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Original article

Need for pharmacoeconomic consideration of antiepileptic drugs monotherapy treatment in persons with epilepsy

Sudhir C. Sarangi [a,1,*], Nivendeep Kaur [a,1], Manjari Tripathi [b]

[a] Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India
[b] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Objective: Newer antiepileptic drugs (AEDs) are expected to have less adverse effects (AEs) and drug interactions as compared to conventional AEDs but the high cost is the major limitation for their use. This study evaluated variation in the cost of treatment with newer and conventional AEDs through its correlation with treatment efficacy and AEs in persons with epilepsy (PWE).

Methods: This cross-sectional study included PWE (28.9 ± 9.9 years) having focal and generalized seizures on conventional [valproate, carbamazepine, phenytoin] or newer AEDs [levetiracetam, oxcarbazepine] for >6 months. Seizure frequency during the study (6 months) was compared to that within 6 months before the study. Other parameters assessed were Quality of life in epilepsy, Pittsburgh Sleep Quality Index, Gastrointestinal Quality of life Index, and Liverpool AEs Profile. The cost of treatment was determined as direct, indirect, and intangible costs. The incremental cost-effectiveness ratio (ICER) analysis was also performed.

Results: Out of 214 PWE, 51.4% were on newer AEDs. Newer and conventional AEDs did not differ significantly in seizure frequency reduction (60.29 vs. 53.09%), quality of life parameters, though these were improved significantly during the study period. The direct medical cost and total cost of treatment were lesser with conventional AEDs ($p < 0.001$ in both) than newer AEDs, but the intangible cost did not differ. The total cost of treatment was significantly influenced by factors (as per regression analysis) including the type of AEDs (significant difference between valproate, carbamazepine, and levetiracetam), frequency of seizures, cost of medicine (70.34% of total cost), hospital admission, and treatment of AEs. As per ICER, newer AEDs need an additional USD 8.39 per unit reduction in seizure frequency.

Conclusion: Newer AEDs have comparatively better efficacy, though not significant than conventional AEDs. However, the additional cost per unit improvement is quite high with newer AEDs, necessitating pharmacoeconomic consideration in epilepsy treatment.

1. Introduction

Epilepsy is a common neurological disease globally and poses a social and economic burden to the country(Megiddo et al., 2016; Gourie-Devi et al., 2003). According to WHO, 50 million people are sufferers of epilepsy worldwide, out of which 80% belong to developing countries (Radhakrishnan, 2016). It is estimated that 12 million persons with epilepsy(PWE) live in India; contributing to almost 20% of the global burden(Radhakrishnan, 2016). The management of PWE comprises of three main objectives: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. In India, seizure types commonly encountered are focal seizure (33.6%) and generalized seizure (45.5%) (Haroon et al., 2012). Although monotherapy is recommended in PWE approximately 30% of patients are not controlled with monotherapy regimens (Simoens, 2010). The International League Against Epilepsy (ILAE) Commission on economic aspects has highlighted the need for a thorough appraisal of the economic aspects of epilepsy(Beran and Pachlatko, 1997). The annual economic burden of epilepsy in India is 88.2% of GNP (Gross National Product)

* Corresponding author at: Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India.
E-mail address: scsarangi@aiims.gov.in (S.C. Sarangi).
[1] Equal contribution.

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per capita, constituting 0.5% of the GNP of India(Thomas et al., 2001). The treatment gap in epilepsy in India ranges from 22%in urban settings to as high as 90% in villages(Radhakrishnan, 2016). Poor socio-economic status, prolonged treatment, indirect cost due to loss of productivity impose a heavy economic burden on the rural population and affect the quality of life. Although newer AEDs are known to have fewer adverse effects (AEs) and drug interactions, high cost is a major limitation for their use in a resource-poor country, that is why conventional AEDs are commonly prescribed in developing countries(Sarangi et al., 2018; Radhakrishnan, 2016; Hasan et al., 2010). There is a huge challenge for a physician to provide quality patient care with minimum cost in PWE as there is so much variation among different AEDs in terms of efficacy, quality of life, cost, and AEs profiles. As limited studies are comparing the cost-effectiveness of different AEDs, pharmacoeconomic evaluation of the newer AEDs concerning conventional AEDs can help in understanding whether the incremental cost of newer AEDs is worth paying in terms of greater efficacy and safety. This study primarily compared the AED treatment efficacy, quality of life, and cost of treatment during 6 months follow up between newer and conventional AEDs administered as monotherapy to PWE having focal or generalized seizures.

2. Materials and Methods

2.1. Study design

This prospective observational study was conducted in the Department of Pharmacology and Department of Neurology, in a tertiary care hospital from June 2016 to May 2019 after ethical approval (IECPG-412/29.06.2016). The study was conducted in accordance with the Indian Council of Medical Research ethical guidelines for biomedical research and Indian Good Clinical Practice guidelines (Clinical Trials Registry-India reg no.-CTRI/2017/10/009997).

