



Research Article

A PROSPECTIVE DRUG UTILIZATION STUDY ON ANTI EPILEPTICS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Anti-epileptic drugs (AEDs) are the primary therapeutic models for epileptic patients and have been demonstrated to control seizures, which decreases the morbidity and mortality associated with epilepsy. A large number of AEDs have become available for the management of epilepsy; many of these agents are now utilized for conditions other than epilepsy. This study was aimed in assessing the prescribing patterns of anti-epileptics in various diseases (both epilepsy and Non epilepsy), utilization pattern of AEDs as mono therapy/ poly therapy, to monitor and report different Adverse Drug Reactions (ADRs) with these AEDs. A prospective observational study was conducted among 250 AED used individuals. The collected data was analysed for AEDs utilisation patterns, ADRs associated with these AEDs, Naranjo's assessment scale was used to check the severity of ADRs and Central Drug Standard Control Organisation (CDSCO) form is used to report the identified ADRs to Pharmacovigilance Programme of India (PVPI). Out of 250 patients, seizures were most commonly observed diagnosis in males 178 (71.2 %). Majority of patients 47 (18.8 %) were in the range of 31-40 years of age group. Highest number of patients was from psychiatry 97 (38.8 %). Seizures were commonly diagnosed followed by alcohol dependent syndrome. Commonly prescribed AED was Phenytoin in 92 (27.87 %) patients and gum hyperplasia was most commonly observed ADR with Phenytoin. Phenytoin was most frequently prescribed AED followed by sodium valproate. As Phenytoin is enzyme inducing drug and will show nonlinear pharmacokinetics, therapeutic drug monitoring is essential.

Keywords: Epilepsy, Antiepileptic drugs, Drug utilization, adverse drug reaction.

INTRODUCTION

Drug utilisation evaluation are defined as an ongoing, authorised and systematic prescribing patterns, develop criteria and standards for optimal drug use. Drug utilization studies were originally known as drug utilization review (DUR) in the 1970's and early 1980's. The terms Drug Utilisation Review (DUR) and Drug Utilisation Evaluation (DUE) are interchangeable. Drug Utilization Evaluation (DUE) is a discipline that aims to understand how and why drugs are used as they are, so that drug use and health outcomes can be improved. Drug Utilization Evaluation (DUE) can improve the prescribers to make educational programmes as a result improves prescribing and proper drug usage. Drug Utilization Evaluation (DUE) is generally classified into two types such as Quantitative and Qualitative. The major difference between qualitative and quantitative DUE studies is that qualitative DUE includes the concept of criteria.¹ The aim of drug utilization study is to improve rational use of drugs in populations. Drug utilization study in itself does not necessarily provide answers, but it contributes to rational drug use.² Studies on the process of drug utilization focus on factors related to prescribing, dispensing and administering and taking of medication, and its associated events as a result they document the extent of inappropriate prescribing of drugs and also the associated adverse, clinical, ecological and economic consequences. Thus DUE plays a key role in helping the healthcare system to understand, interpret and improve the prescribing, administration and use of medications³. Drug

utilisation studies in epilepsy plays an important role. Such studies provide data on the prevalence of exposure to different AEDs (older and newer) in a population with epilepsy in order to inform pharmaco-epidemiological and drug safety studies in AEDs⁴.

Epilepsy is defined as a disorder characterized by the disturbance in the electrical activity of the brain. Patients with epilepsy also may display neuro-developmental delay, memory problems, and/or cognitive impairment. In the Central Nervous System there exists a balance between neuronal firing with the neurotransmitters, but in epilepsy there will be hyper excitability of the neurons is seen. The areas in which these types of neurons are seen are known as epileptic foci. If this focus is at one hemisphere in brain it is partial whereas foci in two hemispheres are known as generalized⁵.

Anti-epileptics are defined as the drugs used to treat the altered electrical imbalances in the central nervous system. They maintain the homeostasis of the neuronal firing by proper maintaining the ion influx/efflux. These AEDs find's many applications due to their multiple mechanisms and actions at different sites. The usage and stoppage of AEDs is a very big challenge due to their untoward effects. If a decision is made to start AED therapy, mono therapy is preferred and approximately 50 % to 70 % of all patients with epilepsy can be maintained on one drug^{6,7}. Apart from epilepsy these find their applications in

the Management of pain, Neuro-muscular disorders, Neuro-protection, Psychiatric disorders⁸⁻¹⁰.

