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TRENDS IN ANTIEPILEPTIC DRUGS PRESCRIPTION PATTERN AMONG PATIENTS VISITING A TERTIARY CARE CENTER

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ABSTRACT: The objectives were to observe the drug pattern of epileptic patients with their seizure type, to analyze the type of therapy received by the patients, to observe if epileptic patients are receiving an appropriate dose, to identify the side effects in epileptic patients associated with drug treatment and to observe the cost of conventional and newer antiepileptic drugs (AED's). This was a cross-sectional observational study conducted in the Neurology department. A total of 150 patients were selected based on the inclusion and exclusion criteria. Demographic details and clinically relevant details such as therapy, dose of the drug, side effects experienced pertaining to the objectives of the study were collected using the self-prepared proforma. Symptomatic localization (64%) was the most commonly observed epilepsy syndrome. The commonly observed type of therapy among the patients was dual therapy. AED dose prescribed for most of the adult population was at a sub-optimal level, as explained by the daily defined dose/ prescribed daily dose (DDD/PDD) ratio (<1). Carbamazepine and oxcarbazepine were prescribed at a suboptimal level in the paediatric population. Excessive somnolence, fatigue, weight gain were the most commonly reported side effects. The observed mean cost of newer drugs was more than conventional drugs. Despite the appropriate selection of AED, patients had increased frequency of seizures with the incidence of side effects. This problem could have been overcome by prescribing optimal doses and avoiding the use of polytherapy wherever possible.

INTRODUCTION: Epilepsy is one of the most common neurological conditions representing a heterogeneous collection of disorders that have in common recurrence of seizures.

A seizure is a single (finite) event of abnormal discharge in the brain, and epilepsy is a chronic disorder with abnormal recurrent seizures, and the epileptic syndrome is an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together [1].

In worldwide, 60-90% of people with epilepsy receive no treatment or is inadequately treated [2]. The majority of people with epilepsy have a good prognosis if they receive appropriate treatment [3]. There is still a lack of documentation of safety aspects regarding many of newer AEDs drugs, as

the use in special patient populations like children, women of childbearing age, and elderly [4].

AEDs are drugs with considerable inter-individual variability and are susceptible to cause adverse effects and drug interactions. Changes in prescription patterns, exposure of specific drugs to certain patient groups, a combination of drugs, generic substitution, potential for drug abuse and the use of AEDs in other disorders than epilepsy are examples of issues to be investigated in detail [5].

The general approach for epilepsy management involves identification of goals and development of care plan [6]. The overall goal of antiepileptic therapy is to prevent seizures and avoid untoward side effects with the regimen that is convenient and easy to follow. The choice of most appropriate AED depends on the classification of seizures and age of patient [7]. The initiation of therapy for newly diagnosed patients is with a single antiepileptic drug. Monotherapy is normally the first line of treatment, as it has less drug interactions and side effects, lower cost, better tolerability, medication adherence, and quality of life [8].

Despite advances in the treatment of epilepsy, 30-40% of patients remain uncontrolled on a single AED. Combination therapy is recommended when two successive AEDs given as monotherapy have failed. Agents with a low risk of pharmacokinetic interactions are preferred for combination therapy, and the success of combination therapy can be improved by paying attention to mechanisms of action and using lower dosages. With correct, early, and uninterrupted therapy, up to 75% of patients with epilepsy eventually become seizure-free, many of them within 5 years after diagnosis. About 25% of patients may not respond to any kind of therapy. AEDs are highly successful in suppressing seizures in most patients [9].

In recent years, new AEDs that combine high efficacy with a low incidence of adverse effects have been developed (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide). These newer AEDs are used as an adjunct to conventional AEDs in children with intractable epilepsy. Newer drugs are more efficacious and have better safety as compared to conventional AED. However, caution must be exer-cised for possible drug interactions with conventional AEDs before using them as an adjunct. Moreover, many of these newer AEDs have been recently launched in the Indian market, and costs of some of them are largely prohibitive [10].

MATERIALS AND METHODS: A cross-sectional observational study was conducted over a period of six months in the Neurology Department of PSG Hospitals, Peelamedu, Coimbatore. The study was approved by the Institution Human Ethics Committee (IHEC, PSG IMS & R) of the hospital. The protocol was approved on 22/2/2018, Proposal number: 18/018.

Patients in the neurology department with epilepsy were selected for the study. Both genders and all age groups were included. Pseudo-seizure patients, patients having a seizure history of less than 1 month, patients having pathological liver & renal disorders, and patients who are not willing to participate were excluded from the study. Patient data collection form included demographic details, clinical details such as Treatment referral, Engel seizure score, Epilepsy diagnostic code, Drug and dose, Cost of AED's per month, AED related side effects, No. of AED's.