2.2. Study subjects

After obtaining written informed consent, PWE of >18 years, either gender with focal or generalized onset of seizures on monotherapy of newer {e.g. levetiracetam (LEV), oxcarbazepine (OXC)} or conventional {e.g. valproate (VPA), carbamazepine (CBZ), phenytoin (PHT)} AEDs since last 6 months were screened for the study. The PWE having other neurological, psychiatric, or chronic diseases (except epilepsy) and on AED polytherapy were excluded from the study. Data regarding detailed demography, seizure history, and prescribing information of AEDs, treatment efficacy parameters, cost of treatment were collected using individual case report form. Enrolled PWE were followed up for 6 months and the above information was collected at the end of follow up also. In between, PWE were contacted telephonically for additional study-related information.

2.3. Treatment efficacy assessment

The efficacy of AED treatment was assessed through seizure control status and quality of life. Seizure control status was assessed by comparing the frequency of the seizures in the last 6 months prior to study initiation to that of the frequency of seizures during 6 months of study.

The validated scales that were used to assess the quality of life were i.e. Patient weighted Quality of life Index in epilepsy (QOLIE-10), Pittsburgh Sleep Quality Index (PSQI), and Gastrointestinal Quality of life Index (GIQLI). AEs profile was compared using the Liverpool Adverse effect profile (LAEP) questionnaire.QOLIE-10 is a brief survey consisting of 10 questions that are based on health and daily activities of PWE and would assess parameters like energy, emotions, daily activities, mental functions, medication effects, worry about seizures, and overall quality of life. The maximum score of QOLIE-10 is five with a lower score depicting a better quality of life. PSQI, a scale to assess the quality of sleep, contains nine self- rated questions, with question number 4 and 5 are having subsets. The components of PSQI are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of sleep medications, and daytime dysfunction. The maximum score is 18 and ≥ 5 is indicative of poor sleep quality. GIQLI containing 36 questions was used to assess the patient's quality of life based on gastrointestinal complications. A higher score represents an improved GIQLI with a maximum score of 144. AEs of AED treatment was assessed through LAEP scoring with a maximum score of 76. Lower the score represents lesser AEs. Prior permission was obtained for using these questionnaires.

2.4. Cost of treatment

The cost of treatment by patients was divided into direct, indirect, and intangible costs. Direct costs included direct medical costs and direct non-medical costs. Direct and indirect costs can be easily measured in monetary terms, but the measurement of intangible costs in monetary terms is difficult and need some assumptions. A well designed and validated proforma was given to the subjects to note down the cost related parameters daily to prevent recall bias. As the cost of each parameter (medicine, investigations, hospital stay, food, and others) can vary significantly based on the place, time and person's financial status, a standardized format was used in this study to have uniformity in the cost calculation for all subjects. (Cost was calculated considering 1 USD $\cong$ 74.82 INR, as on 17 August 2020)

2.4.1. Direct medical cost

Direct medical costs were related to medical interventions and included the cost of medicines (AEDs), additional drugs taken as supplement/adjuvant/due to AEs, hospital stay, and laboratory investigations during 6 month follow up period. The cost of the medicines was calculated according to the Current Index of Medical Specialties (Current Index of Medical Specialties, 2018)considering the brand name and the total number of doses of medicine consumed during 6 months follow up period. This was also done for medicines covered under the insurance/reimbursement scheme.

Cost of medicine for 6 months = Cost/day $\times$ (30 days $\times$ 6 months).

The variation in the dose of AED during the study period was also considered for the total cost of medication calculation. The expenses on behalf of alternative medicines or traditional treatments were not considered for this study.

In the absence of any detailed information on expenses for medicines and AEs treatment, the expenditure as per actual informed by PWE was taken into consideration. Cost of hospital admission and stay was calculated irrespective of the type of hospital (Govt./private) using a standardized format the 'Revised Rates of Hospital Charges' of our hospital for ordinary room accommodation i.e. USD 26.73 (INR 2000) (Revised Rate List of Hospital Charges, 2018). Similarly, the cost of food during the stay period was considered as per the private ward diet charges of 'Revised Rates of Hospital charges' and was USD 2.67 (INR 200) per day. Investigations done in our hospital during the study period were calculated according to the Revised Rates of Hospital Charges; those done in the private setup were calculated according to Central Government Health Scheme(CGHS) Delhi rate list 2014 (Rate

list Delhi NCR, 2014). EEG was done in our hospital is free of cost, so it's cost were added according to the CGHS rate list, 2014.

