Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: www.saspublishers.com

OPEN ACCESS

Pharmacology

Comparison of Older, Newer and Combinations Used of Anti-Epileptics: A Hospital Based Cross Sectional Study

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| **Received:** 26.05.2019 | **Accepted:** 03.06.2019 | **Published:** 11.06.2019
DOI: 10.36347/sjams.2019.v07i06.001

Abstract | **Original Research Article**

Background: Seizure disorders are most often treated with pharmacotherapy. Optimal antiepileptic drug (AED) treatment completely controls seizure episodes in 60% to 95% of epileptic patients. Choice of appropriate AED depends on several factors such as correct epilepsy diagnosis, patient's convenience and risk of ADRs. ***Objective:*** To compare the use of older, newer and combination of anti-epileptics prescribed to patients diagnosed with epilepsy. ***Methodology:*** After getting approval from the Institutional Ethics Committee, the study was conducted by the Department of Pharmacology in association with the Department of Medicine, Government Medical College, Srinagar. The patients coming to the Neurology Department, SMHS Hospital were studied. The participants were provided with explicit explanation for their inclusion in the Study by instituting Written Informed Consent, duly translated in local Vernacular. It was a cross-sectional, observational study for a period of one and a half year. An assessment of the causality and allocation of ADRs was done using Naranjo's monitoring scale and WHO-UMC scale. The severity of ADRs was determined by using the modified Hart Wig and Siegel Scale (1992). ***Results:*** The most frequently prescribed drugs to the study population were phenytoin (31.3%), valproate (23.1%) and carbamazepine (14.1%). The other drugs prescribed to the study population included clobazam (6%), oxcarbazepine (5.2%), leviteracetam (3.7%), phenobarbitone (3%), lamotrigine (3%), topiramate (3%) and gabapentin (0.7%). The drug combinations prescribed to the study population included valproate plus lamotrigine (1.5%), valproate plus topiramate (1.5%), phenytoin plus lamotrigine (1.5%), carbamazepine plus leviteracetam (1.5%) and phenytoin plus gabapentin (0.7%). ADRs were present in 57.6% of the patients on older antiepileptics as compared to 39.4% of the patients on newer antiepileptics and 22.2% of the patients on a combination of two drugs. There was significant statistical relationship between ADRs and the use of older and newer anti-epileptic drugs when classified as such with a p-value of 0.041. ***Conclusion:*** The prevalence of the use of old antiepileptics was more than either newer antiepileptics or a combination in our study population. The prevalence of ADRs though was significantly lower in the use of both newer antiepileptics and the combination of antiepileptics than the use of older antiepileptics.

Keywords: Comparison, Older, Newer, Combinations, Anti-Epileptics, Based Cross Sectional Study.

INTRODUCTION

Epilepsy is a common chronic neurological disorder which is characterized primarily by repeated seizures caused by recurrent, abnormal and excessive synchronous discharges from cerebral neurons associated with neurobiological, cognitive, psychological and social disturbances [1,2]. The terms epilepsy, seizure and convulsion are not synonymous. A seizure always is a symptom of abnormal function in the CNS rather than a disease in itself. Seizures are to be distinguished from epilepsy, which is a chronic condition in which seizures occur repeatedly due to an underlying brain abnormality. A convulsion is a forceful involuntary contraction of skeletal muscles. Epilepsy may develop after a particular identifiable event (e.g., asphyxia, head injury, meningitis), in which case it is called symptomatic epilepsy, or it may develop without any identifiable cause, and then it is called idiopathic epilepsy. Sometimes the term "secondary epilepsy" was used for symptomatic epilepsy and "primary epilepsy" for idiopathic epilepsy. The terms primary and secondary are only used in relation to seizures and not in relation to epilepsy[3]. A secondary generalized seizure is a seizure which starts in one place and then becomes generalized, while a primary generalized seizure is one generalized from its onset. Epilepsy is also remarkably uniformly distributed

around the world. There are no racial, geographical or social class boundaries. It occurs in both sexes, at all ages, especially in childhood, adolescence and increasingly in ageing populations. More than 60 million people around the world are living with epilepsy, i.e., 1% of the world's population. The number grows dramatically each year [4]. Epilepsy affects 1 in 100 adults and 1 in 20 children. According to the Epilepsy Foundation, approximately 1 in 26 people of all ages will develop epilepsy at some point, implying that incidence is approximately 0.3 – 0.5% in different world populations with a prevalence rate of five to ten per thousand people [5]. Approximately 80% of these individuals live in the developing countries [6]. It is estimated that there are 55, 00,000 persons with epilepsy in India [3].