The trends observed in the prescription patterns were analyzed based on the seizure type and drug pattern, type of therapy, dose of the prescribed drugs, AED related side effects, and cost of the drugs with the help of self-prepared proforma and Engel seizure score. The statistical analysis was done using mean and standard deviation calculation, percentage calculation, bivariate correlation, curve estimation.

RESULTS: During our study period, 165 patients were approached, among which 15 patients were not willing to participate in the study. Out of 150 patients, 28% (n=42) were from corporation, 29% (n=43) were from municipality and 43% (n=65) were from Panchayat.

57% (n=86) were male and 43% (n=64) were female patients. 22.7% (n=34) were between 0-10 y, 27.3% (n=41) were between 10-20 y, 24% (n=36) were between 20-30 y, 15.3% (n=23) were between 30-40 y, 6.7% (n=10) were between 40-50 y, 2% (n=3) were between 50-60 y, 1.3% (n=2)

were between 60-70 y and 0.7% (n=1) were between 70-80 y .

24% (n=36) had family history and 76% (n=114) did not have family history. According to the duration of epilepsy among the 150 patients, 60.7% (n=91) were between 0-10 y, 23.3% (n=35) were between 10-20 y, 12% (n=18) were between 20-30 y, 2.7% (n=4) were between 30-40 y, 1.3% (n=2) were between 40-50 y.

TABLE 1: DEMOGRAPHIC AND CLINICAL DETAILS (n=150)

Characteristics	Mean ± SD
Age (year)	22.4±14.2
Age at onset of epilepsy (year)	11.9±11.6
Duration of epilepsy (year)	10.5±9.8
	Number (%)
Gender	
Male	86 (57%)
Female	64 (43%)
Adults	96 (64%)
Paediatrics	54 (36%)
Place of residence	
Corporation	42 (28%)
Municipality	43 (29%)
Panchayat	65 (43%)

The treatment referral pattern showed as 0.7% (n=1) were general practitioners, 8% (n=12) were paediatricians, 0.7% (n=1) were physicians, 88% (n=132) were neurologists, 1.3% (n=2) were neurosurgeons, 1.3% (n=2) were practitioners from other systems.

83% (n=124) showed good compliance and 17% (n=26) showed poor compliance. The frequency of seizures among 150 patients was analysed based on Engel Seizure Score that showed, 2% (n=3) were seizure free, off AEDS, 0.7% (n=1) were seizure free, AED need uncertain, 16.7% (n=25) were seizure free, need AEDS, 0.7% (n=1) had non disabling nocturnal seizures, 26.7% (n=40) had frequency of 1-3/yr, 7.3% (n=11) had frequency of 4-11/yr, 20.7% (n=31) had frequency of 1-3/month, 12.7% (n=19) had frequency of 1-6/week, 8% (n=12) had frequency of 1-3/day, 3.3% (n=5) had frequency of 4-10/day and 1.3% (n=2) had frequency of >10/day. Seizure frequency in paediatrics approximated to around Engel score 6.37 whereas for adults it was 5.47.

According to the epilepsy diagnostic code, 7% (n=11) had benign/idiopathic localization, 64%

(n=95) had symptomatic/cryptogenic localization, 19% (n=28) had idiopathic generalized, 9% (n=14) had cryptogenic/symptomatic generalized and 1% (n=2) were undetermined. 31% (n=46) were under monotherapy, 37% (n=56) were under dual therapy and 32% (n=48) were under polytherapy.
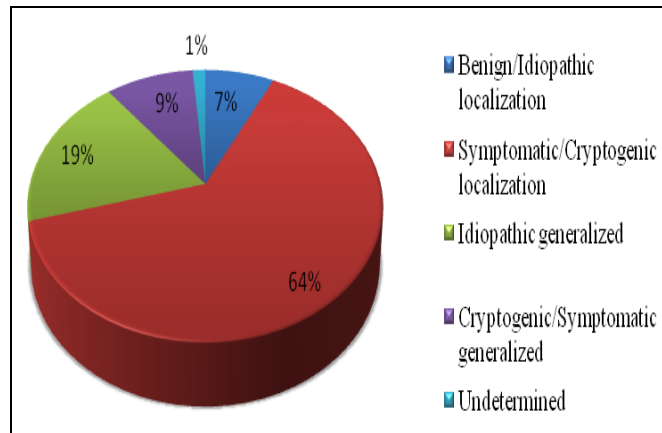