2.4.2. Direct non-medical cost

Direct non-medical costs are expenses borne for transportation, lodging, and food for PWE (excluding expenses for attendants). The frequency and distance traveled by PWE in kilometers to reach our hospital was calculated which was then multiplied by the cost of per km traveling as per train fare (fare per Km of sleeper class Mall/Express according to the Fare table for 2017–18 of Indian Railways)(Fares Tables, 2017-2018). PWE was asked about the number of days he lodged for the treatment purpose (irrespective of lodging at relative's house) during the study period and lodging cost was calculated based on daily allowance given for lowest pay level in pay matrix of Travelling Allowance Rules of Seventh Pay Commission i.e. USD 6.01 (INR 450) per day (Travelling allowance rules, 2018). The expenses of food taken during their travel and stay period were calculated; if it was less than USD 6.68 (INR 500) per day then it was taken into account as per actual. In case PWE expressed it as > USD 6.68 (INR 500) per day then USD 6.68 (INR 500) for each day was considered as per the minimum reimbursement given for food for lowest pay level in pay matrix of Travelling Allowance Rules of Seventh Pay Commission, by Ministry of Finance, Government of India(Travelling allowance rules, 2018).

2.4.3. Indirect cost

The cost incurred by PWE (excluding attendant's loss) due to loss of productivity/absenteeism from work because of the seizures, for coming to hospital due to epilepsy or due to any AEs during the study period was termed as an indirect cost. The cost was calculated by taking into account the minimum rate of wages given by the Labour Department, Office of Labour Commission that is according to the education status of PWE (Labour Department Notification, 2017). The categories taken into account were-http://www.delhi.gov.in/wps/wcm/connect/doit_labour/Labour/Home/Minimum+Wages/.(Accessed on October (2018)

a. Non-Matriculate- USD 7.55 (INR 565) per day.
b. Matriculate but not graduate- USD 8.31 (INR 622) per day.
c. Graduate and above- USD 9.05 (INR 677) per day.

2.4.4. Intangible costs

The intangible health care parameters associated with epilepsy considered in the study were discomfort, pain, suffering, anxiety, and fatigue. Cost for each of them was calculated by asking the subject, how much money (to mark on a scale ranging from 0 to 100 percentages) out of their monthly wages (as in indirect cost calculation), they are willing to pay to get relief from each of these. This was assessed at the time of enrolment and the end of six months' follow up.

2.5. Data analysis

Treatment efficacy parameters and cost of treatment parameters were shown as per their respective scores and their percentage change was recorded at enrolment time and after 6 months follow up. Since the quality of life in epilepsy is an essential health-related parameter and has been subject to research in previous studies, it was selected for an estimate of the required sample size. The calculations were done using statistical software and the mean QOLIE-10 score of Indian persons with epilepsy in a previous study from our hospital(Haroon et al., 2012). According to that study, the average score of QOLIE-10 for the valproate treated group was 1.89 ± 0.86 and for levetiracetam group was 1.65 ± 0.70. This was obtained after getting an average of individual scores of 10 questions in QOLIE-10. Considering this score and keeping significance value (α) as 5% and power of study as 70%, the sample size was calculated to be 91 in each group. Considering 10% loss to follow up, it is needed to recruit 100 patients in each group i.e. newer and conventional AEDs.

Data were expressed as mean ± SD or in percentage for parametric data and in median and interquartile range (IQR) for non-parametric data. Student's *t*-test was used for parametric data comparison and the Mann-Whitney *U* test was used for non-parametric data comparison. The multiple linear regression analysis was done to identify the significant predictors affecting the total cost of treatment and quality of life parameters. Statistical significance was considered for p-value $\leq$ 0.05. Incremental Cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs (incremental cost) by the difference in health care outcome measure or effect (incremental effect). It provided a ratio of extra cost per one unit of health outcome change, thus helped in deciding cost-effective therapy. Following formula was used for ICER calculation:

$$\text{ICER} = \frac{CostA - CostB}{EffectA - EffectB}$$

3. Results

3.1. Demographic characteristics

Out of 240 PWE, 214 completed the study, and 26 were lost during follow up due to the stoppage of AED treatment or the addition of one more AED or refusal to continue in the study. The PWE were on conventional AEDs [48.6% (n = 104)] or newer AEDs [51.40% (n = 110)]. Out of 214 PWE, maximum numbers were on LEV (47.66%) followed by VPA, CBZ, PHT, and OXC. There were 52.8% males and the preponderance of generalized seizure 76.2%. About 79.9% of PWE belong to the age group 18–35 years, signifies higher epilepsy prevalence in younger subjects. Female PWE were commonly prescribed newer AEDs; this may be due to the risk of teratogenicity and more hormonal side-effects caused by conventional AEDs. (Table 1)

3.2. Seizure frequency reduction

It was observed that there was a major reduction in seizure frequency (56.09%) in all the PWE during 6 months study compared to those 6 months before enrolment. Conventional AED group reported 53.06% decline in seizure frequency; whereas newer AEDs group had 60.29% (p = 0.35) (Table 2).

