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A prospective study: Drug utilization evaluation of anti-epileptic drugs in a multispecialty hospital

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Abstract
Background: Anti-epileptic drugs (AEDs) are commonly used throughout the world. This is because they are mainly used to treat epilepsy which is one of the most neurological disorders all over the world. Anti-epileptic drugs are classified into older generation and newer generation drugs. The older generation drugs include phenytoin, phenobarbital, valproic acid, ethosuximide and carbamazepine. The newer generation drugs include felbamate, gabapentin, lamotrigine, topiramate, zonisamide, tiagabine, oxcarbazepine, pregabalin, levetiracetam, rufinamide, lacosamide, vigabatrin, clobazam, ezogabine, perampanel and eslicarbazepine acetate.
Objectives: To analyze the usage of anti-epileptic drugs, the cost of treatment, to find out any drug related issues with the treatment given (drug induced seizures, pregnancy, interactions, side effects or adverse effects, drug safety and effect of drug) and to study the effect of the old and newer anti-epileptic drugs in terms of effect, side effects, adverse drug reactions (ADRs.)
Methods: The study was done at the PSG Hospitals, Coimbatore from December 2017 to April 2018. Information was collected and filled in the data collection form from patient files after giving informed consent. The results were calculated using percentages.
Results: Two hundred and thirteen patients were selected. The use of older anti-epileptic drugs was present in 22 cases (10%) while 122 patients received the newer anti-epileptic drugs (57%) and those who received a combination of both were 69(32%). Levetiracetam was the most highly prescribed of all the drugs and also for the newer drugs at 126 times (33%) while phenytoin was most prescribed of the older drugs 56(15%). Seizure cases were 145(68%) non seizure cases were 68(32%). The total number of adverse drug reactions present in all the cases were 54. Older drug adverse drug reactions were fewer than newer drug adverse drug reactions at a ratio of 37% to 63% respectively. The costs of newer anti-epileptic drugs were seen to be higher than those of older generation anti-epileptic drugs. The average costs of the drugs (both injection and tablets) was found to be Phenobarbital 7.93/-, Phenytoin 32.735/-, Carbamazepine 11.62/-, Valproic acid 45.4/-, Clonazepam 84.5/-, Clobazam 66.22/-, Gabapentin 148.7/-, Pregabalin 68.7/-, Lacosamide 37.16, Lamotrigine 94.9375, Oxcarbazepine 19.06/-, Topiramate 79.33/-, Perampanel 55/-, Zonisamide 102/-, Levetiracetam 236.48/-.
Conclusion: The use of newer anti-epileptic drugs has increased greatly. Monotherapy of anti-epileptic drugs is still quite common. The costs of newer anti-epileptic drugs are quite high as compared to older anti-epileptic drugs. Overall, the newer drugs had more adverse drug reactions cases as compared to the older generation drugs.

Keywords: DUE, older AEDs, newer AEDs

Introduction

Anti-epileptic drugs (AEDs) are commonly used throughout the world. This is because they are mainly used to treat epilepsy which is one of the most neurological disorders all over the world. It affects quite a large number of people. Its prevalence in developed countries is about 5-8 cases [1] per population while in developing countries it is about 40 per 1000 population [2]. Furthermore, the distribution of epilepsy is not uniform throughout the age groups [3]. This means that AED usage varies among the various age groups in India, is estimated that there are over 5,500,000 people with epilepsy alone [4].

Recent times however, have seen the course of AEDs change. Over the past 20 years we have seen the development of the newer anti-epileptic generation drugs. The older generation drugs include phenytoin, phenobarbital, valproic acid, ethosuximide and carbamazepine. The newer generation drugs include felbamate, gabapentin, lamotrigine, topiramate, zonisamide, tiagabine, oxcarbazepine, pregabalin, levetiracetam, rufinamide, lacosamide, vigabatrin, clobazam, ezogabine, perampanel and eslicarbazepine acetate [5]. This has seen AEDs being prescribed not only for epilepsy or seizure related cases but also for other indications such as non-epileptic seizures, topiramate and valproic acid for migraine prophylaxis, valproic acid and

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carbamazepine for bipolar disorder, gabapentin and pregabalin for neuropathic pain [6-7]. Other AEDs such as lacosamide and pregabalin are not indicated for epileptic disorders as monotherapy. As for polytherapy, studies show that it is used among 19-24% of epilepsy cases [8-10].