WHO defined ADR as any reaction to the drug which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, cure or diagnosis of disease or for the modification of physiological system. ADRs with AEDs are very common manifested by their long term usage.

Methodology

A Prospective observational study was conducted over a period of 6 months (July to December 2018) in inpatient wards of General Medicine, Pediatrics, General Surgery and Psychiatry at Sri Venkateswara Ramnarayan Ruia Government General Hospital (SVRRGGH), Tirupati. Patients of either gender who were received anti-epileptics with or without co-morbidities were included in the study. Ethical clearance permission (SPSP/2018-2019/PD02) was obtained from the Institutional Ethical Committee of Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupathi, India.

Method of data collection

A specially designed proforma was used for collecting data which includes patient demographics, past medical history, family and surgical history, co-morbidities, diagnosis and present medications prescribed for each patient. The data was obtained by direct patient

interview and from patient case profiles. All inpatient cases in general medicine, pediatrics, general surgery and psychiatry wards were screened for AEDs. The collected AEDs were analyzed for utilization patterns, for categorization of the therapy given, to classify different types of seizures percentage of AEDs prescribed, different indications of these drugs and to identify the ADRs associated with these AEDs. Naranjo's assessment scale was used to check the severity of ADRs and CDSO form was used to report the identified ADRs to Pharmacovigilance Programme of India (PVPI).

Statistical analysis

Microsoft Office Excel 2007 was used to project the data both in numbers and percentages.

RESULTS

A total of 250 patients were analysed during the study period. Among them 178 (71.2 %) were male and 72 (28.8 %) were female patients. The majority of patients were found in between the age group of 31-40 years was 18.8 %, followed by 21-30 years was 17.6 % and the least were among 0-1 year was 7.2 %. The highest number of patients received the AEDs were from Psychiatry 97 (38.8 %) department and least number of patients received AEDs were from General Surgery 2 (0.8 %). Out of 250 patients 76 (30.4 %) were diagnosed with seizures followed by schizophrenia 26 (10.4 %), alcohol dependent syndrome 22 (8.8 %), delirium and dementia 1 (0.4 %) respectively (Figure 1).

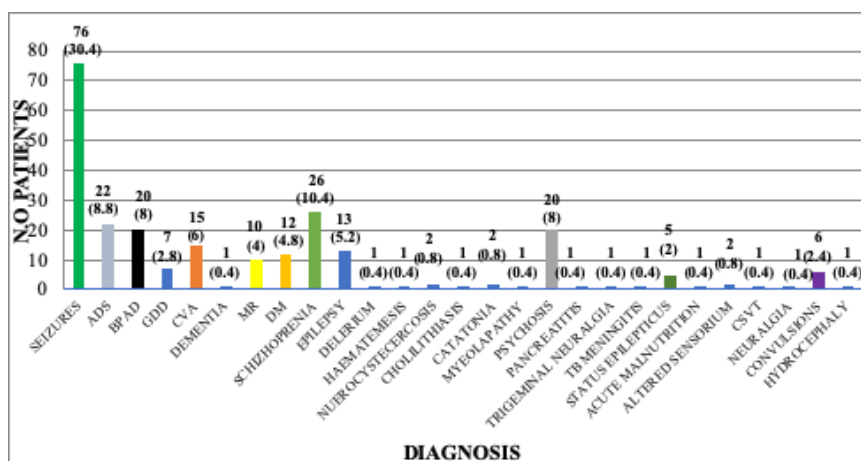


Figure 1: Disease wise distribution of patients received AEDs

A total of 338 anti epileptics were prescribed to 250 patients. Out of which phenytoin was most commonly prescribed anti-epileptic with the frequency of 93 (27.51 %) followed by sodium valproate 66 (19.5 %) and topiramate 1 (0.29 %).