Epilepsy is a neurological disorder which demands immediate medical attention and often long term therapy and these disorders are most often treated with pharmacotherapy on long term basis. Optimal antiepileptic drug (AED) treatment completely controls seizure episodes in 60% to 95% of epileptic patients. Choice of appropriate AED depends on several factors such as correct epilepsy diagnosis, patient's convenience and risk of ADR's [7]. A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly used as first line drugs. They are relatively less expensive than the newer antiepileptics. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the newer ones and currently used as add-on or alternative therapy. They have lesser adverse effects and have few, if any, drug interactions [8, 9]. An adverse drug reaction (ADR) is a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis and treatment of disease or for modification of physiological function [10]. ADR's are considered among the leading causes of morbidity and mortality causing hospital visits and admissions [11].

ADR profile of psychotropic drugs and is yet to gain the momentum needed to cope with the demands of a country that is already under pressure of overpopulation, malnutrition and high disease burden [12]. Over the last two decades, around 12-13 newer antiepileptic drugs have been introduced. However, studies comparing the newer antiepileptic drugs with the older antiepileptic drugs have been scanty. For years when only a handful of antiepileptic drugs were in the market, patients were forced to choose between a life of seizures and a life of intolerable adverse drug reactions. With the advent of newer antiepileptics though has come the hope of not just better efficacy but also reduced adverse drug reactions and improved safety.

OBJECTIVES

- To compare the use of older, newer and combination of anti-epileptics prescribed to patients diagnosed with epilepsy.

MATERIALS AND METHODS

After getting approval from the Institutional Ethics Committee, the study was conducted by the Department of Pharmacology in association with the Department of Medicine, Government Medical College, and Srinagar. The patients coming to the Neurology Department, SMHS Hospital were studied. The participants were provided with explicit explanation for their inclusion in the Study by instituting Written Informed Consent, duly translated in local Vernacular. It was a cross-sectional, observational study for a period of one and a half year.

INCLUSION CRITERIA

- All patients with seizures of either sex or age group (>18 years of age) who were prescribed anti-epileptic drugs were included in the study.
- ADRs which were voluntarily recorded by a doctor were also included in the study.

EXCLUSION CRITERIA

- Patients who were unable to co-operate.
- Patients with inability to give consent.
- Patients treated with traditional medicines alone.
- Drug over-dose (deliberate or unintentional).
- Cases of relapse due to non-compliance.
- Patients with status epilepticus and seizures associated with acute conditions like stroke or other illnesses like hypertension, diabetes, chronic pulmonary obstructive disease, etc.

After reading the basic demographic profile, following information was collected from them (patients or their guardians); duration of illness, number of previous hospitalizations, type of epilepsy, severity of illness, current anti-epileptic treatment, number of drugs, drugs names, dose at the time of the visit, duration of present treatment and the reason for initiating current treatment (first episode, drug substitution).

An assessment of the causality of ADRs and was done using Naranjo's monitoring scale [13] and WHO-UMC scale [14]. Severity of ADR was assessed by using modified Hart Wig and Siegel Scale [15].

Data was entered in Microsoft Excel. Continuous data was summarized as mean (±) standard deviation or the five number summaries as appropriate. Categorical variables were summarized as percentages. Chi-square test was used to test for independence of

two categorical variables. Bar charts and pie charts were used for graphical presentation of data.

RESULTS

Table-1: Distribution of the study population according to age

Age (years)	Frequency	Percent
< 20 years	2	1.5
21-30 years	39	29.1
31-40 years	51	38.0
41-50 years	32	23.9
51-60 years	8	6.0
61-70 years	2	1.5
Total	**134**	**100.0**

Mean 36.6 years, S.D +/- 10.07

Table 1 shows the age distribution of the study population. The average age of the patients was 36.6 years with a standard deviation of 10.07 years and a range of 18 years to 70 years. Most of the patients were in the age group of 31-40 years (38.0%) followed by the age group of 21-30 years (29.1%), 41-50 years (23.9%), 51-60 years (6%), 61-70 years and 18-20 years (1.5% each).