Despite all this advances, still the question begs. Why is AED usage still soaring? While not all the patients using AEDs suffer from epilepsy use AEDs, a fairly good number does. The probable reasons as to why this is so could range anything from medication errors, patient noncompliance, drug costs that make the patients to stop medication in the course of treatment, dosage errors all the way to poor management of the diseases. Over the years' prescription patterns of AEDs has changed with the advent of newer AEDs. Cost management is also a huge factor in the treatment gap [11]. In India, average percentage of price according to different brands is seen to be very wide. It is also most of the recurring cases are due to lack of drug compliance which is probably as a result of this thus lowering the drug cost, creating awareness and switching to cost effective therapy could help in medication adherence and eventually in aiding the AED usage.

There have been many AEDs in the past and even more AEDs keep on evolving yet still epilepsy is one of the most common neurological disorders. Newer AEDs are needed because there are still patients who have epilepsy that is refractory to established AEDs. Moreover, there is need for new AEDs without pharmacokinetic drug interactions, drugs whose mechanism allows for synergistic combination therapy yet with fewer drug interactions and adverse effects compared to the old ones. AEDs have been seen to cause major malformations since the 1960s [12] and is increased about two to threefold[13] It is also noted that they tend to produce behavioral teratogenesis. However, a study conducted in Denmark showed no increased risk in major defects in the first trimester for newer AEDs such as lamotrigine, oxcarbazepine, topiramate, gabapentin and levetiracetam. while about 35% of the patients have CNS related comorbidities which may result in increased risk of interactions [14-15]. Most AEDs are known to cause teratogenicity and among the various effects include, cleft lip/palate, urogenital effects, congenital heart disease, neural tube defects [16-19]. It is important to gain understanding of mechanisms of action, adverse event profiles of AEDs so as to be able to maintain a rational and effective combination therapy. This overall will help improve treatment and ultimately the patient's quality of life.

The aims of the study were to perform drug utilization evaluation of the anti-epileptic drugs and to analyze the usage of AEDs, the cost of treatment, to find out any drug related issues with the treatment given (drug induced seizures, pregnancy, interactions, side effects or adverse effects, drug safety and effect of drug) and to study the effect of the old and newer AEDs in terms of effect, side effects, ADRs.

Materials and Methods
This was a prospective observational study conducted at the PSG Hospitals, Coimbatore. The study was carried out between December 2017 and April 2018 after getting approval from the Institutional Human Ethics Committee of PSG hospital with the project number of 17/359. During this period, a total of 213 patients were selected for the study. The data was collected from patients who gave consent, were above 18 years of age and received one or more AEDs. Patients that were below 18 years, had a psychiatric related disorder, that did not give consent were exempted from the study.

A data collection form was filled that entailed information pertaining to age, gender, diagnosis (which was the classified as a seizure related case or non-seizure case), abnormal lab values, drugs prescribed with dosage and frequency, any adverse reactions and cost of the drugs. The costs of the drugs were acquired from HIS (Hospital Information System) and compared to the drug cost of the same tablet with other available brands. The various comparisons made in the statistics was done carefully by using percentages. This was done in every category so as to clearly portray the study findings. During statistical analysis, the cases were divided into gender, ages, AEDs received, drug combinations received, according to drug usage (seizure or non-seizure cases), according to ADR cases and lastly cost. The drugs were classified into older and newer AEDs. The older AEDs comprised of drugs that were approved before 1990. In our study this included Carbamazepine, Phenytoin, Phenobarbital, Valproic acid. Newer drugs included drugs approved after 1990. This included Oxcarbazepine, Levetiracetam, Lamotrigine, Topiramate, Clobazam, Pregabalin, Gabapentin, Clonazepam, Lacosamide, Perampanel, Zonisamide. The significance of the newer versus older drugs in terms of ADR was also done by the use of the SPSS in which the one sample T-test was used.