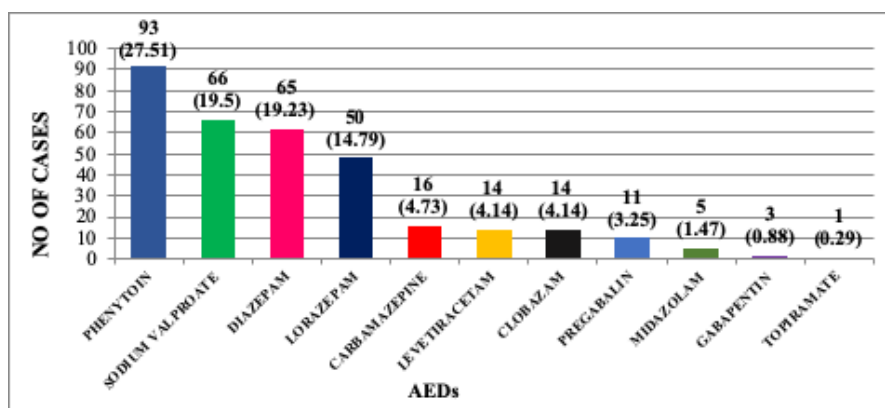


Figure 2: Number and percentage of different types of AEDs prescribed

Out of 250 patients, 72 % of the patients were prescribed with single AED, while 28 % of patients were prescribed with poly therapy AED.

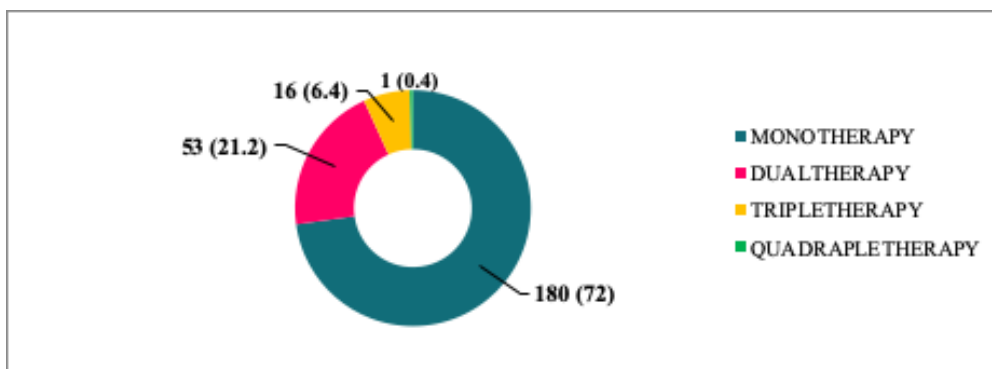


Figure 3: Therapy wise distribution among patients

Table 1: Lists the conditions for which anti epileptics were prescribed as mono therapy

Drug	N.O Cases	Indications
Phenytoin	51	Seizures, Convulsions, Mood Stabilizer
Diazepam	28	Behavioral Disorder, Sedation, Altered sensorium, Schizophrenia
Lorazepam	33	Sedation Seizures, Psychosis, Calm
Carbamazepine	7	Seizures, MR, Mood Stabilizer
Levetiracetam	4	Seizures, Neurocysticercosis
Sodiumvalproate	34	Seizures, BPAD, Mania, Sedation
Midazolam	2	Sedation
Pregabalin	9	Neuropathic Pain, Neuralgias
gabapentin	2	Neuralgias
Clobazam	10	Epilepsy, Convulsions

Table 2: Lists the conditions for which anti epileptics were prescribed as dual therapy

Combinations	N.O Cases	Indications
Phenytoin + Diazepam	17	Seizures, Epilepsy
Levetiracetam + Valproate	3	Seizures
Phenytoin + Valproate	6	Seizures
Phenytoin + Levetiracetam	4	Seizures
Phenytoin + Midazolam	1	Sedation
Phenytoin + Carbamazepine	3	Epilepsy
Diazepam + Lorazepam	4	Seizures
Valproate + Lorazepam	6	Mood Stabilizer, Sedation
Valproate + Diazepam	5	Seizures, BPAD
Carbamazepine + Clobazam	1	Seizures
Carbamazepine + Diazepam	1	BPAD
Diazepam + Levetiracetam	1	Seizures
Pregabalin + Carbamazepine	1	Neuralgias

Table 3: Lists the conditions for which anti epileptics were prescribed as triple therapy