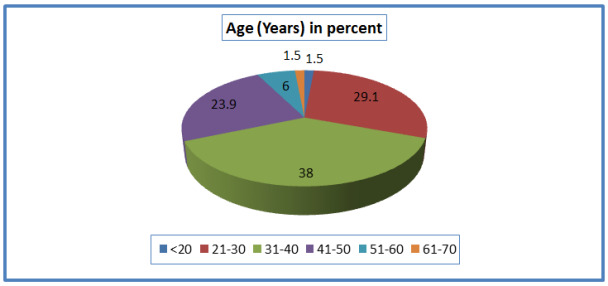


Table-2: Distribution of the study population according to sex

Sex	Frequency	Percent
Male	87	64.9
Female	47	35.1
Total	**134**	**100.0**

Table 2 shows the distribution of the study population according to sex. The study population comprised of eighty seven males (64.9%) and forty seven females (35.1%).

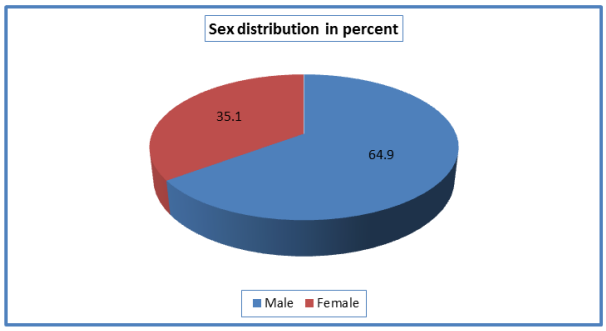


Table-3: Distribution of study population according to residence

Residence	Frequency	Percent
Urban	50	37.3
Rural	84	62.7
Total	**134**	**100.0**

Table 3 shows the distribution of the study population according to their residence. Eighty four (62.7%) patients resided in rural areas and fifty (37.3%) were from urban areas.

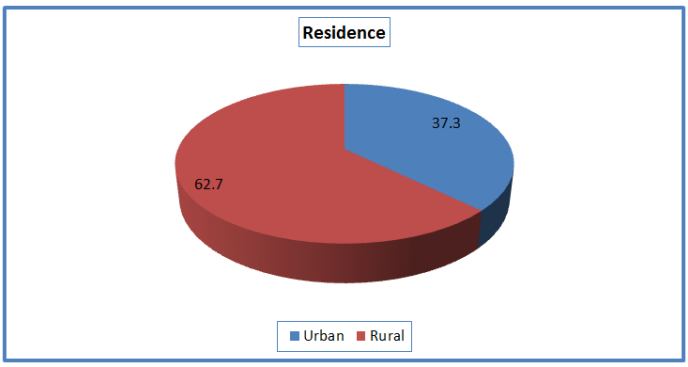


Table-4: Distribution of study population according to diagnosis

Diagnosis	Frequency	Percentage
Idiopathic Generalized Epilepsy	55	41
Simple Febrile Seizures	30	22.4
Complex Partial Seizures	24	18
Symptomatic Epilepsy	6	4.8
Simple Partial Seizures	15	11
Absence Seizures	6	4.8

Table 4 shows the distribution of the study population according to the diagnosis. Idiopathic generalized epilepsy (41%) followed by simple febrile seizures (22.4 %) and complex partial seizures (18%), were the three most common diagnoses in our study. Other seizure types included symptomatic epilepsy (4.8%), simple partial seizures (11%) and absence seizures (4.8%).

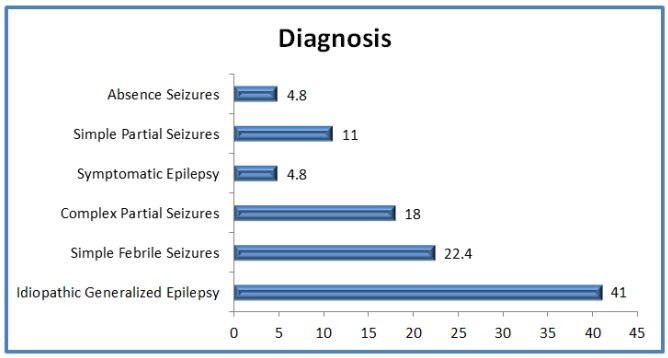


Table-5: Antiepileptic drugs used in study population

Name of drug	Frequency	Percent
Phenytoin	42	31.3
Valproate	31	23.1
Carbamazepine	19	14.2
Oxcarbazapeine	7	5.2
Clobazam	8	6.0
Phenobarbitone	4	3.0
Gabapentin	1	0.7
Lamotrigine	4	3.0
Topiramate	4	3.0
Levitracetam	5	3.7
Valproate + Lamotrigine	2	1.5
Valproate + Topiramate	2	1.5
Phenytoin + Gabapentin	1	0.7
Carbamazepine + Leviteracetam	2	1.5
Phenytoin + Lamotrigine	2	1.5
Total	**134**	**100.0**