Results
A total of 213 cases that met the criteria were taken for this study. The male patients were found to be 127(60%) while the female were 86(40%). The data was then analyzed to find out which ages received AEDs the most 18-29 were 49(23%), 30-39 were 37(17%), 40-49 were 30(14%), 50-59 were 36(17%), 60-69 were 32(15%), 70-79 were 18(8%), 80-89 were 11 (5%). It was found that the ages between 18-29(23%) had the most number of AEDs consumed. The cases were examined and analyzed into the drugs the patient was receiving. This was either as an older AED, newer AED or both older and newer AEDs. 22 patients received the older AEDs (10%) while 122 patients received the newer AEDs (57%) and those who received a combination of both were 69(33%).

We had a total of 15 AEDs given 383 times. In this we had various combinations and brands given to the patients. The older drugs administered were phenytoin, phenobarbital, valproic acid and carbamazepine. The newer generation drugs included, oxcarbazepine, levetiracetam, lamotrigine, topiramate, clobazam, pregabalin, gabapentin, clonazepam, lacosamide, perampanel and zonisamide. Older AEDs were given as follows phenytoin 56(15%), Valproic 30(8%), carbamazepine 15(4%) and phenobarbital 5(1%). Newer AEDs were as follows levetiracetam126(33%), oxcarbazepine 42(11%), pregabalin 33(9%), clobazam 30(8%), lacosamide 19(5%), clonazepam 8(2%), topiramate 7(2%), zonisamide 5(1%), gabapentin 3 (1%), lamotrigine 3(1%), perampanel 1(0%).Levetiracetam was the most highly prescribed of all the drugs and also for the newer drugs at 126 (33%) while phenytoin was most prescribed of the older drugs 56(15%). The Figures 1-3 below show the percentage of old and new AEDs that were prescribed.
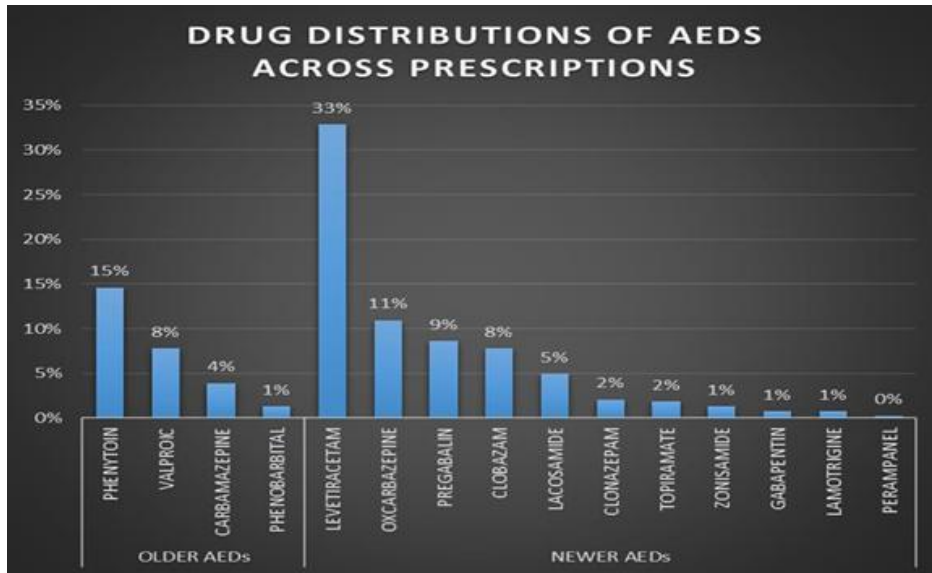
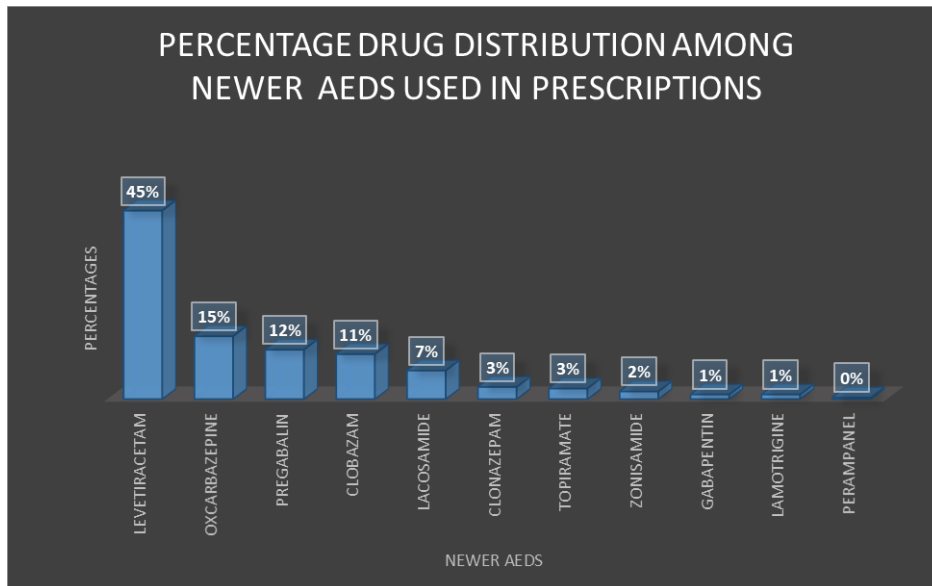**Fig 1:** Percentage distribution of all the AEDs across prescriptions