Combinations	N.O Cases	Indications
Phenytoin + Carbamazepine + Diazepam	1	Seizures
Phenytoin + Valproate + Diazepam	4	Epilepsy, Seizures
Phenytoin + Lorazepam + Diazepam	2	Seizures
Phenytoin + Carbamazepine + Valproate	2	Unprovoked Seizures
Phenytoin + Clobazam + Pregabalin	1	Seizures
Lorazepam + Valproate + Topiramate	1	Psychiatry
Lorazepam + Valproate + Diazepam	2	BPAD
Clobazam + Levetiracetam + Gabapentin	1	Seizures
Valproate + Clobazam + Lorazepam	1	Epilepsy
Lorazepam + Valproate + Midazolam	1	Sedation, Seizures

Quadruple therapy

In the present study quadruple therapy (Phenytoin + Valproate + Levetiracetam + Midazolam) was prescribed in one patient for the management of seizures.

A total of 6 ADRs were recorded in 7 of the 250 patients (2.8 %). The majority of the ADRs occurred with the two most widely used AEDs—phenytoin and sodium valproate. Causality was assessed using the Naranjo algorithm for identified ADRs. The majority of ADRs were considered possible and probable. The details of ADRs were summarised in Table 4.

Table 4: Adverse reactions to antiepileptic drugs

ADR Identified	Suspected Drug	Fate Of Suspected Drug	Causality Relationship	Score
Gum Hypertrophy (2)	Phenytoin	Withdrawn	Possible	7
Constipation	Lorazepam	Continued	Probable	4
Dark Color Stools	Sodium Valproate	Changed	Possible	6
Rash	Carbamazepine	Continued	Possible	6
Drowsiness	Sodium Valproate	Continued	Probable	6
Irritability	Levetiracetam	Continued	Possible	6

DISCUSSION

Drug utilization evaluation is as an ongoing, authorized and systematic quality improvement process, which is designed to review drug use or prescribing patterns, develop criteria and standards for optimal drug use. Anti-epileptics drugs are the drugs that are used to modify the altered neurological functions. The therapeutic goals of anti-epileptic drugs are to reduce the frequency of recurrent seizure and to minimize the adverse effects. Although AEDs are primarily prescribed for epileptic seizures, they are also used for other co-morbidities, such as neuropathic pain, particularly diabetic neuropathy and post herpetic neuralgia, migraine prophylaxis and bipolar disorder.

In our study out of 250 patients 178 (71.2 %) was found to be males and 72 (28.8 %) was found to be females indicating that men predominated over women. Murthy NV *et al* and Arulkumaran *et al.*, studies showed males were more predominant than females in AED prescribed patterns which support our study^{11,12}.

Majority of the patients were found in psychiatry department 98 (39.2), followed by general medicine 81 (32.4 %), paediatrics 70 (28 %), surgery 1 (0.4 %). There were less number of cases found in surgery department because of the less usage of AEDs.

Most frequent diagnosis encountered in our study was seizures 76 (30.4 %), followed by schizophrenia 26 (10.4 %), ADS22 (8.8 %), BPAD 20 (8 %), psychosis 20 (8 %), CVA 15 (6 %), DM 12 (4.8 %), MR 10 (4 %), GDD 7 (2.8 %). Here, in this study we found the patients with co-morbidities were 130 (52 %) and without co-morbidities were 120 (48 %). It indicates that epilepsy with co-morbidities were more in our study. The most commonly observed co morbidities included in our study were diabetes mellitus, hypertension, stroke, altered sensorium, acute gastro enteritis, developmental delays. Study from Germany found cerebrovascular accident, dementia, and intra cerebral hematoma as a most common co-morbidities¹³.

The key in treating epilepsy is correct diagnosis of the seizure type. In our study, most patients were suffering from GTCS 60 (60 %) followed by unclassified seizures 14 (14 %), tonic seizures 6 (6 %) and the least type of seizures noted were complex partial, fever provoked, absence seizures and atonic seizures 1 (1 %). GTCS was more common since at the time of diagnosis the patient may develop generalized seizures and it is difficult in differential diagnosis by physician. The other study Ayalew MB *et al.* reported that GTCS (305, 86.) was most frequently observed¹⁴.