The most frequently prescribed drugs to the study population were phenytoin (31.3%), valproate (23.1%) and carbamazepine (14.1%). The other drugs prescribed to the study population included clobazam (6%), oxcarbazepine (5.2%), leviteracetam (3.7%), phenobarbitone (3%), lamotrigine (3%), topiramate (3%) and gabapentin (0.7%). The drug combinations prescribed to the study population included valproate plus lamotrigine (1.5%), valproate plus topiramate (1.5%), phenytoin plus lamotrigine (1.5%), carbamazepine plus leviteracetam (1.5%) and phenytoin plus gabapentin (0.7%).

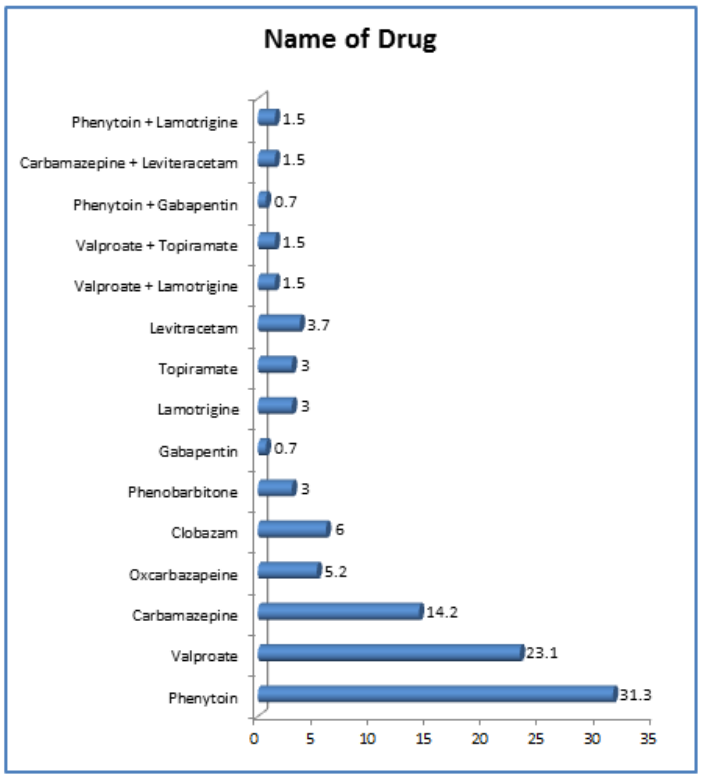


Table-6: ADR status in patients according to drugs used

Drugs used	ADR		Total
	Present	Absent	
Phenytoin	24	18	42
Valproate	17	14	31
Carbamazepine	9	10	19
Oxcarbazapeine	4	3	7
Clobazam	4	4	8
Phenobarbitone	3	1	4
Gabapentin	1	0	1
Lamotrigine	2	2	4
Topiramate	1	3	4
Levitracetam	1	4	5
Valproate + Lamotrigine	0	2	2
Valproate + Topiramate	0	2	2
Phenytoin + Gabapentin	1	0	1
Carbamazepine + Leviteracetam	0	2	2
Phenytoin + Lamotrigine	1	1	2
Total	**68**	**66**	**134**

Table 6 shows the ADR status in the study population according to the drugs used. The proportion of patients with ADRs varied with the drug used. Maximum number of ADRs were reported with phenytoin (24) followed by valproate (17) and carbamazepine (9). Four ADRs were reported each with the usage of oxcarbazepine and clobazam, three with phenobarbitone, two with lamotrigine and one each with gabapentin, topiramate and leviteracetam. With combinations used, one ADR each was reported with phenytoin plus lamotrigine and phenytoin plus gabapentin and none were reported with the combinations valproate plus lamotrigine, valproate plus topiramate and carbamazepine plus leviteracetam.