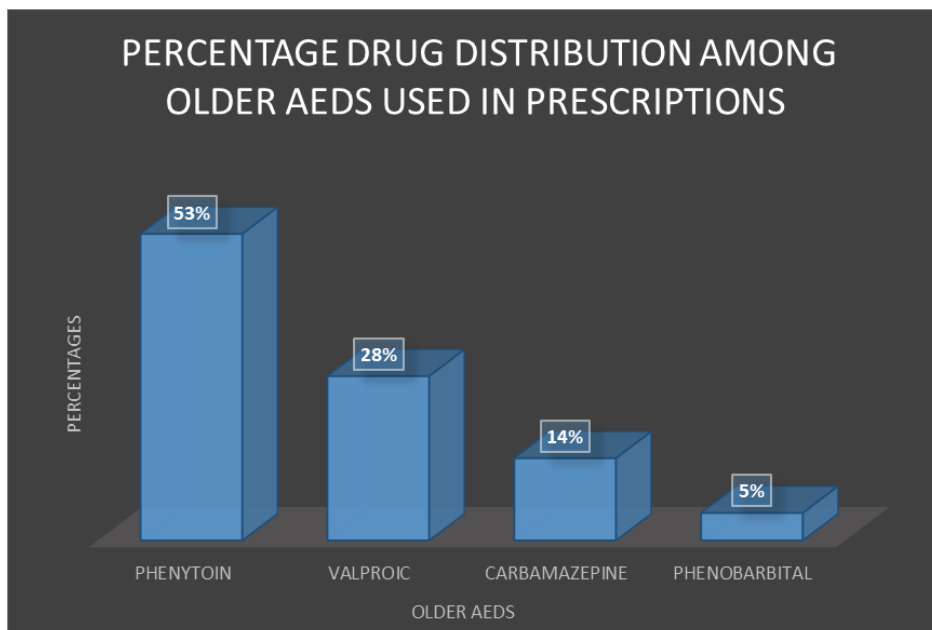**Fig 2:** Percentage drug distribution among newer AEDs used in prescriptions

Fig 3: Percentage drug distribution among older AEDs used in prescriptions

Looking at drug usage, various combinations arose. Monotherapy, dual therapy and more than 3 drugs. Of the 111 monotherapy cases and of this 90 (81%) were newer drugs. The older drugs were 21 (19%). In the case of dual therapy, newer drugs 25 (44%) while both older and newer AEDs were

