ORIGINAL ARTICLE

A Drug Utilization Study of Antiepileptic Drugs Use in a Tertiary Care Hospital of Central India

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Abstract

Aims and Objectives: *The main objectives of the study were to describe the drug utilization pattern of anti-epileptic drugs (AEDs), to get an insight into the type and etiology of various forms of epileptic seizures, to review drug use and/or prescribing patterns, to study the effects (beneficial and adverse) of antiepileptic drugs.* ***Materials and Methods:*** *The present study was a prospective, non-randomized controlled single blinded trial, done at NKPSIMS and RC, Nagpur, India.* ***Results:*** *Out of 146 participants, 76 were male and 70 were females. Monotherapy was given in 102 patients (69.8%) while polytherapy was given in 44 patients (30.1%). Amongst the monotherapy, phenytoin was most commonly prescribed in 25 patients (17.1%) while levetiracetam and vigabatrin were least prescribed (1.3 and 2.7 respectively). Amongst the fixed dose combinations (FDCs) phenytoin + phenobarbital was most commonly prescribed.* ***Conclusion:*** *The findings of the present study should be generalized by performing such regular studies elsewhere in other parts of the country, so as to help in meticulous planning in order to reduce the expenditures in health care without affecting efficacy.*

Keywords*: Antiepileptic drugs, Drug utilization study, Epilepsy*

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Introduction

An epileptic seizure is a transient paroxysm of uncontrolled discharges in neurons causing an event that is discernible by the person experiencing the seizure and/or observer.[1,2]Epilepsy is not a disease, but it is a syndrome of different cerebral disorders of the central nervous system which is characterized by excessive discharges of large numbers of neurons.[3,4,5]The risk of having epilepsy at some point in average life span of any individual varies between 2%-5%.[6]Worldwide prevalence of the active epilepsy ranges from 4 to 5 per 1000 populationand in India, the prevalence rate of epilepsy ranges between 4.15 and 7.03 per 1000 population.In newly diagnosed cases, 60% are partial and 40% generalized.[7]Epileptic seizures have many causes, including a genetic predisposition for certain seizures, head trauma, stroke, brain tumors, alcohol or drug withdrawal, and other conditions.[2,8] The etiology of seizure is multifactorial in any given individual and it best thought of as an interaction between genetically determined seizures thresholds, underlying predisposing pathologies or metabolic derangements and acute precipitating factors.[9] During the assessment phase, it is critical to establish an accurate diagnosis of the seizure type and classification. It is recommended that the guidelines established by the ILAE (International League Against Epilepsy)

commission of epidemiology and prognosis be followed in epidemiologic studies of epilepsy. The choice of the most appropriate drug treatment for a patient with seizures depends upon the accurate classification of the seizures and the type of epilepsy or epileptic syndromes.[10]Treatment goals is the same for all patients irrespective of seizure types and age, which is complete control of seizures, without causing any untoward reaction due to the medicationand improved quality of life.[11,12,1314,15]A recent study reported that the problem is nearly 2½ times higher in rural areas as compared to urban areas[16,17], where they are not receiving any treatment.Particular focus should be placed on a safe diagnosis, seizure and syndrome classification, and choice of pharmacological and surgical options for a range of patient populations with different health-care requirements.[18]The ultimate goal is seizures freedom without adverse effects of medication.Monotherapy is the usual dictumas it has less drug interactions and side effects; lower cost, better tolerability, medication adherence, and quality of life, but polytherapy is needed for patients with multiple seizure types or refractory diseases. The choice of most appropriate antiepileptic drug (AED) depends on classification of seizures and age of patient, mechanism of action, ease of dosing, efficacy, long term adverse effects, neuropsychiatric profile, sedative burden, interaction with other medications, seizure types and other co-morbid conditions should be considered.[15]The lack of control over seizure recurrence has a major impact not only on the patients' clinical and psychosocial status but also on economic consequences that could potentially overload the health care system due to avoidable expenses with regard to medications, hospitalizations, and examinations.[13]An important portion of the high costs related to the treatment of epilepsy is devoted to the purchase of second-generation antiepileptic drugs (AED), which are more expensive than first-generation agents.Drugs such as gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine, and zonisamide are the newer ones and currently used as ad-donor alternative therapy. They have lesser adverse effects and have few, ifany, drug interactions.[19,20]The interest in drug utilization studies began in the early 1960s, and its importance has increased since then due to increase in marketing of new drugs, wide variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs.[21]

Aims and Objectives

The main objectives of the study were

1. To describe the drug utilization pattern of anti-epileptic drugs (AEDs),
2. To get an insight into the type and etiology of various forms of epileptic seizures,
3. To review drug use and/or prescribing patterns,
4. To study the effects (beneficial and adverse) of antiepileptic drugs,
5. To promote appropriate drug use through patient counseling and other intervention,
6. Provision of results for the clinicians, so as to aid in selecting appropriate antiepileptics

Publication of the report in the journals to serve as information to the health care professionals.