3.3. Quality of life parameters

The comparison between newer and conventional AEDs did not reveal any significant difference concerning any quality of life parameters i.e. QOLIE-10, PSQI, GIQLI, and adverse effect profile (LAEP), when compared at enrolment time and after 6 months of follow up. (Table 2) The mean QOLIE-10 score in all PWE at enrolment was 2.38 ± 0.69 and after 6 months follow up was 1.84 ± 0.58 (p < 0.001). A similar reduction in the QOLIE-10 score was noted for both conventional and newer AEDs (p < 0.001, in each). Similar improvement was found with PSQI score in all PWE and also among conventional and newer AEDs (p < 0.001, p = 0.001, p = 0.003, respectively) (Table 2).

The mean LAEP score in all PWE at enrolment and 6 months follow up was 31.59 ± 9.95 and 28.21 ± 8.89, respectively (p < 0.001). Among PWE on conventional and newer AEDs, likewise, a significant reduction in the LAEP score was found (p = 0.02, p < 0.001) (Table 2). The mean GIQLI score in all PWE at enrolment time and 6 months follow up period was 121.95 ± 21.08 and

Table 1
Demographic, seizure, and AED treatment parameters among PWE enrolled in the study.

Parameters	Total PWE (n = 214) Number (%)	PWE on Newer AED (n = 110) Number (%)	PWE on Conventional AED (n = 104) Number (%)	p-value between newer and conventional AED groups
A) **Demographic Characteristics:**				
Age				
18–35 year	171(79.9)	92 (83.6)	79 (76.0)	0.17
>35 years	43 (20.1)	18 (16.4)	25 (24.0)	
Sex				
Male	113 (52.8)	39 (35.5)	74 (71.2)	<0.001
Female	101 (47.2)	71 (64.5)	30 (28.8)	
Education				
Undergraduate	83 (38.8)	41 (37.3)	42 (40.4)	0.67
Graduate	131 (61.2)	69 (62.7)	62 (59.6)	
Monthly Household Income				
≤ 15,000 INR (USD 200.39)	74(34.6)	37 (33.6)	37 (35.6)	0.77
> 15,000 INR (USD 200.39)	140 (65.4)	73 (66.4)	67 (64.4)	
B) Seizure Related-				
Type of Epilepsy				
Focal	51 (23.8)	19 (17.3)	32 (30.8)	0.02
Generalized	163 (76.2)	91 (82.7)	72 (69.2)	
Duration of Epilepsy				
≤10 years	128 (59.8)	73 (66.4)	55 (52.9)	0.04
> 10 years	86 (40.2)	37 (33.6)	49 (47.1)	
Baseline Seizure Frequency				
≤ 1 attack/year	106 (49.5)	60 (54.5)	46 (44.2)	0.13
>1 attack/year	108 (50.5)	50 (45.5)	58 (55.8)	
Seizure free period in years				
≤ 2 years	120 (56.1)	64 (58.2)	56 (53.8)	0.58
> 2 years	94 (43.9)	46 (41.8)	48 (46.2)	
B) **Type of AED Treatment**				
Valproate			44(20.56)	
Carbamazepine			44 (20.56)	
Phenytoin			16 (7.48)	
Levetiracetam		102 (47.66)		
Oxcarbazepine		8 (3.74)		

AED: Antiepileptic drugs; PWE: Persons with epilepsy

Table 2
Changes in the treatment efficacy parameters considered in the study.

Parameters	Total PWE (n = 214)			PWE on newer AED (n = 110)			PWE on conventional AED (n = 104)			p-value between % change of newer and conventional AED groups
	At enrolment	End of study	% change Median (IQR)	At enrolment	End of study	% change Median (IQR)	At enrolment	End of study	% change Median (IQR)	
QOLIE-10 (Mean ± SD)	2.38 ± 0.69	1.84 ± 0.58	20.87 (3.44–36)	2.42 ± 0.71	1.84 ± 0.57	19.05 (4.54–36.66)	2.33 ± 0.67	1.85 ± 0.59	21.05 (1.42–35.50)	0.65
	p < 0.001			p < 0.001			p < 0.001			
PSQI Median (IQR)	4 (2–5)	2 (1–4)	30.95 (0–50)	4 (2–5)	2 (1–4)	33.33 (0–55.55)	3 (2–5)	2 (1–4)	10 (0–50)	0.24
	p < 0.001			p < 0.001			p < 0.001			
LAEP (Mean ± SD)	31.59 ± 9.95	28.21 ± 8.89	11.11 (-3.63–23.33)	32.41 ± 10.50	27.91 ± 8.63	13.16 (0–25)	30.72 ± 9.30	28.53 ± 9.18	8.26 (-11.12–21.65)	0.09
	p < 0.001			p < 0.001			p = 0.02			
GIQLI (Mean ± SD)	121.95 ± 21.08	130.82 ± 16.99	−3.54 (-15.57–0.73)	119.75 ± 21.56	130.85 ± 16.74	−4.34 (-25–0.72)	124.27 ± 20.41	130.78 ± 17.34	−2.66 (-12.69–0.74)	0.11
	p < 0.001			p < 0.001			p < 0.001			
Seizure frequency per PWE in 6 months duration	0.82	0.36	56.09	0.68	0.27	60.29	0.98	0.46	53.06	0.35

