently prescribed newer AEDs	
Clobazam	70 (50.6)
Levetiracetam	29 (21)
Lamotrigine	23 (18)
Topiramate	05 (3.6)
Zonisamide	03 (2.2)
Oxcarbazepine	01 (0.7)
Alprazolam	01 (0.7)
Lorazepam	01 (0.7)
Socioeconomic class (SEC) of patients*	
Lower middle	53 (39.6)
Upper middle	45 (33.6)
Upper lower	29 (21.7)
Upper	07 (5.2)
Lower	None

Figure 1: Direct cost to epilepsy patients prescribed 1–4 AEDs

*SEC was assessed according to Kuppuswamy's scale

Table 2: Response ratio of newer AEDs

Baseline seizures	Response ratio	AEDs
03	−0.76	Levetiracetam + Zonisamide + Phenytoin + Lacosamide
17	−0.69	Valporic acid + Levetiracetam + Lamotrigine
19	−0.64	Levetiracetam + Clobazam + Sodium valproate
06	−0.62	Levetriacetam + Zonisamide + Topiramate
04	−0.50	Sodium valproate + Lamotrigine + Clobazam
08	−0.48	Lamotrigine + Clobazam
16	−0.45	Lamotrigine + Clobazam
21	−0.42	Sodium valproate + Lamotrigine + Clobazam
01	−0.33	Sodium Valproate + Lamotrigine + Clobazam
05	−0.20	Levetiracetam +Z onisamide + Topiramate + Lamotrigine
02	−0.20	Levetiracetam
03	−0.14	Sodium valproate + Lamotrigine + Clobazam

Table 3: Pearson correlation coefficients for the components of QOLIE-10 and quality of life scores of antiepileptic drugs

QOLIE-10 item	Pearson correlation coefficient with QOLIE-10*			Scores (Mean ± SEM)					
	Min	Max	Total	Carbamazepine	Valproate	Phenytoin	Lamotrigine	Levetiracetam	Clobazam
Item 1- Energy level	0.691	0.955	1.646	1.62 ± 1.15	1.45 ± 0.60	1.70 ± 0.73	1.38 ± 0.49	1.29 ± 0.46	1.56 ± 0.76
Item 2- Felt blue	0.500	0.933	1.433	1.40 ± 0.79	2.60 ± 1.39	1.70 ± 0.86	1.52 ± 1.20	1.54 ± 0.65	1.50 ± 0.91
Item 3- Driving Problem	0.450	0.837	1.287	2.71 ± 1.90	3.30 ± 1.94	2.25 ± 1.86	2.61 ± 1.93	3.25 ± 1.96	3.08 ± 2.0
Item 4- Memory Problem	0.458	0.975	1.433	1.71 ± 1.30	1.55 ± 0.51	1.35 ± 0.48	1.52 ± 0.60	1.58 ± 0.71	1.41 ± 0.52
Item 5- Work Limitation	0.493	0.946	1.439	1.59 ± 1.16	2.20 ± 1.76	1.20 ± 0.52	1.38 ± 0.49	1.29 ± 0.41	1.40 ± 0.66
Item 6- Social Limitation	0.478	0.975	1.453	1.31 ± 0.64	1.15 ± 0.36	1.45 ± 0.94	1.14 ± 0.35	1.37 ± 0.87	1.25 ± 0.44
Item 7- Physical Effect	0.613	0.837	1.450	1.21 ± 0.55	1.55 ± 0.75	1.50 ± 0.60	1.95 ± 0.97	1.37 ± 0.49	1.37 ± 0.48
Item 8- Mental Effect	0.673	0.843	1.516	1.71 ± 0.95	1.60 ± 0.50	1.65 ± 0.48	1.19 ± 0.40	1.37 ± 0.57	1.50 ± 0.56
Item 9- Fearful of having fit	0.450	0.953	1.403	1.25 ± 0.67	1.35 ± 0.48	1.55 ± 0.75	1.38 ± 0.49	1.20 ± 0.46	1.35 ± 0.48
Item 10- how things are going	0.565	0.916	1.481	2.31 ± 0.53	2.15 ± 0.36	2.55 ± 0.82	2.61 ± 0.74	2.29±0.46	2.37±0.90

Number of patients included was 106. Most commonly prescribed AEDs were selected irrespective of whether prescribed alone or in combination. Two-tailed significance of Pearson correlation coefficient was $P < 0.001$, QOL scores not significant (ANOVA followed by Dunnett's *t* test)

older drugs with newer AEDs did not reveal a significant difference.

