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RESEARCH ARTICLE

Standard approach to antiepileptic drug therapy in focal epilepsy at a tertiary care hospital in Bengaluru: A retrospective cohort study

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ABSTRACT

Background: Epilepsy is a common neurological disorder which demands long-term therapy and thereby carries a huge medical, social, psychological, and economic impact on a developing country. In India, it is estimated that 6-10 million people suffer from epilepsy which accounts for 1/5th of the global epilepsy burden. About 2/3rd of the newly diagnosed epilepsies are focal. The overall aim of treating epilepsy should be complete control of seizures, without causing any untoward reaction due to the antiepileptic therapy. **Aims and Objectives:** The primary objectives are to analyze the pattern of antiepileptic drugs (AEDs) used in focal epilepsy and to assess the retention rate (success rate) at 1-year follow-up. The secondary objectives are to evaluate the effectiveness of substitution versus add-on in treatment failure cases and to assess the profile of adverse drug reactions (ADRs) reported. **Materials and Methods:** This is a retrospective cohort study spanning from January 2009 to January 2014. Patients diagnosed as focal epilepsy attending Neurology outpatient department attached to BMCRI were included in the study. Data were collected through the integration of case records to retrieve the information regarding the demographic and clinical details, AEDs, and ADRs. Retention rate with initial AED was determined at the end of 1-year follow-up. Efficacy was assessed in terms of adequate seizure control between substitution and add-on therapies in all treatment failure cases. The results were analyzed by descriptive statistics, Chi-square, and Fisher's exact tests. **Results:** Out of 134 patients, 57% were males and 43% were females. The age ranged from 14 to 82 years. Monotherapy accounted for 67% of the total epileptic patients, in which 42% continued with initial, 25% substituted to alternative AED, and 33% of them required add-on therapy. The most common AEDs prescribed as monotherapy were carbamazepine (35.07%) and phenytoin (11.94%) and as add-on were carbamazepine with valproate (4.47%) and carbamazepine with phenytoin (4.47%). Carbamazepine showed higher retention rate among all initial AEDs at the end of 1-year follow-up (odds ratio: 2.1, 95% confidence interval: 1.03-4.24). On Fisher's exact test, substitution therapy was better than add-on in adequate seizure control (P = 0.026). The overall incidence of ADRs was 21.6%. Drowsiness and agitation and tiredness were the common ADRs reported. **Conclusion:** Despite the availability of newer AEDs, the domain of pharmacotherapy in focal epilepsy is still dominated by conventional AEDs. Carbamazepine has showed better retention rate at 1-year follow-up. Our study suggests that substitution therapy is a better alternative than add-on therapy in all treatment failure cases with initial AEDs.

KEY WORDS: Focal Epilepsy; Antiepileptic Drugs; Monotherapy; Substitution; Add-on; ADRs

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INTRODUCTION

Epilepsy is a common neurological disorder with an estimated prevalence of 4-10 cases/1000 individuals worldwide.[1] In India, it is estimated that 6-10 million people suffer from epilepsy which accounts for nearly 1/5th of the global epilepsy burden. About 2/3rd of the newly diagnosed

epilepsies are focal.[2] In 2012, epilepsy was responsible for approximately 20.6 million disability-adjusted life years, with significant implications in terms of health-care needs, loss of work productivity, and sometimes premature mortality.[3] Antiepileptic drugs (AEDs) are the mainstay therapy of epilepsy and choosing the better AED may provide early relief, alleviate adverse clinical outcome, improve prognosis, and reduce financial burden in affected patients.[4]

Pharmacotherapy with AEDs is still a matter of debate as the "natural history" of newly diagnosed epilepsy in response to AEDs is not well understood. Monotherapy is the usual dictum for the treatment of newly diagnosed epilepsy, and specific AEDs are selected based on the nature of the disease, the efficacy and tolerability of the agent, and the characteristics of the patient.[5] Furthermore, about 50% of the patients can be managed successfully with the initial AED that they are prescribed with. Substitution is unavoidable when the patient develops intolerable adverse effects, but when seizures persist, despite a maximum tolerated dose of the first AED, it is unclear whether or not substitution should be tried before adding another AED.[4,6]

Clinically relevant information regarding the effectiveness of AEDs provided by randomized control trials is limited as they are carried out in well-controlled research settings and the results are difficult to transfer to general practice. Studies have increasingly been focusing on observational studies in a real-world clinical practice setting.[7] Hence, the present study was undertaken to analyze the pattern of drug utilization in focal epilepsy and to assess the retention rate (success rate) at 1-year follow-up. The primary objective of this study was to evaluate the effectiveness of substitution versus add-on therapy in treatment failure cases and also to study the adverse effect profile of AEDs as secondary objective.