AEDs: Antiepileptic drugs; PWE: Persons with epilepsy; QOLIE-10: Patient weighted Quality of life Index in epilepsy; PSQI: Pittsburgh Sleep Quality Index; GIQLI: Gastrointestinal Quality of life Index; LAEP: Liverpool Adverse effect profile; IQR: Interquartile Range

Table 3
Depicting different cost parameters and their comparison between conventional and newer AEDs groups.

Cost Parameters in USD Median (Interquartile Range)	Total PWE (n = 214)	Newer AEDs (n = 110)	Conventional AEDs (n = 104)	p-value between newer and conventional AED groups
Direct Medical Cost-	44.48 (15.20–84.98)	82.24 (51.00–124.62)	20.26 (12.76–39.71)	<0.001
1.Cost of Medicines	40.90 (13.64–82.28)	82.28 (51.00–115.39)	14.77 (10.36–31.14)	<0.001
2.Cost of Hospital stay and admission	29.41 (29.41–51.46) (n = 4)*	29.41 (n = 1)*	29.41 (29.41–73.51) (n = 3)*	0.28
3.Cost of Investigations	5.35 (3.98–25.37) (n = 49)*	7.14 (3.82–46.11) (n = 20)*	5.35 (3.98–15.99) (n = 29)*	0.10
4.Cost of Adverse effects treatment	1.34 (0.65–8.69) (n = 11)*	2.00 (0.39–20.00) (n = 8)*	1.07 (0.98–2.54) (n = 3)*	0.14
Direct Non-Medical Cost-	2.14 (1.20–11.23)	1.42 (1.20–11.12)	2.40 (1.20–13.46)	0.49
1.Cost of Transportation	1.68 (1.20–3.79)	1.39 (1.20–3.66)	2.14 (1.15–3.97)	
2.Cost of Lodging	12.00 (12.00–24.06) (n = 46)*	15.04 (10.53–24.06) (n = 24)*	12.00 (12.00–24.06) (n = 22)*	0.92
3.Cost of Food	8.42 (3.84–13.37) (n = 72)*	8.02 (3.68–20.05) (n = 35)*	9.62 (4.68–13.37) (n = 37)*	0.60
Indirect Cost	18.10 (9.05–35.46) (n = 90)*	18.10 (9.05–35.46) (n = 40)*	18.10 (9.05–35.46) (n = 50)*	0.11
Total cost of treatment (Direct medical + Direct non-medical + indirect)	77.90 (33.93–124.65)	104.77 (79.81–172.44)	44.04 (20.30–71.35)	<0.001
Intangible Cost (Difference between intangible cost at enrolment and end of study) @	0 (-368.75–0)	0 (-403.12 – 108.58)	0 (-284.39–0)	–

* Cost of this parameter was found only in a some PWE (n).
@ Minus symbol in intangible cost represents a reduction in intangible cost. AEDs: Antiepileptic drugs; PWE: Persons with epilepsy

130.82 ± 16.99respectively (p < 0.001). A significant improvement in GIQLI score was found in both groups (p < 0.001, p < 0.001), when compared at enrolment and after 6 months (Table 2).

3.4. Cost of treatment

The direct medical cost in conventional AED group [USD 20.26 (IQR 12.76–39.71)] was significantly high (p < 0.001) in newer AED group [USD 82.24 (IQR 51.00–124.62)]. Among the different components, cost of hospital stay and admission, investigations and expenses on treatment of AEs were reported only in a limited number of PWE i.e. 4, 49, and 11, out of total 214 PWE, respectively and the analysis was done for them only. Though these components were included in direct medical cost calculation, the direct medical cost was solely dependent on the cost of medicines (Table 3).

The median direct non-medical cost for all PWE was USD 2.14 (IQR 1.20–11. 23). The comparison between conventional and newer AEDs did not reveal any significant difference concerning direct non-medical cost. The direct non-medical cost included several components that vary individually and components like cost the of lodging and food were reported in only 46 PWE and 72 PWE, respectively. Only 90 PWE had expenditure in the form of indirect cost and the median indirect cost of all PWE was USD 18.10 (IQR 9.05–35.46). The same value was obtained for conventional and newer AEDs groups.

The median value of the total cost of treatment was found to be USD 77.90 (IQR 33.93–124.65) in all PWE irrespective of drug treatment. The treatment with newer AEDs was found to be costlier when compared with conventional AEDs. However, total cost variation was solely dependent upon the cost of medicines as the other components were found in a limited number of subjects in both the groups. The cost of medicines accounted for 70.34% (IQR 44.71%-92.the 04%) of total cost of treatment in all PWE (Table 3).

