



Original Research Article

A prospective observational study on drug utilization of antiepileptic medications used during treatment at a tertiary care teaching hospital

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ABSTRACT

Aims and Objectives: The aim of the present study was to assess the utilization pattern of antiepileptic drugs and its management which in turn contributes to the promotion of optimal and rational therapy improving patient's quality of life.

Subject and methods: It was a prospective observational study carried over a period of six months that includes the prescription data of 150 epileptic patients collected from neurology department (OPD) and prescription pattern of the antiepileptic drug was studied. The data was collected using a designed data collection form and analyzed.

Results: 80.4% of 150 cases belonged to age group 15-45 years and 76.52% were males. The majority (>60% cases) were unskilled workers and of low socio-economic status. Family history of seizures was present in 18.9% of cases. Mean age of onset of seizure was found to be 28.32 years. The proportion of generalized tonic-clonic seizure cases was 84.4%. Secondary seizures were seen in 15 (25.8%) cases with the most common cause being alcohol withdrawal (22.4%). Focal seizures were present in 5.17% of cases. Monotherapy was the most commonly followed and phenytoin was the most popular anti-epileptic drug (AED) used. Non-compliance with AEDs was seen in 25.8% of cases. Drowsiness was the commonest ADR reported (6.28%). Phenytoin accounted for almost all of the ADRs collected and evaluated.

Conclusion: Idiopathic generalized epilepsy was the commonest type of epilepsy recorded. Monotherapy was preferred in most of the cases and frequent use of newer AED namely levetiracetam. Seizure manifestations and treatment compliance vary widely in the studied population. In-depth analysis of each seizure type will give more information about the factors associated with it.

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INTRODUCTION

Drug utilization research holds a crucial place in clinical practice as it forms the basis for making amendments in the drug dispensing policies at local and national levels. The ultimate goal of such a study is to facilitate rational drug use. Also, since it helps in developing strategies to

utilize health resources in the most efficient manner, it is particularly needed in a developing economy like India where 72% of all health care burdens is borne by the patients (WHO, 2018; Mittal et al., 2014).

Patients with epilepsy who were receiving long-term monotherapy with carbamazepine (CBZ), phenytoin (PHT), or sodium valproate (VPA) exhibited altered circulatory markers of vascular risk that may contribute to the acceleration of the atherosclerotic process, which is significantly associated the duration of AED monotherapy. This information offers a guide for the choice of drug in patients with epilepsy who require long-term AED therapy, particularly in aged and high-risk individuals (Chaug et al., 2012).

Conventional AEDs as a monotherapy are commonly prescribed in developing countries with limited resources. Though most prefer PHT as initial monotherapy followed by CBZ and sodium valproate based on the seizure type, this behavior is highly variable not only in different countries but also among primary and tertiary care hospital setups within a country (Pellock, 1994).

Local socioeconomic, cultural and ethnic factors, the genetic profile of an individual and availability of drugs also affect the treatment regimens. Moreover, baseline differences in patient's demographic, seizure frequency and severity limit the direct comparison of individual trials. It is thus necessary to monitor and balance the goal of seizure control against adverse treatment effects. Different strategies are required for different scenarios and different patients. There are limited studies reporting the association of AEs with treatment regimens as well as seizure outcome simultaneously (Joshi et al., 2017).

AED harmful effects potent hepatic enzyme-inducing properties, predominantly on the cytochrome P450 system, inducing AEDs may lead to drug interactions and alter various metabolisms, including lipid metabolism. Through their potent hepatic enzyme-inducing properties, predominantly on the cytochrome P450 system, inducing AEDs may lead to drug interactions and alter various metabolisms, including lipid metabolism. Indeed, several studies have shown that adults with epilepsy treated with inducing AEDs have increased serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, lipoprotein (a), as well as C reactive protein and homocysteine (Renoux et al., 2015).

Certain patient groups like patients on antiepileptic drugs seem to be at increased risk of developing a cutaneous drug reaction. The incidence of developing a cutaneous reaction increases with the number of drugs taken. Cutaneous ADRs (CADRs) are a common occurrence and awareness about the same is essential for diagnosis and prevention. Studies had identified combined use of phenytoin and carbamazepine as a most important risk factor for serious CADR like

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Singh et al., 2015).

Despite that several antiepileptic drugs (AEDs) being introduced in the past two decades, many patients do not respond to a single AED. Several studies have been conducted indicating the superiority of the combination of AEDs over monotherapy. The present study was carried out to measure and compare medication utilization in a patient population treated with antiepileptic drugs.