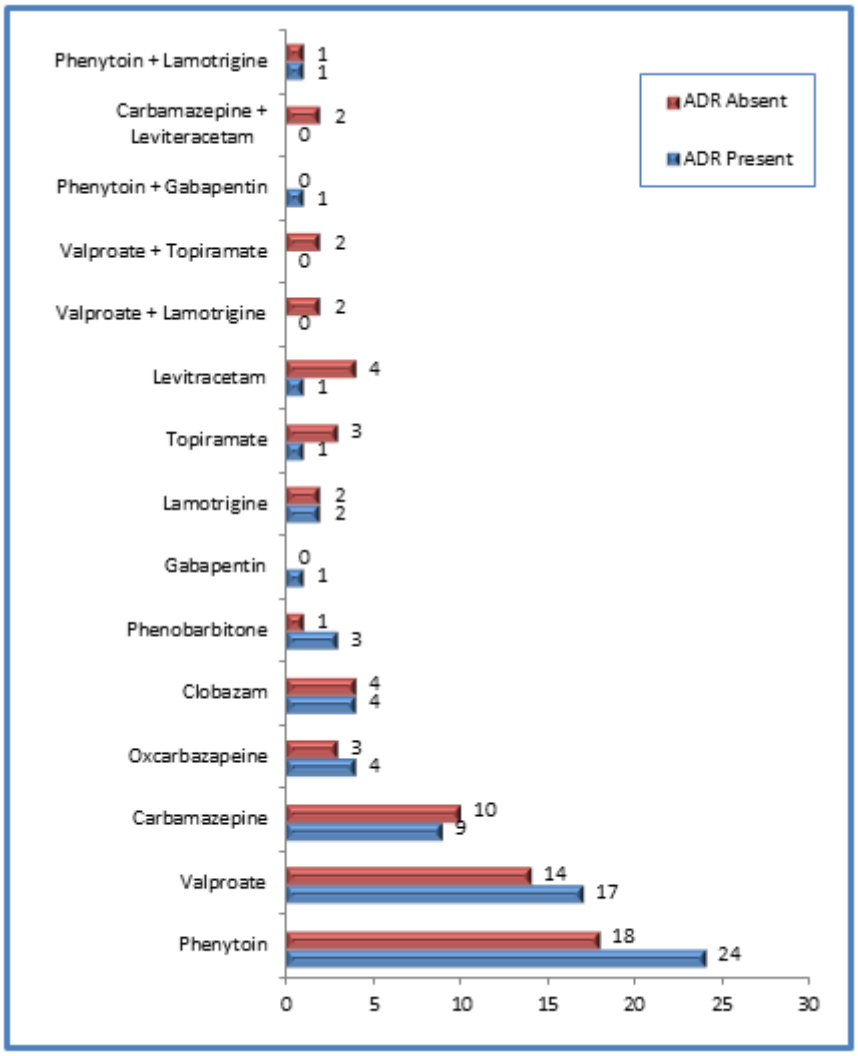


Table-7: Severity of ADR according to drug used

Drug	Mild	Moderate	Total
Phenytoin	35	4	39
Valproate	28	2	30
Carbamazepine	16	3	19
Oxcarbazepine	6	1	7
Clobazam	7	1	8
Phenobarbitone	4	1	5
Gabapentin	1	0	1
Lamotrigine	3	1	4
Topiramate	2	0	2
Leviteracetam	0	1	1
Valproate + Lamotrigine	2	0	2
Valproate + Topiramate	2	0	2
Phenytoin + Gabapentin	0	1	1
Carbamazepine + Leviteracetam	0	0	0
Phenytoin + Lamotrigine	0	0	0
Total	**106**	**15**	**121**

Four moderate ADRs were reported with the use of phenytoin, two with valproate, and three with carbamazepine, one each with oxcarbazepine, phenobarbitone, clobazam, lamotrigine and leviteracetam. Amongst combinations, one moderate ADR was reported with phenytoin plus gabapentin. No moderate ADRs were reported with the use of gabapentin and topiramate and combinations of valproate plus lamotrigine, valproate plus topiramate, carbamazepine plus leviteracetam and phenytoin plus lamotrigine. Mild ADRs were seen with all the drugs used except leviteracetam amongst the individual drugs and phenytoin plus gabapentin, carbamazepine plus leviteracetam and phenytoin plus lamotrigine amongst the combinations.