In GTCs which accounts for frequent diagnosis; phenytoin was the first drug of choice as mono therapy in most cases. The reason for high use of phenytoin was lower cost with free supply at government hospitals. In febrile seizures, most commonly clobazam and carbamazepine was used. To treat status epilepticus phenytoin and its combination with other antiepileptic like diazepam and sodium valproate was used. Focal and atypical seizures there were high use of phenytoin. Absence seizure was

treated with sodium valproate and simple febrile seizures were treated with clobazam in our study; a study from Mysore, South India also seen similar pattern of epilepsy¹⁵.

This study highlighted that Phenytoin was the most commonly prescribed anti-epileptic drug followed by sodium valproate, diazepam. Similar results were obtained by Sobhana *et al.* The reason for discrepancies may be due to factors like availability, affordability, place of practice, type of epilepsy and preference of treating neurologist. Utilization pattern of AEDs in all the prescription were analysed, among them mono therapy was prescribed to 180 (72 %) patients and most common drug prescribed was Phenytoin to 93 (27.4 %) patients, similarly dual therapy was prescribed to 53 (21.2 %) patients and common two drug therapy prescribed was Phenytoin and diazepam to 17 patients, followed by triple therapy to 16 (6.4 %) patients and drugs prescribed in triple therapy was phenytoin, diazepam and sodium valproate given in 3 patients and Quadruple therapy phenytoin, sodium valproate, levetiracetam, midazolam was prescribed to 1 (0.4 %) patient. Arulkumaran *et al.* study revealed that about 76.87 % patients were managed with mono therapy¹¹.

Mono therapy was the therapy of choice in majority of patients. It is important to maintain patients on mono therapy as compliance is better, side effects are less. Chances of drug-drug interactions are increased with poly therapy as most of AEDs are hepatic microsomal enzyme inhibitors/ inducers and also they have narrow therapeutic index¹⁶.

As there is raising trend of prescribing AEDs for pain and mood disorders, the most common type of pain disorder was diabetic neuropathy for which pregabalin and gabapentin were prescribed in our study. For psychomotor disorders, mood disorders including anxiety and depression, AEDs were the most common indication in our study. In paranoid schizophrenia, most commonly prescribed drugs were sodium valproate and diazepam. In bipolar disorder, sodium valproate was prescribed frequently. In cholelithiasis, we found midazolam for sedation. In alcohol dependent syndrome, lorazepam drug was prescribed. In cerebrovascular accident, phenytoin and diazepam are used. In behavioural problem, topiramate was used as add on therapy. We found levetiracetam drug used in developmental delay disorder. These findings reveal that frequency of use of AEDs in non-epileptic conditions is same that of the epileptic use. A similar finding was seen in Pragna M Patel *et al.* study¹⁷.

The presence of adverse effect from AEDs is additional challenge for epilepsy patients. In the analysis of ADRs of AEDs, 7 (2.8 %) ADRs were noted in total of 250 patients whereas in a study conducted at Kathmandu, it was reported in 35.13 %¹⁸. In our study, we found the most common ADR was gum hypertrophy in 2 patients followed by drowsiness, rash, irritability and the most common drug involved in ADR was phenytoin followed by sodium valproate whereas in a study conducted at Hyderabad drowsiness was most common ADR and carbamazepine and phenytoin were most common drugs responsible for ADRs¹⁹. The causality relationship between the ADRs and the respective drugs

comes under “possible” category as per Naranjo's ADR probability scale.

CONCLUSION

The most prescribed AEDs are observed in psychiatry indicating high rate of AEDs are using in psychiatric conditions apart from epilepsy. Phenytoin was most frequently prescribed AED followed by sodium valproate. As phenytoin is enzyme inducing drug and will show nonlinear pharmacokinetics, so therapeutic drug monitoring is essential. ADRs profile of these AEDs also very high as a result proper monitoring of suspected reactions to a drug is essential, which further increases the compliance to the therapy and finally increases quality of life to the patient. As these drugs are mostly acting on the CNS, effects related to CNS are also very common. So, proper patient counselling is also essential to these patients on AED therapy in preventing noncompliance. Through our study different indications of AEDs apart from epilepsy was described. With this hope in future we expect some other possible indications to the AEDs.

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