SUBJECTS AND METHODS

This is the prospective observational study carried out in the Department of General Medicine of a tertiary care teaching hospital for a period of 6 months. A total of 150 patients were selected for the study. The present study was approved by the Institutional Ethics Committee (MCP/IEC/PD/PR/23).

The study included all patients admitted to the Department of General Medicine, Osmania General Hospital, Hyderabad, Telangana with age group of more than 25 years; those presented with the symptoms of epilepsy included that of generalized epilepsy and partial epilepsy that all the types of seizures and physical examination and appearance of symptoms and other clinical findings like computerized tomography (CT Scan) obtained within 24 hours of admission; and the patients that are already diagnosed epilepsy and the patients with co-morbidities. The patients under 18 years age group, pregnant women, lactating women, and patients have undergone majors surgery was excluded from our study to have a better outcome of the study. The patients who are HIV positive were also excluded from the study.

The data was collected in a designed data collection form. The calculations of parameters were done based on the data collected. All prescriptions issued during this period immediately following each day's consultation with the neurologist were copied out and recorded on case record forms. The present study was conducted on a patient pool of 150.

The following data were retrieved from the prescription and the patient's medical records: demographic data (age and gender), known or newly diagnosed epileptic patient, type and aetiology of epileptic seizure, clinical pattern in various types of seizures (aura, uprolling of eyes, level of consciousness, salivation, incontinence, drowsiness, cyanosis, muscle flaccidity, jerking movements, vertigo) relation between types of seizures and types of drug regimen (monotherapy or polytherapy). All the relevant and necessary data were collected from patient's case notes like prescription

prescribed by the physician, AED data (i.e. type of drug and formulation and availability), and ADR data. The type of reaction, causality, onset, severity, and outcomes of ADRs was collected according to a detailed semi-structured questionnaire. If an ADR was detected it was subjected to WHO probability scale to assess the causality relationship between the medication and the adverse reaction with the help of a neurologist. Afterward, the severity of the reaction was determined as mild, moderate or serious. When an ADR was

associated with more than one medication, the agent most likely to be responsible for the adverse reaction was included in the final analysis. The epileptic seizures were grouped according to the classification of the International League against Epilepsy Complex partial, Simple partial, Tonic-clonic, Absence, Myoclonic, Clonic, Tonic, Atonic and Status epilepticus. The following etiologies were considered: idiopathic, trauma, infection, tumor, drug-induced, systemic disease, metabolic/toxic and degenerative.

RESULTS

Table 1. Seizure types and their frequency.

Types of seizures	Cases (150)	Percentages
GTCS	80	53.3%
Focal seizures	15	10%
Complex partial seizures	06	4%
Alcohol withdrawal seizures	38	25.3%
Atypical seizures	06	4%
Status epilepticus	05	3.33%

Table 2. Types of seizures and drugs prescribed.

Seizure Types	Common drug prescribed alone or in combination	Second common drug prescribed or alone	Other drug prescribed
GTCS	Phenytoin(71.25%) P+ Phenobarbitol(10%) P+Sodium Valproate(6.25%) P+Levetiracetam(5%)	Levetiracetam(16.2%)	Phenobarbitol Carbamazepine Oxcarbamazepine Diazepam Midazolam
Focal Seizures	Phenytoin(42.85%)	Levetiracetam(28.57%)	Sodium Valproate Diazepam
ComplexPartial seizures	Levetiracetam(100%)	Phenytoin(66.6%)	Levetiracetam Oxcarbamazepine diazepam
Atypical Seizures	Phenytoin(100%)	Levetiracetam(33.3%)	Leveticetam Sodium valproate
Alcohol Withdrawal seizures	Phenytoin (100%)	Diazepam(50%)	Lorazepam Midazolam

The most commonly prescribed anti epileptic drugs (AEDs) in our study was Phenytoin.

Table 3. Percentage of anti-epileptics prescribed.

Drugs	Usage Rate	Percentage(%)
Phenytoin	77	51.33%
Levetiracetam	23	15.33%
benzodiazepine	26	17.33%
carbamazepine	6	5%
Sodium Valproate	14	9.33%
Oxcarbamazepine	4	3.33%

Phenytoin was the most common drug used 77 (51.33%) followed by levetiracetam 23 (15.3%) other commonly prescribed drug were benzodiazepines 26 (17.33%), Carbamazepine 6(5%) and Sodium valproate 14 (9.33%), Oxcarbamazepine 4 (3.33%).