32 (56%). There were no combinations involving two old drugs only. In the case of administration of 3 or more drugs, two new drugs were administered in 7 cases (16%) while both older and newer AEDs were given in 38 cases (45%). There were no combinations involving two old drugs only.
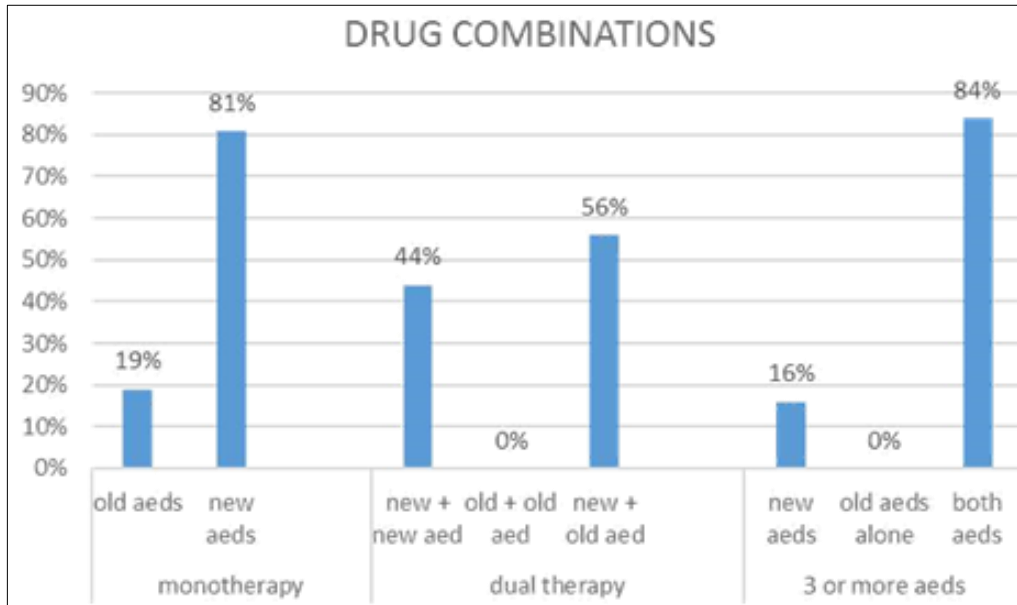

Fig 4: Drug combinations

The average number of AEDs was also calculated. In this we took the total number of AEDs which was 383 and divided it by the total number of patients which was 213. In this, we found the average number of AEDs administered to be 1.79812 overall the older drugs were prescribed 106 times (28%), newer drugs 277 times (72%).

We divided the cases into seizure and non-seizure case. This was to give an insight into AED usage. Of the 213 cases, we see that the seizure case being 145(68%) while non-seizure cases took 68 (32%). A look at the seizure cases, we found the newly diagnosed cases were 51(35%) while the old diagnosis case was 71(49%). This was further divided into those that received older AEDs, newer AEDs and those that received both. This was tabulated to be 9(13%), 23(32%) and 39(55%) respectively. The new diagnosis patients in this category were 51. This was further divided into those that received older AEDs 3(6%), newer AEDs 35(69%) and those that received both AEDs were 13(25%). The most common seizure type was the generalized type of seizure which accounted for 58% with GTCS accounting for 58% of the total number of cases. Partial seizures were at 10% while the unclassified were 32%. As for the non-seizure cases, of this newer AEDs were received by 51(75%) of the patients while older AEDs were received by 8(12%) and 9(13%) received both.