Discussion

There has been a recent interest to conduct drug utilization studies (DUS) involving economic aspects in epileptic patients. This is mainly due to an increased usage of newer AEDs that have escalated the costs of epilepsy treatment. In spite of a high economic burden of epilepsy in India,[11] not many studies have looked into the impact of newer AEDs on the cost of epilepsy treatment. The present study aims to look at this aspect on Indian epileptic patients.

About 134 epileptic patients were studied during a period of 4 months at the Neuroscience OPD of AIIMS, New Delhi. We found a higher percentage of male epileptics (67.9%) as compared with females (32.1%) [Table 1]. Similar observations (higher male:female ratio) have been reported in India[12] and Denmark[13] indicating that epilepsy is slightly more prevalent in the male gender. However, a 1:1 male:female ratio has been reported in Sri Lanka.[14] While the reasons behind gender differences are not clear, it has been generally observed that men have a higher incidence of focal epilepsy while women are influenced by genetic factors or hormones leading to

a higher incidence of generalized epilepsy.[13] Maximum patients included in the study were between the age groups of 11–20 years (35.9%) followed by 21–30 years (27%). A higher percentage of patients were found to have generalized tonic-clonic seizures (GTCS) (45.5%) followed by focal seizure (33.6%). Absence and reflex seizures constituted only 1.5% of patients. In recent years, the number of drugs approved for epilepsy has been doubled. Newer AEDs provides clinicians with a wider choice to help patients achieve therapeutic efficacy even for those not responding to a conventional AED. The main reason for introducing a newer AED is the persistence in seizure activity.[15] We found that a higher percentage of patients prescribed more than one AED (68.7%) [Table 1]. A similar higher incidence of polytherapy (79%) has been reported in Italy with over one-third of patients being prescribed more than three AEDs.[15] The reasons for polytherapy could be due to an increase in prescription of second generation AEDs, most of which are approved only as add-ons. Our observations are in contrast to several other studies where a higher percentage of patients were prescribed monotherapy (70–96%) in India,[6,12] Sri Lanka,[14] and Nigeria.[16] The wide use of polytherapy is a concern particularly, since there is no evidence from randomized controlled studies that shows polytherapy is superior to monotherapy in achieving seizure control.[15,17]

Valproic acid and/or sodium valproate was found to be the most commonly prescribed conventional AED (37.8%) followed by carbamazepine (31.1%), and phenytoin (20%) [Table 1]. Other studies have reported carbamazepine to be one of the most commonly prescribed drugs.[14,16] Although use of phenytoin has declined due to more side effects as compared with either carbamazepine or sodium valproate, we still found phenytoin use in 20% of prescriptions. This is because of higher efficacy of phenytoin in controlling epileptic seizures. In USA, phenytoin continuous to be the most commonly used AED (48%).[18] Among the newer AEDs, clobazam constituted 51% of prescriptions (even higher than carbamazepine) and was the most commonly prescribed drug. The second and third most commonly prescribed newer drugs were levetiracetam (21%) and lamotrigine (18%), respectively. A higher use of clobazam has been reported earlier both as montherapy and as an add-on.[19] The reason could be that it is a nonsedating, well tolerated benzodiazepine (BZD) with low cost and higher efficacy in most seizure types.[20] Unlike our study, clobazam was prescribed to only 14% of patients in Italy while levetiracetam was prescribed to 35% of patients.[15] Among the AED combinations, most frequently used combination was sodium valproate + clobazam followed by carbamazepine + clobazam. Other studies have reported levetiracetam as one of the components of combination[21] or carbamazepine + sodium valproate to be the most frequently used combination.[14]