The total cost was analyzed among the groups based upon different demographics, seizure-related parameters, which did not reveal any significant difference (Table 4). However, the newer AEDs group was having a higher total cost as the compared to conventional AEDs group (p < 0.001). Similarly, the individual AED groups were showing an overall significant difference as per variation in total cost (p < 0.001), this difference was significant for the comparison between carbamazepine, levetiracetam, and valproate as per posthoc analysis.

It was found that the median change in intangible components was 0 in all the groups. The minus value represents that there is a need to spend less amount for intangible cost at the end of the study period as compared to the cost before enrolment (Table 3). The number of PWE with a reduction in intangible cost during 6 months follow up for the intangible parameters did not have any significant difference between newer and conventional AEDs.

3.5. Factors influencing total cost of treatment

The regression model with the total cost of treatment as outcome variable demonstrated that following factors have a significant impact on total cost: type of AEDs (p = 0.006), frequency of seizures before enrolment (p = 0.03), number of seizures in the study period (p = 0.02), cost of medicine (p < 0.001), cost of hospital admission (p = 0.007), cost of treatment of AEs (p = 0.03), cost of investigations(p < 0.001), lodging (p = 0.03), and food (p = 0.03) (Table 5).

3.6. Factors influencing percentage change in QOLIE-10, PSQI, LAEP, GIQLI score

In the regression model with QOLIE-10 as an outcome variable, the seizure-free period in years had a significant association (p = 0.03, CI of coefficient 0.250–5.665). Similarly while considering percentage change in PSQI as an outcome variable, the cost of transportation (p = 0.05, CI of coefficient 0.000–0.048), and percentage change in LAEP (p = 0.002, CI of coefficient 0.066–0.298) were significantly associated. In the regression model with the percentage change in the LAEP score as an outcome variable, the only percentage change in PSQI (p = 0.002, CI of coefficient 0.124–0.562) was significantly associated. In the regression model with the percentage change in GIQLI score as an outcome variable, the percentage change in QOLIE-10 {p < 0.001, CI of coefficient −0.347-(-0.101)} was significantly associated.

Table 4
Showing the difference in the total cost of treatment due to different demographic, seizure, and AED related parameters.

Variables		Total Cost in USD, Median (Range)	p-value
Age in years	18–35 years	79.46 (7.27–499.39)	0.33
	35 years	74.21 (6.75–245.04)	
Gender	Female	83.35 (6.75–499.39)	0.43
	Male	67.13 (7.73–386.20)	
Education Status	Undergraduate	76.18 (7.57–289.05)	0.37
	Graduate	79.21 (6.75–499.39)	
Income (monthly)	≤ 15,000 INR (USD 200.39)	74.15 (6.75–386.20)	0.32
	> 15,000 INR (USD 200.39)	81.20 (7.27–499.39)	
Type of seizure	Focal	70.21 (7.70–386.20)	0.30
	Generalized	83.03 (6.75–499.39)	
Duration of epilepsy in years	≤ 10	79.33 (6.75–499.39)	0.75
	>10	73.60 (7.27–386.20)	
Seizure frequency at the onset of seizures	≤ 1 attack/year	82.29 (7.70–499.39)	0.67
	>1 attack/year	67.18 (6.75–386.20)	
Seizure free period in years	≤ 2 years	83.19 (7.27–499.39)	0.56
	>2 years	63.70 (6.75–386.20)	
Type of AEDs	Conventional drugs	44.04 (6.75–365.05)	<0.001
	Newer drugs	104.77 (8.15–499.39)	
Drugs	CBZ	23.03 (6.75365.05)	<0.001 (CBZ vs. VPA- p = 0.02, CBZ vs. LEV- p < 0.001, VPA vs. LEV- p < 0.001)
	LEV	106.48 (8.15–499.39)	
	OXC	92.98 (26.46–134.14)	
	PHT	49.08 (14.71–178.64)	
	VPA	50.49 (16.23–212.36)	

AEDs: Antiepileptic drugs; Carbamazepine (CBZ), Levetiracetam (LEV), Oxcarbazepine (OXC), Phenytoin (PHT), Valproate (VPA)

3.7. Incremental cost-effectiveness ratio (ICER)

As per ICER analysis, USD 607.30 will be the added cost for one unit extra improvements in QOLIE-10 score for newer AEDs as compared to conventional AEDs. Similarly for PSQI, LAEP, GIQLI one unit extra improvement will have an added cost of USD 60.73, 26.29, 13.23 respectively for newer AEDs as compared to

Table 5
Multiple linear regression analyses for the total cost of treatment.