MATERIALS AND METHODS

Sample Selection

This is a retrospective cohort study, based on the data retrieved from patient records in the outpatient clinic of the Department of Neurology, BMCRI, from January 2009 to January 2014. During this period, a total of 576 patients with focal epilepsy attended the neurology outpatient department of BMCRI. Among them, 134 patients with epilepsy met our inclusion criteria from hospital database. Patients aged 5 years and above with focal epilepsy who were in follow-up for at least 1 year from the last AED added and had a complete set of desired information (patients' identity, age, sex, occupation, seizure frequency, and the drug usage profile with any adverse event) in record files were included in the study. A large number of patients (442) were excluded from the study as they either did not return to follow-up or they had incomplete case records.

Operational Definitions[8,9]

Effectiveness

It is measured as treatment retention rate at the end of follow-up and percentage reduction of seizure frequency from the time of drug initiation.

Treatment retention rate

It is the percentage of patients who were maintained on the initial AED at the end of follow-up period.

Treatment failure

Discontinuation of the original AEDs, addition or substitution by another AED.

Study Procedure

Demographic characteristics, seizure frequency, and drug data of the study participants at the time of initial visit were noted. The data were reviewed to evaluate the effectiveness of AED in terms of retention rate of the drug with maximum tolerated dose at the end of 1-year follow-up visit. Among the treatment failure cases, the response to substitution or add-on therapy was reviewed at the end of the 2nd year follow-up (Figure 1). All adverse drug reactions (ADRs) mentioned in case records were recorded.

In Treatment Failure Cases, the Efficacy was Assessed in Terms of Seizure Control among: (ILAE Classification)

- Adequate seizure control: Completely seizure free and reduction of seizure rate >50% from past 6 months of the last follow-up
- Inadequate seizure control: Reduction of seizure rate between 0% and 50%, no remission in seizure frequency, and worsening of seizures from past 6 months of follow-up.

Statistical Analysis

Data were recorded in the Microsoft Excel and were analyzed using descriptive statistics to study the characteristics of the AED prescription. An odds ratio (OR) is a measure of association between an initial monotherapy and treatment retention rate, and Fisher's exact test was used for comparisons of substitution and add-on therapy. The significance of the results was determined at 95.0% confidence interval (CI), and $P < 0.05$ was considered statistically significant.

RESULTS

Out of 576 patients with focal epilepsy who visited the Neurology Department of BMCRI, 134 were selected through the eligibility criteria. There was a male (57%) predominance. Majority of the patients belonged to age

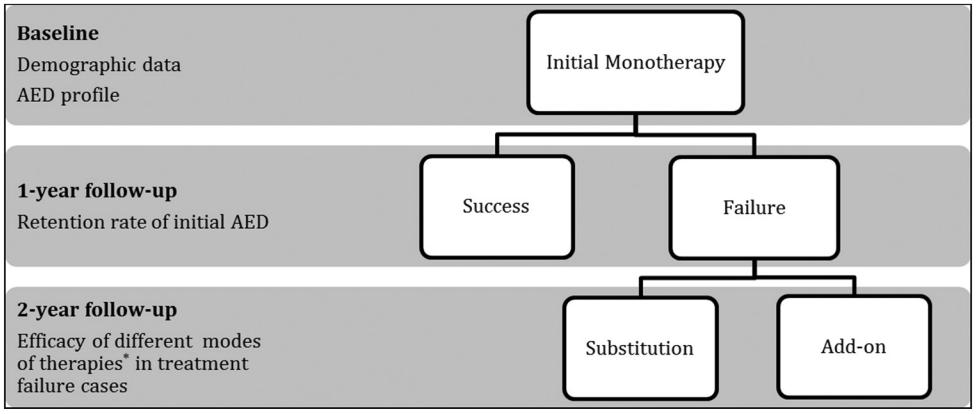

Figure 1: Study design (*Efficacy was assessed in terms of seizure control: ILAE classification)

group of 21-40 years (35%). Almost three-fourth (73.44%) were not gainfully employed. The duration of epilepsy was grouped as 1-10 years (53.13%), 11-20 years (14.04%), and ≥20 years (5.22%) (Table 1).