The SES of the patients was determined with the help of Kuppuswamy's socioeconomic scale which is considered to be an important tool in hospital and community-based research in India.[8] It was revised in the year 2003 and it takes into consideration the education, occupation, and family income of the subjects. In our study, we found majority of patients (39.6%) belonged to lower middle group [Table 1]. This is a cause of concern, due to an increasing burden on patient for increasing cost of therapy. We compared the monthly costs of each AED prescribed and found a much higher cost for some of the newer AEDs including the lamotrigine (Rs 1009), levetiracetam (Rs 2305), and lacosamide (Rs 3885) as compared with the mean monthly costs of older drugs like carbamazepine (Rs 167), sodium valproate/valproic acid (Rs 366), or phenytoin (Rs 97). Among the newer drugs, clobazam, a BZD, had the lowest cost (Rs 227), one of the reason probably for the most commonly prescribed drug in our study where patients mainly belonged to the lower middle group.

The use of various diagnostic tests like EEG, CT scan, and MRI are also important predictors of total cost. In general, EEG is advocated to most patients. At this hospital, EEG was free of cost and the OPD consultation fee was nominal (Rs 10). The costs of MRI and blood tests, etc., contributed in addition to the cost of AEDs. Figure 1 shows an increase in direct cost by increasing the number of AEDs in the prescription. A significant increase in cost, as observed from our study, suggests the need to encourage the use of cost effective AED to reduce economic burden of epilepsy. Polypharmacy and frequent use of newer AEDs, which are comparatively expensive than older AEDs like carbamazepine and sodium valproate, have escalated cost of epilepsy treatment in India. Less expensive drugs like phenobarbitone are seldom used now.

The efficacy/response of newer AEDs must be weighed against their costs. We calculated RR, to determine the efficacy of newer AED, wherever added, in the treatment regimen. In our study, RR was calculated for 12 patients as only these were found to have the baseline seizures at the initiation of therapy (January) and were prescribed add-on newer AEDs. A value above −0.5 indicated at least 50% or more reduction in seizures when observed after 12 weeks. We observed a RR > −0.5 in case of combinations: Levetiracetam + Zonisamide + Phenytoin + Lacosamide (−0.76), Valporic acid + Levetiracetam + Lamotrigine (−0.69), Levetiracetam + Clobazam + Sodium valproate (−0.64), and Levetiracetam + Zonisamide + Topiramate (−0.62) [Table 2]. Since the sample size is small, it is difficult to arrive at any conclusion regarding the efficacy of combinations. Nevertheless, > 50% reduction in seizures was observed in 4 out of 12 patients who were prescribed add-on newer AEDs.

QOL constitutes one of the humanistic aspects of pharmacoeconomics evaluations. We used QOLIE-10 which is a self-administered questionnaire designed for completion by patient alone. It comprises of 10 items. We recorded the answers either personally or telephonically after the end of 1 month. We also determined Cronbach's alpha, a marker of reliability to indicate how closely related a set of items as a group. Relative coefficient of 0.7 or higher is considered acceptable in most situations. We found a reliability coefficient of 0.94. Further, all domains of QOL correlated well with each other indicating that these domains were inter-linked. A close look at the QOL mean scores of 6 most commonly prescribed AEDs revealed a low score ranging from 1 to 3 for most of the domains of QOLIE-10 for both older and newer drugs. The energy level, fear of future seizure (anxiety) and other parameters indicating general well being of a person were almost comparable for both older and newer AEDs. The scores on driving ability were slightly worse as compared with other domains. There were no obvious differences even in the memory problem unlike various clinical reports indicating impairment of cognitive functions following AEDs.[22] Overall, QOL did not appear to be much affected (probably because of short duration of our study) and significant differences between older and newer AEDs were not discernible.

To conclude, our study indicates an increasing trend toward usage of newer AEDs in clinical practice, an increase poly-therapy (pointing toward a higher number of intractable cases) with significant escalations in the cost of therapy. The QOL domains following AED therapy, whether conventional or newer drug, were not much affected except driving ability. Thus, despite introduction of several new AEDs in the treatment armamentarium, a cost-effective therapy, especially for intractable cases where two or more drugs are required, is the need of the hour. However, our study was limited to one hospital with limited number of patients and was designed for limited duration of time. Shorter duration of current study (4 months) can interfere with the outcome of RR/QOLIE since seizure events outside this time frame may have effect on efficacy/QOL. There is definitely a need to conduct long-term multi-centric studies involving direct comparisons of cost with therapy response and QOL.

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