Variable	Coefficient (B)	95% Confidence interval of B	p-value	Coefficient (Beta)	t score
Type of antiepileptic drugs (newer and conventional)	1659.44	478.985–2839.907	0.006	0.138	2.77
Type of seizure	−645.00	−1686.676–396.666	0.22	−0.046	−1.22
Age in years	−42.45	−1147.097–1062.189	0.94	−0.003	−0.07
Education Status	168.04	−837.322–1173.410	0.74	0.014	0.33
Income	244.75	−734.839–1224.339	0.62	0.019	0.49
Sex	130.08	−863.813–1123.974	0.79	0.011	0.25
Seizure frequency at the onset of seizures	−374.48	−1294.193–545.214	0.42	−0.031	−0.80
Seizure free period in years	−18.94	−922.541–884.656	0.96	−0.002	−0.04
Duration of epilepsy in years	37.82	−758.633–834.281	0.92	0.004	0.09
Frequency of seizures before enrolment	381.33	37.692–724.974	0.03	0.222	2.18
No. of seizures in the study period	−561.45	−1056.160- (-66.751)	0.02	−0.224	−2.23
Cost of medicine	0.80	0.664–0.947	<0.001	0.539	11.24
Cost of Hospital Admission	1.41	0.390–2.438	0.007	0.153	2.72
Cost of treatment of adverse effects	1.22	0.109–2.335	0.03	0.082	2.16
Cost of investigations	1.03	0.591–1.471	<0.001	0.178	4.62
Direct Medical Cost	−0.06	−0.055–0.042	0.79	−0.011	−0.25
Cost of Lodging	0.95	0.075–1.830	0.03	0.148	2.14
Cost of food	0.90	0.057–1.743	0.03	0.427	2.10
Cost of transportation	0.40	−0.719–1.527	0.47	0.569	0.71
Indirect Cost	2.06	−2.345–6.475	0.35	2.235	0.92

Table 6
Incremental cost-effectiveness ratio (ICER) value between the two groups.

Parameters	Newer AED group	Conventional AED group	Difference	Incremental cost-effectiveness ratio
The total cost of treatment in USD	104.77	44.04	60.73	
Improvement in QOLIE-10 mean scores at the end of the study as compared to enrolment	0.58(2.42–1.84)	0.48(2.33–1.85)	0.1	60.73/0.1 = 607.3[#]
Improvement in PSQI median scores at end of study as compared to enrolment	2(4–2)	1(3–2)	1	60.73[#]
Improvement in LAEP mean scores at the end of the study as compared to enrolment	4.5(32.1–27.91)	2.19(30.72–28.53)	2.31	60.73/2.31 = 26.29[#]
Improvement in GIQLI mean scores at the end of the study as compared to enrolment	−11.1[*](119.75–130.85)	−6.51[*](124.27–130.78)	4.59	60.73/4.59 = 13.23[#]
% change in seizure frequency in 6 months duration	60.29	53.06	7.23	60.73/7.23 = 8.39[#]

[*] depicts improvement in GIQLI score between 0 and 6 months follow up period.
[#] added cost for newer AEDs to improve the parameter by one unit as compared to conventional AEDs. AEDs: Antiepileptic drugs; QOLIE-10: Patient weighted Quality of life Index in epilepsy; PSQI: Pittsburgh Sleep Quality Index; GIQLI: Gastrointestinal Quality of life Index; LAEP: Liverpool Adverse effect profile

conventional AEDs. According to ICER for per unit reduction in seizure frequency, the added cost for newer AEDs will be USD 8.39 (Table 6).

4. Discussion

In a developing country like India having a prevalence of epilepsy as 1%, it is hard to tackle the extensive medical, social, and economic challenges incurred as a sequel of epilepsy(Amudhan et al.,2015). Our study reported that 61.21% of PWE were graduates which is in contrast to other studies that concluded epilepsy is associated with low education status of PWE(Hesdorffer et al., 2005). Previous studies have reported a wide variation in the use of newer AEDs throughout India depending upon different regions and hospital settings, ranging from 3% in Eastern India to 40–50% in central/southern India(Sil et al., 2012; Sigamani et al., 2010). Out of 214 patients enrolled in our study, 51.4% PWE were prescribed newer AEDs i.e. LEV and OXC in focal and generalized epilepsy. This is in accordance with the previous study conducted in our hospital (Kumar et al., 2020). LEV constituted a major part out of all AEDs considered in the study as it was prescribed to 47.46% PWE. The studies and trials conducted previously depicted a high proportion of LEV prescriptions that lead to consideration by the National Institute for Health and Care Excellence (NICE) to include LEV as a potential first-line agent in focal seizures and adjunctive in generalized seizures(Sigamani et al., 2010; Sarangi et al., 2019; Glauser et al., 2 006). It was found that 76.16% of PWE had generalized seizures when compared to focal seizures and this is supported by various studies done in different regions and different hospital setups around India that recorded a high percentage of generalized seizures ranging from 58.5 to 79% (Sarangi et al., 2014; Koul et al., 1988). And this study also found that significantly more number of PWE having generalized seizures were prescribed newer AEDs. The PWE who had epilepsy duration of less than or equal to 10 years were remarkably more on newer AEDs as compared to conventional AEDs, the reason may be due to the increasing trend of prescribing newer AEDs.