Table 4. Distribution of relationship between types of seizures and types of drug regimen (monotherapy or polytherapy).

Types of seizure	Monotherapy	Dual therapy	Polytherapy
GTCS	57	20	10
Focal seizure	3	4	0
Alcohol withdrawal	25	6	10
Complex partial	0	5	5
Atypical seizure	0	5	0

Distribution of data based on relation between types of seizures and types of drug regimen was found that Monotherapy is the highest type of drug regimen in generalized tonic clonic seizures was found to be 57 cases out of 150 cases i.e Monotherapy followed by Dual therapy i.e 20 cases out of 150 and Polytherapy i.e. 5 cases out of 150 cases.

Table 5. Distribution based on Percentage of ADR Types.

ADR Type	No. ADRs reported	Percentage %
Allergic	0	0%
Cardiovascular	0	0%
Dermatological	7	46.6%
CNS	5	33.3%
Hematological	1	6.6%
Renal	0	0%
Gastrointestinal	1	6.6%
Respiratory	0	0%
Others	1	6.6%

Distribution of subjects based on percentage of ADR types was found to be the highest no. of percentage in ADR type i.e. Dermatological was found to be about 46.6% in which the highest no. of ADRs have been reported.

Table 6. Distribution of ADR'S with antiepileptic.

Drugs	No of ADR'S
Phenytoin	07
Carbamazepine	01
Sodium Valproate	05
Levetiracetam	02

From the above table it was found that the highest no. of ADRs reported with Phenytoin among other anti epileptic Drug was found to be 7.

DISCUSSION

The most effective method to access and evaluate the prescribing pattern of the physician is considered to be a prescription based survey. The main objective of the present prospective and observational study was to study prescribing patterns of drugs in epilepsy in a teaching care hospital and to check the rationality of the prescription. For checking the rationality of the prescription, in which the drugs prescribed were checked for any adverse drug interactions on Medscape, Micromedex and the prescriptions showing serious adverse effects. The result of the present study indicates that nearly half (80.4%) of the 150 cases belonged to the age group (15-45 years) and 2/3rd (76.52%) were males. The majority (>60% cases) were unskilled workers and of low socio-economic status groups. Family history of seizures was present in 18.9% of cases. Mean age of

onset of seizure was found to be 28.32 years. The proportion of generalized tonic-clonic seizure cases was 84.4%. Secondary seizures were seen in 15 (25.8%) cases with the most common cause being alcohol withdrawal (22.4%). Focal seizures were present in 5.17% of cases.

Monotherapy was the most commonly followed treatment regimen and phenytoin was the most popular anti-epileptic drug (AED) used. Non-compliance with AEDs was seen in 25.8% of cases. Out of the 150 seizure cases, nearly half 58 (55.769%) belonged to the age group (15-45 years).

Almost 2/3rd of cases, i.e., 79 (76.52%) were males and 50 (41.6%) were females. Mean age of the subjects was 28.32 years. 35 (60.33%) out of 150 cases were active cases of epileptic seizures. 86.7% of cases were unskilled workers and 82.9% of cases belonged to low socio-economic status. Family history of seizures was present

in 19 (18.9%) out of 150 cases. The proportion of generalized tonic-clonic seizure (GTCS) cases was 80 (78.8%). For analyzing the prescribing pattern in Epilepsy, the pharmacotherapy of antiepileptics was classified as monotherapy, dual therapy, and multiple therapies. Out of 150 prescriptions that were analyzed 85 % patients underwent monotherapy followed by dual therapy (40%) and polytherapy (25%) whereas less no of patients were found to be treated with Multiple therapy (25%). Higher % of patients were treated with Phenytoin was the most common drug used 77 (51.33%) followed by levetiracetam 23(15.3%). Other commonly used drugs were benzodiazepines 26(17.33%), Carbamazepine 6(5%), and Sodium Valproate 14 (9.33%), Oxcarbamazepine 4(3.33%). Out of 150 seizure cases, 43 (74.1%) patients were compliant with the AEDs. The present study which is comparatively revised with these previous research studies such as Nolan et al. (2013) studied which carried out on phenytoin versus valproate therapy in both adults and children for partial onset seizures and generalized onset tonic-clonic seizures and reported that no overall differences between the drugs for these outcomes were found. Smith et al. (1987) studied on phenytoin versus valproate monotherapy for partial onset seizures and generalized onset seizures tonic-clonic seizures and reported the test for an interaction between treatment and seizures type (generalized versus partial onset) was no significance for all outcomes. Nolan et al. (2013) mentioned that phenytoin, diazepam, and ranitidine accounted for most of the drug interactions. This study concludes that patient education and observation were necessary for proper utilization of drugs. Habib et al. (2013) concluded that the effectiveness of AED in terms of reduction of seizure frequency was highest for phenytoin (100%) and phenobarbital (98%) followed by carbamazepine (96%) and valproic acid (95%) Adverse drug reaction (ADR) were observed among 140 (24.5%) of those with monotherapy. Joseph et al. (2013) reported that nearly half (44.4%) of the 196 cases belonged to the productive age group (15-45 years) and 2/3rd (60.7%) were males. The majority (>80% cases) were unskilled workers and of low socio-economic status groups. Family history of seizures was present in 8.4% cases. Mean age of onset of seizure was found to be 19.9 years. The proportion of generalized tonic-clonic seizure cases was 78.1%. Secondary seizures were seen in 66 (33.7%) cases with the most common cause being trauma to the head (24.2%). Refractory seizures were present in 2.7% of cases. Monotherapy was the most commonly followed treatment regimen and phenytoin was the most popular anti-epileptic drug (AED) used. Non-compliance with AEDs was seen in