The number of patients on monotherapy, add-on combination with one AED, and add-on combination with two AEDs was 89 (66.41%), 30 (22.38%), and 15 (11.19%), respectively. About 35.07% of the patients received carbamazepine as monotherapy followed by phenytoin in 11.94% and phenobarbitone in 8.95% patients. Among the combinations of add-on therapy, carbamazepine with sodium valproate (4.47%) and carbamazepine with phenytoin (4.47%) were most commonly used as dual therapy. Carbamazepine, sodium valproate, and phenytoin (2.98%); carbamazepine, sodium valproate, and phenobarbitone (2.98%) were used as triple therapy (Table 2).

The most commonly prescribed initial AED in the study population was carbamazepine (n = 72), followed by phenytoin (n = 28), phenobarbitone (n = 13), levetiracetam (n = 13), and sodium valproate (n = 8). Out of 72 patients prescribed with carbamazepine, 36 patients (50%) continued with the same and the rest 36 patients (50%) were failure cases at the end of 1-year follow-up. Those 36 patients who failed with initial carbamazepine were prescribed substitution therapy (n = 15) or add-on therapy (n = 21). The detailed description about substitution and add-on for all failure cases of initial AED is depicted in Table 3.

Patients on carbamazepine as initial AED are 2.1 times more likely to have better retention rate as compared to other AEDs at the end of 1-year follow-up (OR: 2.1, 95% CI: 1.03-4.24). The present study depicts overall retention rate at 1-year follow-up with initial AED as 42% (n = 56) and the rest 58% (n = 78) were considered as failure cases. Among 78 failure cases, 25% (n = 33) were substituted to other AEDs and 33% (n = 45) received add-on treatment (Table 4).

Substitution therapy (30/33) showed a significant association with adequate seizure control than add-on therapy (31/45) among the treatment failure cases (P = 0.026) (Figure 2).

Table 1: Demographic profile of the patients (n=134)

Demographic characteristics	Number of patients (%)
Gender	
Male	77 (57.46)
Female	57 (42.54)
Age (years)	
<20	13 (9.70)
21-40	47 (35.07)
41-60	41 (30.60)
>60	33 (24.63)
Occupation	
Employed	35 (26.12)
Not employed	99 (73.88)
Duration of epilepsy (years)	
1-10	72 (53.73)
11-20	55 (41.04)
21-30	7 (5.22)
Number of AEDs used	
Monotherapy	89 (66.41)
Combinations of two AEDs	30 (22.38)
Combinations of three AEDs	15 (11.19)

AED: Antiepileptic drug

A total of 42 ADRs were observed among 29 out of the 134 patients (21.6%). The details of systemic classification and type of reaction are given in Table 5. Drowsiness and agitation were the most commonly reported ADRs in our study.

DISCUSSION

Numerous AEDs are being prescribed as monotherapy for the management of focal epilepsy. These include the older AEDs such as carbamazepine, phenytoin, phenobarbitone, and newer AEDs such as levetiracetam and lamotrigine. Even though carbamazepine has many tolerability issues, it is considered as gold standard first-line drug to treat focal seizures since many years. There is insufficient information

about newer AEDs such as levetiracetam and lamotrigine as monotherapy from clinical studies. However, the clinical experience with levetiracetam so far suggests that it is a well-tolerated and an effective drug for the treatment of focal epilepsy.[10-12] All aforementioned facts illustrate that the choice of AED for initial monotherapy is still controversial. During the last decade, after the failure of the first AED, most clinicians preferred substitution in place of the ineffective one. However, several authors have suggested that add-on with the second drug increases the chance of being seizure free.[13-15] Hence, the present retrospective study was undertaken to provide an insight into the pharmacotherapy of focal epilepsy at a tertiary care center.

Table 2: Treatment of epilepsy (*n*=134)

Treatment	Number of patients (%)
Most commonly prescribed AED monotherapies	
CBZ	47 (35.07)
PHT	16 (11.94)
LEV	12 (8.95)
PHB	9 (6.71)
SV	5 (3.73)
Most commonly prescribed add-on AEDs	
CBZ+SV	6 (4.47)
CBZ+PHT	6 (4.47)
CBZ+SV	4 (2.98)
CBZ+CLO	4 (2.98)
LEV+PBT	3 (2.23)
CBZ+PHT+SV	4 (2.98)
CBZ+PBT+SV	4 (2.98)
CBZ+PHT+CLO	2 (1.49)

CBZ: Carbamazepine, PHT: Phenytoin, LEV: Levetiracetam, PHB: Phenobarbitone, SV: Sodium Valproate, CLO: Clobazam, AED: Antiepileptic drug

In this study, male preponderance (57.46%) was observed. Most of our index population (35.2%) belonged to 21-40 years' age group. The report is similar to results of a study by Suresh et al. in Bengaluru (mean age, 27 ± 2.62 years).[16] In general, epilepsy affects all age groups, but it is presumed that epilepsy is more common in two extremes of ages.[17] The probable reason for the missing peak in the older age group in this study is due to the fact that in India most of the population are younger compared to the number of old people. Majority of the patients (73%) were not gainfully employed, possibly due to decreased quality of life pertaining to morbidity associated with seizure disorder.