Adverse drug reactions
A look at the ADRs, the total number of ADRs present in all the cases was 54. In this, older drug ADR were 20(37%) while the newer drug ADR were 34(63%). Among seizure type cases, older drug ADR were 16(11%) while newer drug ADR were 28(19%). As for the old diagnosis, ADRs present

were found to be 24. Older drug related ADRs 10(14%) while the newer drug ADRs 14(20%). In new diagnosis cases, ADRs present were 8. Older drug related ADRs 4(8%) while the newer drug ADRs 8 (16%). Also we made a comparison where we took the overall number of times the old drugs were prescribed and the total number of ADRs present and expressed it as a fraction of the total number of times the AEDS were prescribed. Older drugs were prescribed 106 times (28%), newer drugs 277 times (72%) total old drug ADR were 20(5%) and total new drug ADR 34(9%). From this we can clearly see that the older drugs had less ADRs but this could probably be due to their lesser usage than the newer drugs. In non-seizure cases, ADRs present were 10. Of this, the newer drugs were 6 (9%) and for the older drugs 4 (6%). Overall the total number of ADRs was compared with the total number of times the old and new AEDs were prescribed. This was done using the one sample T-test and the significance was P value < 0.005. This indeed means that the newer AEDs had more ADRs.

Cost
Lastly, in the final phase of the statistics, we looked at cost analysis. In this, we took a look at all the drugs that had been administered during the course of our study, evaluated them to find out the various brands and their costs. In this, we took the maximum daily dose for each drug and multiplied it by the average cost of the tablet of each drug. For every drug we compared for the various brands so as to get a clear picture as to which, the older or newer drugs were costlier. This was done across all the brands.

Table 1: Cost analysis of drugs.

Older Drugs				
Drug	**Brand Name**	**Maximum daily dose**	**Cost/tablet**	**Average cost**
Phenobarbital	Gardenal	400mg	11.93	7.93
	Phenotone		3.93	
Phenytoin	Eptoin	300mg	4.74	32.735
	Dilantin		5.58	
	Epsolin		4.82	
	INJ Fosolin		115.8	
Carbamazepine	Tegrital	1600mg	13.44	11.62
	Tegrital CR		12.4	
	Zeptol		9.92	
	Zen		10.72	
Valproic Acid	Encorate Chrono	2500mg	47.35	45.4
	Epilex Chrono		47.35	
	Valparin Chrono		47.4	
	Chronotab		39.5	
Newer Drugs				
Clonazepam	Clonotril	20mg	79	84.5
	Lonazep		84	
	Petril		90.5	
Clobazam	Cloba	60mg	58.2	66.22
	Clobanil		55.08	
	Frisium		85.38	
Gabapentin	Gabapin	3600mg	144.4	148.7
	Gabantin		153	
Pregabalin	Pregalin	600mg	48	68.7
	Pregabid		48	
	Maxgalin		87.6	
	Gabawin		91.2	
Lacosamide	Lacosam	400mg	36.92	37.16
	Lacoset		37.4	
Lamotrigine	Lamitor OD	500mg	100	94.9375
	Lametec		106.75	
	Lamez		73	
	Lamitor		100	
Oxcarbazepine	Oxetol	600mg	15.6	19.06
	Vinlep		25.58	
	Oxmazetol		16	
Topiramate	Topamac	400mg	129.6	79.33333333
	Topamed		58	
	Topaz		50.4	
Perampanel	Fycompa	4mg	55	55
Zonisamide	Zonisep	600mg	79.2	102
	Zonegran		124.8	
Levetiracetam	Levipil	3000mg	69	236.4781818
	Keppra		138.6	
	Torleva		80.7	
	Levera		89.4	
	Levepsy		61.23	
	Levenue		86.1	
	Levigress		65.7	
	Levesam		79.05	
	Levexx		72.2	
	INJ Levipil		665.28	
	INJ Keppra		1194	

At the time of the study, 1 dollar = 67.88 rupees

Needless to say, levetiracetam was most expensive with an average cost of 236 rupees. The Levipil injection tabulated to about 665.28 rupees while Keppra was around 1194 rupees. This is quite expensive considering that an old drug such as phenytoin came an average of 32 rupees with the tablets at about 4 rupees while the injection was about 115 rupees. This shows how varied the older generation drugs are as compared to the newer generation ones especially in terms of cost. The average cost of the drug was as follows Phenobarbital 7.93/-,

Phenytoin 32.735/-, Carbamazepine 11.62/-, Valproic acid 45.4/-, Clonazepam 84.5/-, Clobazam 66.22/-, Gabapentin 148.7/-, Pregabalin 68.7/-, Lacosamide 37.16, Lamotrigine 94.9375, Oxcarbazepine 19.06/-, Topiramate 79.33/-, Perampanel 55/-, Zonisamide 102/-, Levetiracetam 236.48/-.