18.1% cases and was more among patients on polytherapy.

CONCLUSION

The present study was done to access the drug utilization evaluation and adverse drug reactions of anti-epileptic drugs prescribed. Nearly half (80.4%) of the 150 cases belonged to age group (15-45 years) and 2/3 is 76.52% were males and in ADRs 40% were females and 60% were males. It was found that the prevalence of epilepsy and ADRs of the antiepileptic drug to be high in males of the age group of 50-60 years. Hence, the study reveals the most commonly used antiepileptic drug was found to be Phenytoin-46%; Carbamazepine-6.6%; Sodium Valproate-33.3%; Levetiracetam-13.3%.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Chaug YC, Chuang HY, Lin TK, Chang CC, Lu CH, Chaung WN, Chen SD, Tan TY, Huang CR and Chan SH, Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis, *Epilepsia*. 2012;53(1):120-8.
- Habib M, Khan SU, Hoque MA, Monda MBA, ATM Hasibul Hasan, Chowdhury RN et al. Antiepileptic drug utilization in Bangladesh: experience from Dhaka Medical College Hospital. *BMC Research Notes*. 2013;6:473
- Joseph N, Kumar GS, Nelliyanil M. Pattern of seizure cases in tertiary care hospitals in Karnataka state of India. *Annals of Indian Academy of Neurology*. 2013; 16(3): 347-351.
- Joshi R, Tripathi M, Gupta P, Gulati S, Gupta YK. Adverse effects & drug load of antiepileptic drugs in patients with epilepsy: Monotherapy versus polytherapy. *Indian Journal of Medical Research*. 2017;145(3):317-326.
- Martin J. Brodie, Frank Besag, Alan B. Ettinger, Marco Mula, Gabriella Gobbi, Stefano Comai, Albert P. Aldenkamp and Bernhard J. Steinhoff. *Epilepsy, Antiepileptic Drug and Aggression: An Evidence Based Review*. 2016; 68(3):563-602.
- Mittal N, Mittal R, Singh I, Shafiq N, Malhotra S. Drug utilization study in a tertiary care centre recommendations for improving hospital drug dispensing policies. *Indian Journal of Pharmaceutical Sciences*. 2014;76(4):308-314.
- Nolan SJ, Marson AG, Weston J, Tudur Smith C. Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset Tonic-Clonic seizures: an individual participant data review. *The Cochrane Database of Systematic Reviews (CDSR)*. 2013;4:CD001769.

Pellock JM. Standard approach to antiepileptic drug treatment in the United States. *Epilepsia*. 1994;35 Suppl 4:S11-8.

Renoux C, Dell'Aniello S, Saarela O, Filion KB, Boivin JF. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: a population-based cohort study. *BMJ Open*. 2015;5(8): e008365.

Singh PK, Kumar MK, Kumar D, Kumar P. Morphological pattern of cutaneous adverse drug reactions due to antiepileptic drugs in eastern India. *Journal of Clinical and Diagnostic Research*. 2015;9(1):WC01-WC03.

Smith DB, Mattson RH, Cramer JA, Collins JF, Novelly RA, Craft B. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone. *Epilepsia*. 1987;28 Suppl 3:S50-8.

WHO. World health organization essential medicines and health products. The pursuit of responsible use of medicines. [(accessed on 10 January 2018)]; Available online:

https://www.who.int/medicines/areas/rational_use/en