FIG. 1: PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO COMMONLY OBSERVED ANTI-EPILEPTIC DRUGS IN THE PRESCRIPTIONS
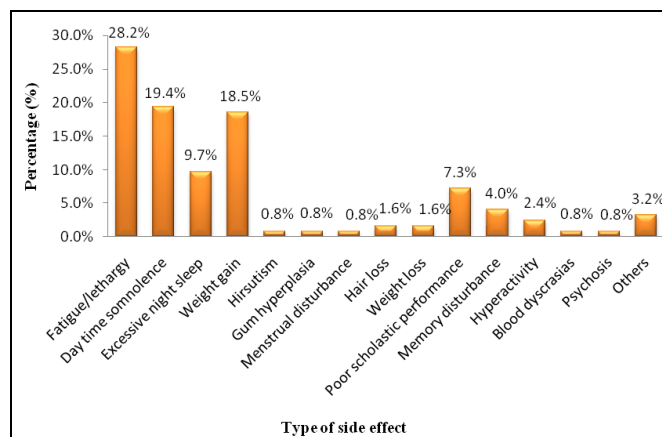

FIG. 2: PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO COMMONLY OBSERVED SIDE EFFECTS IN PATIENTS RECEIVING ANTI-EPILEPTIC DRUGS

Out of 150 patients 50% (n=75) were having side effects and 50% (n=75) were not having side effects.

The anti-epileptic drugs were categorized into conventional and newer drugs. The conventional drugs are Carbamazepine, Phenytoin, Pheno-barbitone, and Sodium Valproate. The newer drugs are Magnesium Valproate, Divalproex Sodium, Sodium Valproate + Valproic Acid, Lamotrigine, Topiramate, Levetiracetam, Zonisamide, Gabapentin, Pregabalin, Vigabatrin and Tiagabine.

TABLE 2: PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO PRESCRIBING TREND OF ANTI-EPILEPTIC DRUGS

Anti-epileptic drugs	Number of patients	Percentage (%)
Conventional	95	36.5%
Newer	165	63.5%

TABLE 3: COMPARISON OF THE COST OF CONVENTIONAL, NEWER AEDS AND COMBINATION OF AEDS

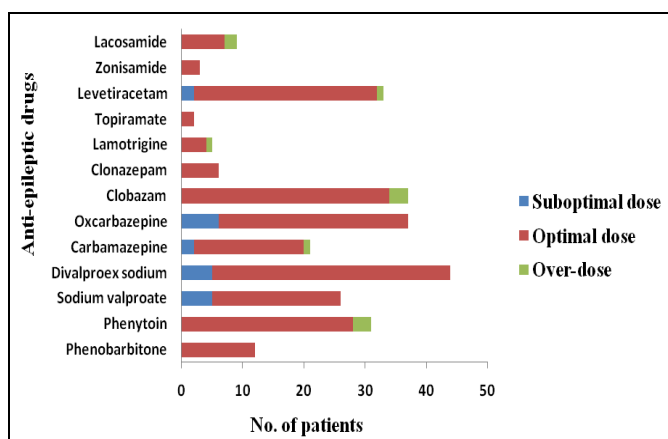|	Conventional drugs	Newer drugs	Combination drugs
N (number)	24	22	104
Total Cost	4831.4	10613	106268
Mean	201.3	482.4	1021
Standard deviation	122.520	316.53	616.318

FIG. 3: BAR GRAPH SHOWING THE DISTRIBUTION OF PATIENTS ACCORDING TO OBSERVED PATTERN OF DOSE AMONG THE PATIENTS RECEIVING ANTI-EPILEPTIC DRUGS

TABLE 4: PAEDIATRIC POPULATION DOSING

AED	(mg/kg)	Range (N)
Phenobarbitone	3-5	1.41 (2)
Phenytoin	3-5	7.22 (7)
Sodium Valproate	20-60	20.96 (8)
Divalproex Sodium	20-60	19.11 (9)
Carbamazepine	20-30	9.7 (2)
Oxcarbazepine	20-30	15.39 (13)
Clobazam	0.3-1	0.43 (17)
Clonazepam	0.1-0.2	0.06 (1)
Lamotrigine	3-5	5.7 (4)
Topiramate	3-5	3.44 (1)
Levetiracetam	20-60	30.28 (24)
Zonisamide	3-5	2.44 (4)
Lacosamide	3-5	3.96 (5)

Among 54 patients in paediatric population, 33% (n=18) were prescribed with sub-optimal dose, 63% (n=34) were prescribed with optimal dose and 4% (n=2) were prescribed with overdose.