We encountered use of carbamazepine (35%) as the most common first-line drug followed by phenytoin (11.9%) and levetiracetam (8.9%). This is in accordance with the study conducted by Thomas et al. in Kerala, wherein carbamazepine (69.23%), clobazam (23.1%), phenytoin (21.5%), and phenobarbitone (15.4%) were the most frequently prescribed drugs.[18] Another study done by Mathur et al. in Hyderabad also showed that carbamazepine was the common drug used in focal epilepsy.[19] In the present study, carbamazepine + sodium valproate (4.47%) and carbamazepine + phenytoin (4.47%) were commonly used as dual therapy and carbamazepine + sodium valproate + phenytoin (2.98%) as triple drug therapy. This shows that pharmacotherapy of focal

Table 3: Different pharmacotherapeutic choices encountered in the treatment of focal epilepsy (*n*=134)

Drugs	Total	Continued as monotherapy (%)	Substitution					Total substitution (%)	Add-on		Total add-on (%)
			CBZ	PHT	PBT	SV	LEV		1 AED	2 AED	
CBZ	72	36 (50)	-	4	6	3	2	15 (21)	16	5	21 (29)
PHT	28	8 (29)	5	-	-	-	3	8 (29)	7	5	12 (42)
PHB	13	3 (23)	2	1	-	-	-	3 (23)	4	3	7 (54)
LEV	13	7 (54)	2	2	-	-	-	4 (31)	2	-	2 (15)
SV	8	2 (25)	2	1	-	-	-	3 (37.5)	1	2	3 (37.5)
Total	134	56 (42)	11	8	6	3	5	33 (25)	30	15	45 (33)

CBZ: Carbamazepine, PHT: Phenytoin, LEV: Levetiracetam, PHB: Phenobarbitone, SV: Sodium Valproate, AED: Antiepileptic drug

Table 4: Efficacy of initial AED in terms of retention rate at 1-year follow-up (*n*=134)

Drugs	Total	Continued as monotherapy (retention rate) (%)	Failure (%)	Odds ratio	95% CI
CBZ	72	36 (50)	36 (50)	2.1	(1.03-4.24)
PHT	28	8 (29)	20 (71)	0.46	(0.18-1.14)
PHB	13	3 (23)	10 (77)	0.38	(0.10-1.46)
LEV	13	7 (54)	6 (46)	1.71	(0.54-5.41)
SV	8	2 (25)	6 (75)	0.44	(0.08-2.28)
Total	134	56 (42)	78 (58)		

CBZ: Carbamazepine, PHT: Phenytoin, LEV: Levetiracetam, PHB: Phenobarbitone, SV: Sodium valproate, AED: Antiepileptic drug

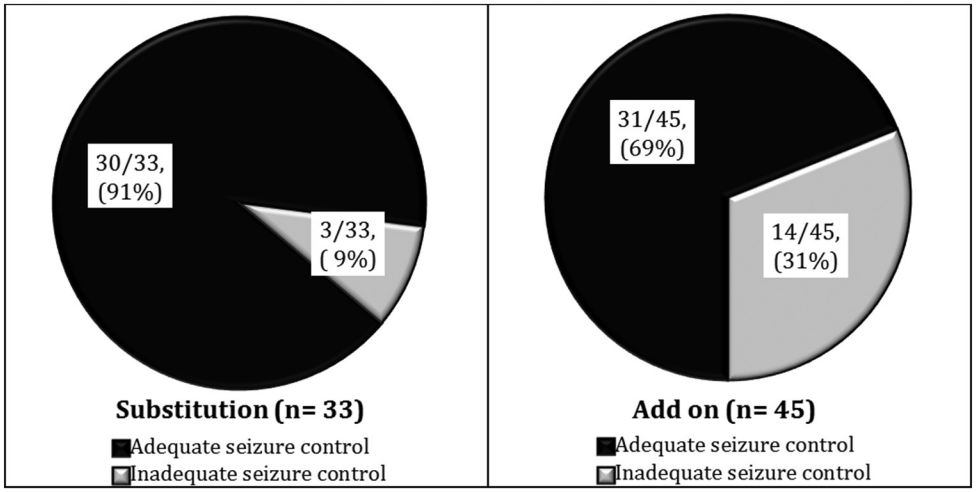

Figure 2: Efficacy of substitution versus add-on in treatment failure cases. Fisher's exact test ($P = 0.026$)