Our results of QOLIE-10 and other quality of life (PSQI and GIQLI) improvement with time i.e. after 6 months of AEDs treatment (study period) is supported by the findings of previous studies done in India; however, this study could not find any significant difference in between newer and conventional AEDs(Kumar et al., 2020; Sarangi et al., 2019; George et al., 2015). It was observed that conventional AEDs decreased the seizure frequency up to 53.06% whereas newer AEDs decreased 60.29% after 6 months of AEDs treatment sh. The earlier reports in the literature have raised doubts on the superiority of newer AEDs in terms of efficacy as well as their long term benefits and largely failed to detect a significant difference in efficacy outcome(Chung et al., 2007; Glauser et al., 2006). No significant difference was found between both groups in PSQI and LAEP scores (Jain and Glauser, 2014; Shvarts and Chung, 2013; Labour Department Notification, 2017). A previ-

ous study done in older adults reported that there was no difference in LEAP scores in between newer and conventional AEDs (Almalag et al., 2018). This comparative score analysis for GIQLI between newer and conventional AEDs is the first of its kind to the best of our knowledge and our study showed that no significant difference in GIQLI scores was found between newer and conventional AEDs. The direct medical cost constituted 82.91% of the total cost of treatment in all PWE which differs from those concluded by two different Indian studies where direct cost reported was much lower. The difference in the direct cost may be attributed to an increased usage of newer AEDs in today's practice which further is adding to the direct medical cost(Thomas et al., 2001; Krishnan et al., 2004). The total annual median cost of medicines as derived from 6 months data of the study was USD 82.24 in the newer AEDs group which is quite higher than conventional AED's cost [USD 14.76 ($p < 0.001$)]; this is in accordance with the previous study conducted in our hospital that found the much higher cost of newer AEDs (LTG and LEV) than conventional AEDs (VPA and CBZ). Other past studies carried out in developed countries about drug acquisition costs showed a wide variation in the contribution of direct medical cost in the total cost of treatment (Gao et al., 2015; Ali et al., 2014). Cost of medicine constituted 96.19% of direct medical cost and 73.33% of the total cost of treatment and previously various studies have highlighted the contribution of the cost of drugs in total direct cost. In our study, direct non-medical cost contributed only 14.86% of the total cost in all PWE. It was found that 42.05% of PWE lost their wages because of epilepsy treatment. A study conducted in 2014 in a tertiary care hospital, India reported that 42.85% of PWE lost their wages during AED treatment(Sinha and Bhaumik, 2014).

In this cost-effectiveness analysis, newer AEDs are found to be with higher cost and a comparatively better outcome, which needs further analysis to determine the potential cost-effective one among newer and conventional AEDs. This has been also determined by the ICER analysis which revealed that there is a higher amount of added cost associated with newer AEDs to achieve one unit extra health outcome in terms of reduction in seizure frequency, the better quality of life, sleep quality, gastrointestinal quality of life and reduction in AEs as compared to conventional AEDs. However, to determine whether the added cost is high or low depending upon the ceiling value of ICER of the country. In India comprehensive information about the cost and effectiveness of a complete menu of programs is deficient, successively there is a lack of a league table to determine optimal/acceptable ICER value (Sakharkar, 2016). The ICER data of the current study may help in the decision-making process in the Indian health-care system as an individualized or case to case basis, based on socio-economic condition.

A recent study in 2018 did analysis of economic burden and factors influencing it and found that factors hospitalization, polytherapy, PWE experiencing illness for <5 years, in severe seizure index or active epilepsy with drug resistance were more likely to bear the greater economic burden (Wang et al., 2018). Our study found that the following factors have a significant impact on total costs like the type of AEDs, seizure-related parameters like frequency of seizures before enrolment, number of seizures in the study period and cost of parameters like medicine, hospital admission, treatment of AEs, investigations, lodging, and food. To best of our knowledge, this study is the first study in India to assess, compare and correlate the improvement in the quality of life and cost of treatment incurred by PWE and evaluated the intangible disease components confronted by PWE during the study period in terms of monetary values. However, this study has certain limitations such as less sample size and short duration to measure the change in the intangible health-related measures. Other intangible components should be considered for further analysis.

5. Conclusion

It can be concluded from this study that treatment efficacy parameters based on the quality of life and reduction in seizure frequency have comparatively more improvement with newer AEDs as compared to conventional AEDs. The cost analysis also revealed that there is a significantly higher expense with the treatment of newer AEDs than conventional AEDs. These study findings along with socio-economic conditions may assist in the individualization of epilepsy treatment in the Indian population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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