Among 96 patients in adult population, 96% (n=92) were prescribed with sub optimal dose and 4% (n=4) were prescribed with overdose.

TABLE 5: ADULT POPULATION DOSING

AED	DDD (mg)	PDD/DDD (N)
Phenobarbitone	90	0.61 (11)
Phenytoin	300	0.76 (25)
Sodium Valproate	1200	0.61 (7)
Divalproex Sodium	1000	0.63 (33)
Carbamazepine	800	0.66 (20)
Oxcarbazepine	1200	0.67 (23)
Clobazam	20	0.70 (29)
Clonazepam	4	0.31 (6)
Lamotrigine	200	0.5 (4)
Topiramate	200	0.25 (1)
Levetiracetam	2000	0.52 (35)
Zonisamide	300	0.66 (1)
Lacosamide	200	0.87 (11)

The curve estimation method was applied, and there was a significant association between the type of AED and compliance. The p-value of significance between the type of AED and compliance was found to be 0.000 at a 100% level of significance. The interpretation was as the number of anti-epileptic drugs increases, the compliance decreases.

The bivariate correlation method was applied, and there was a significant association between the type of AED therapy and side effects. The p-value of significance between intervention and drug-related problems was found to be 0.01 at a 100% level of significance. The interpretation was as the number of antiepileptic drugs increase, the side effects also increase.

The curve estimation method was applied, and there was a significant association between the type of AED therapy and the frequency of seizures. The p-value of significance between the type of AED therapy and frequency of seizures was found to be 0.01 at a 100% level of significance. The interpretation was as the frequency of seizures increases, the number of antiepileptic drugs increases.

DISCUSSION: Epilepsy is a common chronic neurological disorder that requires long-term management and imposes a large burden on the health-care system. Patterns of drug prescription are often inappropriate, and the need for registration of these patterns is essential in an effort to improve prescribing standards. Moreover, unemployment, lower marriage rates, social isolation, and the feeling of stigmatization may follow an adult or midlife chronic epileptic

condition, even if the quality of life is thought to be less severely affected in people with good seizure control.

In the study, 64% of the patients were adults, and 36% were from the pediatric population. This was similar to the study carried out by J.E Machado-Alba *et al*., [11,] which showed adult predominance over the paediatric population.

In our study, there was a higher number of prescriptions with AEDs for male patients (57%) compared to female patients (43%). This result was similar to the study carried out by Venkateswara Murthy N *et al*., [12,] which showed more number of prescriptions were accountable for males than females.

In this study, the area wise distribution of the patients in semirural (Municipality + Panchayat = 72%) was more compared to the urban population (28%). This result was similar to the study carried out by Venkateswara Murthy N *et al*., [12,] which showed the semirural population was more.

In the study, symptomatic/cryptogenic localized (64%) was the most common cause of epileptic seizures, followed by idiopathic generalized (19%). This was similar to the study done by Venkateswara Murthy N *et al*., [12,] which showed cryptogenic epilepsy was the most common cause of epileptic seizures, followed by idiopathic.

A noticeable increase in the use of levetiracetam (18.6%) was seen during our study, which was found to be consistent with the trend and was in accordance with the results reported by J.E. Machado-Alba *et al*. [11]

In the study population, 69% of the patients were receiving combination therapy, which resembles the study carried out by J.E. Machado-Alba *et al*., [11] that showed a majority of the patients were receiving combination therapy.

CONCLUSION: Our study gives an insight into the changes observed in the trend of prescribing patterns of anti-epileptic drugs. Nowadays, multiple AED's are available, and the best antiepileptic therapy is tailoring the drug to the pocket of the patient to ensure optimal seizure control and absence of unacceptable side effects.

Despite the appropriate selection of AED, patients had increased frequency of seizures with the incidence of side effects. This problem could have been overcome by prescribing optimal doses and avoiding the use of polytherapy wherever possible. A shift from the use to conventional drugs to the newer AED's was seen, which dominated the pharmacotherapy of epileptic seizures. Levetiracetam topped the list of prescriptions followed by clobazam and oxcarbazepine.

As more than 50% of drugs were newer, increased availability of newer drugs in hospital formulary would definitely attenuate the economic burden of epilepsy management. The mean cost of conventional drugs is lesser as compared to the newer AED's.

These findings may be used by doctors and healthcare providers in order to make clinical decisions to achieve an optimal therapeutic outcome in patients prescribed with antiepileptic drugs. This helps to mitigate side effects by utilizing monotherapy and the elimination of polytherapy wherever feasible.

CONFLICTS OF INTEREST: All authors have none to declare.

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