Materials and Methods

The present study was a prospective, non-randomized controlled single blinded trial, done at NKPSIMS and RC, Nagpur, India. The study was started after taking approval from Institutional Ethics Committee. The study duration was of one year from June 2014 to May 2015. A total of 146 patients were enrolled for the study after taking duly informed consent and straining them through inclusion and exclusion criteria.

Inclusion criteria

Patients with seizures, of both sex and all age groups, who are prescribed AED/s, and willing to sign informed consent were included in the study.

Exclusion criteria

Patients with acute causes of epilepsy and acute severe attack of epilepsy and patients not willing to sign informed consent form were excluded from the study.

Information extracted from the case files included: Demographic data like age, gender, if he/she is a known case of epilepsy and etiology of seizure, habits (smoker/alcoholic/food habits), past medical history and past medication history, family history, laboratory details, concomitant non-AED medications, types of seizure, and epilepsy according to the International League Against Epilepsy (ILAE) classification[10] and spontaneous reports of adverse effects according to anatomical localization i.e. CNS, eyes, blood picture etc. were registered. Treatment: AEDs prescribed and prescription of the AEDs by generic names, change in seizure frequency during and after the treatment was also noted.Evaluation of AED dosages was performed by calculating the ratio of the prescribed daily dose (PDD) over the defined daily dose (DDD). DDD is a unit of measurement commonly applied in drug utilization researches and is defined as the assumed average maintenance dose per day of a drug used on its main indication in adults.[22]Patients were grouped into socioeconomic classes according to modified Prasad's classification.[23]

Prescribing indicators include

1. Most commonly prescribed AEDs in this study
2. Number of AEDs prescribed using generic names

Latest version of Morisky's medication adherence scale (MMAS-8) was administered on patients to assess the medication adherence behavior. The MMAS have eight questions, out of which seven are yes/no type and one is of subjective choice. One point will be given to each 'Yes' answer. Higher score indicates less adherence.[24] Naranjo's scale was applied to assess the causality of adverse drug reactions associated with AEDs. **Statistical method**: The data of each case file were collected and analyzed by Microsoft Excel 2013.

Results

(Table 1) In the present study, out of 146 participants, 76 were male and 70 were females. Average age of onset of seizures was 18.3 years. Average number of drugs per prescription was 2.19. None of the antiepileptics were prescribed as generics. (Table 2) Maximum of 97 patients were diagnosed with generalized tonic clonic seizures [GTCS] (66.4%) followed by partial seizures (26.7%). Overall, socio-economic class IV and V were most commonly affected. (Table 3) Monotherapy was given in 102 patients (69.8%) while polytherapy was given in 44 patients (30.1%). In polytherapy only 2 drugs were used at once, since ≥3 drugs were not encountered. Amongst the monotherapy, phenytoin was most commonly prescribedin 25 patients (17.1%) followed by valproic acid in 21 patients (14.3%), while levetiracetam and vigabatrin were least prescribed (1.3 and 2.7 respectively). Amongst the fixed dose combinations (FDCs) phenytoin + phenobarbital was most commonly prescribed in 29 patients (19.8%) Maximum side effects were encountered with carbamazepine in 19 patients and phenytoin in 18 patients, while in FDCs maximum side effects were seen with phenytoin + phenobarbital (21 patients). Overall, gastrointestinal tract related side effects like nausea, vomiting, epigastric pain were in majority (29 patients), followed by mouth related side effects like ulcers. PDD and DDD related findings are given in Table 4 and Table 5.

Table- 1: showing socio demographic characteristics and prescribing indicators.

Characteristic	Values
1. Average age in years	44.6 years
2. Sex:	
a. Male	76
b. Female	70
3. Average age of onset of seizures	18.3
4. Average no. of antiepileptics per prescription	2.19
5. Average no. antiepileptics as generics	Nil

Table- 2: Showing diagnosis of epilepsy and seizures and socio-economic class affected.
Note: Socio-economic class defined according to modified Prasad's classification.