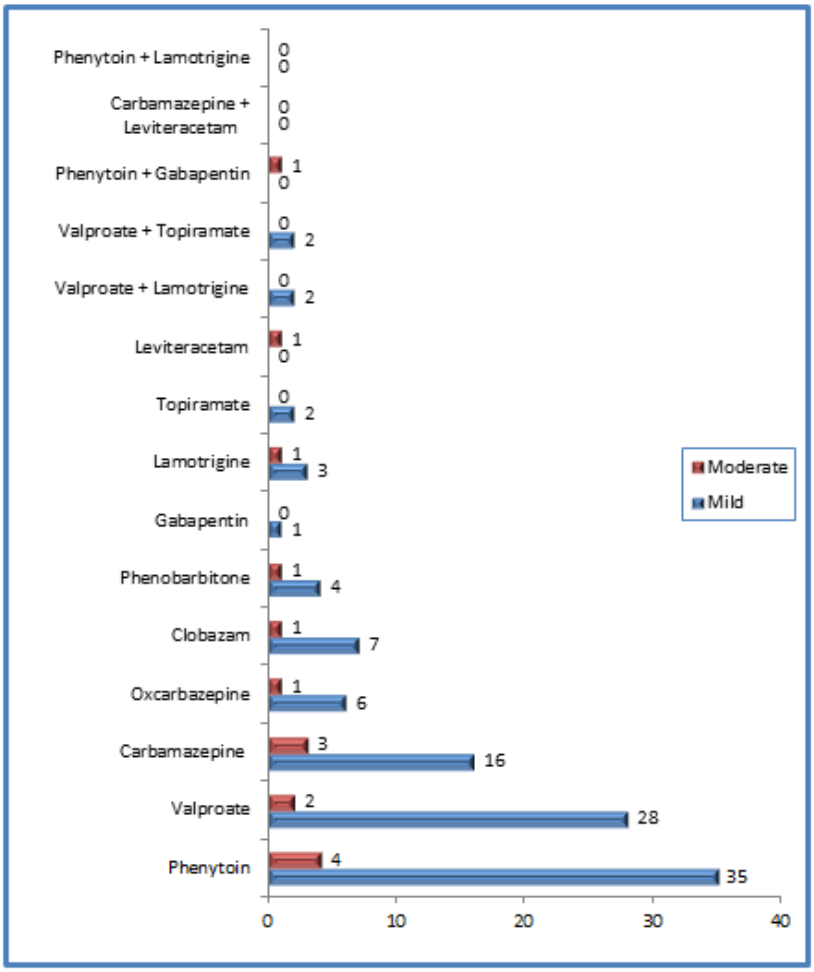
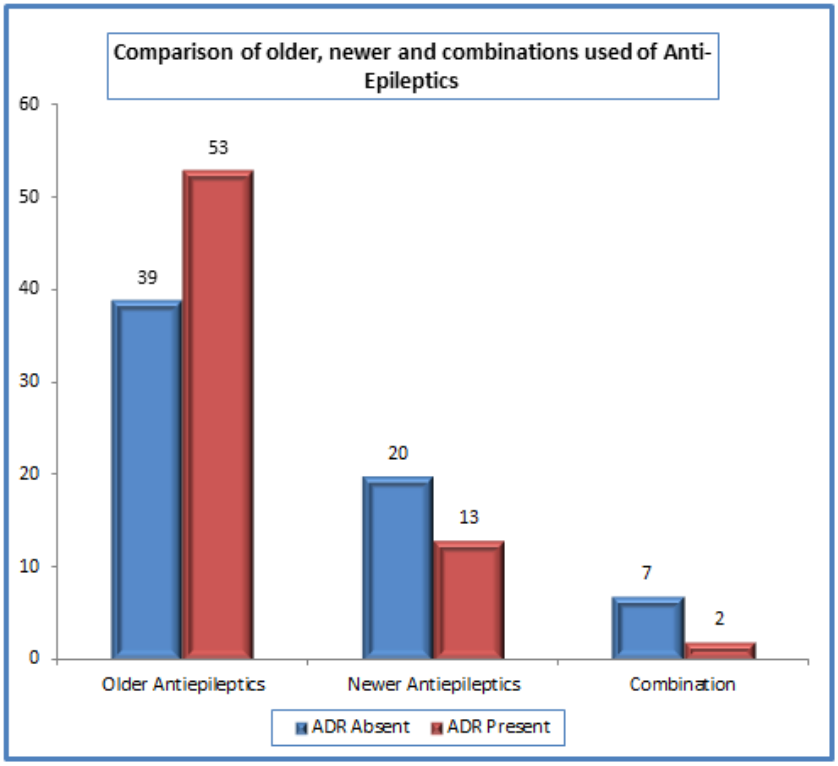