Table 5: Common ADRs reported

System	Reaction	CBZ *n*=72	PHT *n*=28	PHB *n*=13	SV *n*=13	LEV *n*=8	Total *n*=134
Blood	Anemia	2	0	0	1	0	3
Skin	Rash	4	0	0	0	0	4
	Hair loss	0	0	0	1	0	1
Mouth	Gum hypertrophy	0	2	0	0	0	2
	Ulcer	1	0	0	0	0	1
GIT	Nausea	2	0	0	1	0	3
	Vomiting	1	1	0	0	1	3
Liver	Hepatitis	1	1	0	0	0	2
CNS	Agitation	3	2	1	0	1	7
	Drowsiness	3	1	2	0	1	7
	Tiredness	1	0	1	0	1	3
	Numbness	1	0	0	0	0	1
	Headache	2	1	1	0	0	4
Body weight	Weight gain	0	0	1	0	0	1
Total ADR		21	8	6	3	4	42

CBZ: Carbamazepine, PHT: Phenytoin, LEV: Levetiracetam, PHB: Phenobarbitone, SV: Sodium valproate, ADR: Adverse drug reaction, CNS: Central nervous system

epilepsy in our institute is still dominated by conventional agents.

Treatment success was considered as patients' ability to continue with the initial AED. Any patient can retain with a particular AED only if there is adequate seizure control and better tolerability profile. The treatment retention rate at the end of follow-up period on carbamazepine was high compared to phenytoin, phenobarbitone, and valproic acid. Levetiracetam also showed better retention rate but it was not statistically significant, possibly because less number of patients received levetiracetam. Our findings are consistent with the results of Cochrane review of five head-to-head studies in partial epilepsy, wherein the retention rate of carbamazepine was superior to valproic acid.[20] Another study by Heller et al. also showed better retention rate of carbamazepine over phenytoin, phenobarbitone, and sodium valproate.[21] The present study was conducted in a government-run institute where the conventional AEDs such as carbamazepine, phenytoin, and phenobarbitone are available free of cost. This may translate into a lesser economic burden to patients. The author opines that carbamazepine with better retention rate coupled with drug being free of cost implies its use as the most common drug for focal epilepsy in our setup.

The present study depicts overall success rate at 1-year follow-up with initial AED as 42% ($n = 56$) and the rest 58% ($n = 78$) were considered as failure cases. Among 78 failure cases, 25% ($n = 33$) were substituted to other AEDs and 33% ($n = 45$) received add-on treatment. Our study revealed that substitution (30/33) was better than add-on (31/45) therapy in terms of adequate seizure control ($P = 0.026$). Similar views have been expressed in the other studies, namely Semah et al. reported that in cases of refractory seizures after the initial

monotherapy, substitution therapy could be an effective choice than add-on therapy.[22] Another study by Schmidt and Gram also stated that approximately 40% of patients with partial epilepsy who are refractory to one agent will benefit from substitution therapy. If substitution fails, add-on therapy may be helpful in a small minority of patients.[23] Although our findings should be interpreted with caution due to the low statistical power resulting from the relatively small sample size, substitution was associated with better outcome than add-on therapy.

The overall incidence of ADRs in the present study was higher (21.6%) compared to that of Mathur et al. (4.67%) and Roopa et al. (10.2%).[19,24] However, our study finding is in accordance with other similar studies done by Habib et al. and Sanjeev, wherein the percentage of ADR reported was 24% and 16%, respectively.[19,25] Most adverse effects of AEDs belong to the type A category, that is, they are predictable, dose dependent, and explained by the known pharmacological properties of individual agents. Drowsiness and agitation were the most commonly reported ADRs followed by headache and rashes.

The major limitations of the study are smaller sample size as many participants did not return to follow-up or insufficient data in their case records and retrospective design. The study was conducted in single center, thus the generalizability of results is less.

CONCLUSION

Despite the availability of newer AEDs, the domain of pharmacotherapy in focal epilepsy is still dominated by conventional AEDs. The utilization patterns reported here are in agreement with standard guidelines. Carbamazepine has showed better retention rate at 1-year follow-up. The evidence generated from this study states that substitution therapy is a better alternative than add-on therapy in all treatment failure cases with initial AEDs. One may also argue for the need of very robust clinical trials, which could provide some valuable support for the best rational combination therapy.

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