	Number of patients n(%)	Socio-economic class most affected
I. Types of epilepsy:		
1. Localised	45 (30.8)	V
2. Generalised	97(66.4)	V
3. Undetermined	4(2.7)	IV
II. Types of seizures:		
1. General Tonic Clonic Seizures	97(66.4)	V
2. Partial Seizures:	39(26.7)	III
3. Absence seizures	2(1.3)	II
4. Tonic	1(0.6)	IV
5. Atypical	1(0.6)	V
6. Secondary generalised seizures	0(0)	
7. Not classified	4(2.7)	I

Table- 3: Showing antiepileptics prescribed in the present study and side effects encountered.

	n(%)	Seizure free at the end of T/t	Seizure free at the end of F/U	ADR							
				CNS	Eye	Liver	Blood	GIT	Mouth	Skin	Total
1. Monotherapy	102(69.8)	100/98	90/94								
2. Polytherapy:	44(30.1)	29/65	16/69.2								
a. 2 drugs	44(30.1)	29/65	16/69.2								
b. ≥3 drugs	0(0)										
3. Antiepileptics:				0	0	0	0	0	0	0	0
a. VA	21(14.3)	21/100	20/95.2	0	0	0	0	5	0	0	5
b. CRB	12(8.2)	12/100	9/90 %	1	0	2	5	6	0	5	19
c. PH	25(17.1)	25/100	24/96 %	0	0	0	0	2	14	2	18
d. PHR	7(4.7)	6/85.7	6/85.7	0	0	0	1	0	0	1	2
e. LTR	2(1.3)	2/100	1/50 %	1	0	0	0	1	0	0	2
f. CLB	13(8.9)	12/92.3	12/92.3	2	0	0	0	2	0	0	4
g. LTG	5(3.4)	5/100	4/80 %	0	0	0	0	1	0	1	2
h. TOP	4(2.7)	4/100	4/100	1	0	0	0	2	0	0	3
i. DZP	9(6.1)	9/100	8/88.8	3	0	0	0	0	0	0	3
i. VIG	4(2.7)	4/100	2/50 %	1	1	0	0	0	0	0	2
4. FDCs prescribed:											
a. VPA+ PH	9(6.1)	3/33.3	1/50 %	0	0	0	0	4	0	2	6
b. VPA+CRB	6(4.1)	2/33.3	1/100	0	0	0	0	2	0	0	2
c. PH+PHR	29(19.8)	24/82.7	20/80 %	0	0	0	0	4	12	5	21
			TOTAL	9	1	2	6	29	26	16	89

Table- 4: Showing antiepileptics according to ATC classification and PDD, DDD.

Drugs	ATC-DDD code	DDD in mg	PDD in mg
1. VA	N03AG01	1500	1721.4
2. CRB	N03AF01	1000	1000
3. PH	N03AB02	300	423.6
4. PHR	N03AA02	100	122.3
5. LTR	N03AX14	300	300
6. CLB	N05BA09	20	18.7
7. LTG	N03AX09	300	289.2
8. TOP	N03AX11	300	311
9. VIG	N03AG04	2000	1932
10. DZP	N05BA01	10	15
11. VPA+ PH	NA	NA	NA
12. VPA+CRB	NA	NA	NA
13. PH+PHR	N03AB52	NA	NA

Table- 5: Showing drugs in relation to PDD and DDD

PDD>DDD	PDD=DDD	PDD<DDD
Valproic acid	Carbamazepine	Clobazam
Phenytoin	Levetiracetam	Vigabatrin
Phenobarbital		Lamotrigine
Topiramate		
Diazepam		

Discussion

In the present study average age of onsetof seizures was found to be 18.3 years, which was different from finding of other such study.[25]We found that phenytoin and valproic acid were most commonly prescribed drugs, which are also recommended as the first line agents for the treatment of refractory epilepsy according to ILAE guidelines.[10] This finding was also found in similar studies done elsewhere.[11,26] Most common type of seizure was GTCS, which was in accordance with findings of other studies[27,28] and contrast to some others.[25]Although phenytoin has many drawbacks like difficult pharmacokinetic profile management, side effects[29] its low cost and fair seizure control rate allows its large scale use. But it was painstaking to find that despite having advantage of overcoming the shortcomings encountered with conventional antiepileptics,[30] newer ones like topiramate and lamotrigine were used to a very less extent. This may be due to the fact that newer antiepileptics are costly as compared to conventional ones and cost is the major limiting factor, since maximum patients encountered here were socio-economic class IV and V. A total of 22 patients were lost to follow up. PDD greater than DDD was found in case of valproic acid, phenytoin, phenobarbital, topiramate and diazepam. PDD less than DDD was seen with clobazam, vigabatrin and lamotrigine, while PDD and DDD were equal in case of carbamazepine and levetiracetam. Drug utilization studies help to picturise ongoing health care practices, so that lacunae in the system can be identified and strategies can be planned to rectify them. One more point needs to be stressed

out is that there was no use of generics in the present study, despite the fact that generics are comparatively less expensive and it helps in reducing health care costs dramatically.

Conclusion

The findings of the present study should be generalized by performing such regular studies elsewhere in other parts of the country, so as to help in meticulous planning in order to reduce the expenditures in health care without affecting efficacy. Also physicians need to be motivated towards increased use of generics.

Conflict of Interest: *None declared*
Source of Support: *Nil*
Ethical Permission: *Obtained*

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