Table-8: Comparison of older, newer and combinations used of Anti-Epileptics

Drug Classification		ADR		Total
		Absent	Present	
Older Antiepileptics	Count	39	53	92
	%	42.4%	57.6%	100.0%
Newer Antiepileptics	Count	20	13	33
	%	60.6%	39.4%	100.0%
Combination	Count	7	2	9
	%	77.8%	22.2%	100.0%
TOTAL		**66**	**68**	**134**
p= 0.041, chi square test				

ADRs were present in 57.6% of the patients on older antiepileptics as compared to 39.4% of the patients on newer antiepileptics and 22.2% of the patients on a combination of two drugs. There was significant statistical relationship between ADRs and the use of older and newer anti-epileptic drugs when classified as such with a p-value of 0.041.



DISCUSSION

Most of the study participants were in the young and middle age groups (21-50 years) with a mean age of 36.6 years (S.D +/-10.07 years). The male-female ratio was 1.9. There was no statistically significant relationship of ADRs with age (p=0.087) or sex (p=0.957) of the patients under study. These results are similar to those reported by many others [16-18]. Eighty four (62.7%) patients resided in rural areas and fifty (37.3%) were from urban areas. The overall prevalence of ADRs in our study was 73.1%. A study conducted in a tertiary care hospital, Erode, Tamil Nadu by Keerthi Jayalekshmi *et al*.[19] reported an ADR prevalence of 31.1%. Another survey in Iran reported an ADR prevalence of 91.4%. Other studies have reported the frequency of ADRs following anti-epileptic use ranging from 2.95%, 4.67% to 31.11% [16-19].

Idiopathic generalized epilepsy (41%) followed by simple febrile seizures (22.4%) and complex partial seizures (18%), were the three most common diagnoses in our study. Other seizure types included symptomatic epilepsy (4.8%), simple partial seizures (11%) and absence seizures (4.8%). Similar findings have been reported by Shobhana Mathur *et al.* [16].

The most frequently prescribed drugs to the study population were phenytoin (31.3%), valproate (23.1%) and carbamazepine (14.1%). Similar observations have been reported by Shobhana Mathur *et al*. [16]. Also similar results have been reported by other studies also [17-19]. This shows that the pattern of pharmacological therapy for epilepsy in these studies was similar to our study.

The proportion of patients with ADRs varied with the drug used. Maximum number of ADRs were reported with phenytoin (24) followed by valproate (17) and carbamazepine (9). Four ADRs were reported each with the usage of oxcarbazepine and clobazam, three with phenobarbitone, two with lamotrigine and one each with gabapentin, topiramate and leviteracetam. With combinations used, one ADR each were reported with phenytoin plus lamotrigine and phenytoin plus gabapentin and none were reported with the combinations valproate plus lamotrigine, valproate plus topiramate and carbamazepine plus leviteracetam.

Phenytoin was responsible for most number of the ADRs in our study population followed by valproate and carbamazapine which may be explained on the basis of the fact that these drugs were being most commonly prescribed in our study population. Phenytoin being responsible for most of the ADRs has also been reported in other studies as well [16-18].

When classifying the antiepileptic drugs prescribed as older antiepileptics, newer antiepileptics and drug combination, it was observed that ADRs were present in 57.6% of the patients on older antiepileptics as compared to 39.4% of the patients on newer antiepileptics and 22.2% of the patients on a combination of two drugs. There was significant statistical relationship between ADRs and the use of older and newer anti-epileptic drugs when classified as such (0.041). This differs from the study conducted by

Jesso George MD *et al.* where no significant statistical relationship was found between ADRs and the use of older and newer anti epileptics when classified as such[20].

Limitation: A limitation of this study is the insufficient number of patients recruited. Much larger studies are required to adequately and conclusively ascertain the comparison between older antiepileptics, newer antiepileptics and a combination of the two.

CONCLUSION

It is a daunting prospect for a physician to determine the most appropriate antiepileptic drug for a patient. Over the last two decades, around 12-13 newer antiepileptic drugs have been introduced. However, studies comparing the newer antiepileptic drugs with the older antiepileptic drugs have been scanty. For years when only a handful of antiepileptic drugs were in the market, patients were forced to choose between a life of seizures and a life of intolerable adverse drug reactions. With the advent of newer antiepileptics though has come the hope of not just better efficacy but also reduced adverse drug reactions and improved safety.

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