Discussion
The use of AEDs has been with us since the 1900's and is still quite common than it may seem. This is surprising seeing as

in the last 20 years, there has been a phenomenal breakthrough which led to introduction of over 20 newer AEDs [20].

The study population was 213 from which we found that the male population was found to be 127(60%) while that of female was found to be 86 (40%) which was similar to a previous study [21].This shows that the use of AEDs is higher in male patients in both settings. This was either as an older AED, newer AED or both older and newer AEDs. 22 patients received the older AEDs (10%) while 122 patients received the newer AEDs (57%) and those who received a combination of both were 69(32%). This is contrary to most studies which show the use of older AEDs to be more common than newer AEDs [22-23].

There were a total of 15 AEDs given 383 times. In this we had various combinations and forms in terms of the brands given to the patients. Levetiracetam was the most highly prescribed of all the drugs and also for the newer drugs at 126 times which accounted for 33% while phenytoin was most prescribed of the older drugs 56 (15%). The use of levetiracetam as a monotherapy drug despite it not being FDA approved as such [24] was probably due to its ability to have less ADR and effect on liver and kidney [25] Looking at drug usage, various combinations arose. Monotherapy, dual therapy and more than 3 drugs. The use of more combinations of drugs was similar a prior study [26]. Of the 213 patients, 111 received monotherapy. This showed that the use of monotherapy was more as compared to drug combinations [27].

The population was further divided according to age. Results showed that 18-29 were 49 (23%), 30-39 were 37 (17%), 40-49 were 30 (14%), 50-59 were 36 (17%), 60-69 were 32 (15%), 70-79 were 18 (8%), 80-89 were 11 (5%). It was found that the ages between 18-29 had the most number of AEDs consumed. Prior studies [28] showed that most cases of AED use are normally among children and that as they move on into adulthood they get into a plateau phase. In our study ages 18-29 had the highest AED consumption and this could probably due to prior childhood seizure related diagnosis. In the other ages, we see that AED use is quite common. This could be so because most patients receiving the AEDs had seizure related cases which affects people of all ages worldwide [29]. The most common cases were the generalized type of seizures particularly generalized tonic clonic seizures (GTCS) being 54% and is similar to studies [30] which showed that GTCS types of seizures are indeed quite high. This was followed by partial seizures with complex partial seizures at 14%.

Concerning the AEDS usage, in seizure cases, in the old diagnosis cases we found that the use of both new and old AEDs was common at 55% while old and new drugs were used at 13% and 32% respectively. The old drugs caused ADRs at 14% of the patients while the new drugs did so at a higher rate of 20%. As for the newly diagnosed seizure related cases that we came across during the course of study, we found that only 5% were old AEDS while 69% received new AEDs and in combination of the old and new drugs were 25%. This translated to new drug ADRs being more at 16% which doubled the old drugs ADRs. Here, we found that the newer AEDs were commonly used in the hospital while older AEDs were much less. However, combination of the older and newer drugs was quite common. This could be due to the fact most newer AEDs are mainly used as add on therapy [31].

The study also revealed that most AEDs are now being used for other indications other than epileptic or seizure related cases. We saw that newer AEDs were a high 75% comparing to the old AEDs which are only 12%. In the study, we saw the AEDS being used for indications[32] such as migraines, neuralgia, severe headaches, hemorrhages, post stroke cases among others.

Overall, the ADRs present were 54 in that the ADRs caused by the old drugs were 20 which catered for 37% and the newer drugs had 34 cases which accounted for 33%. As seen throughout the study this could be as a result of lesser usage of the older generation drugs. This was probably because of the fact that older generation drugs have severe adverse effects such as teratogenicity while newer AEDs have fewer adverse event (including idiosyncratic, teratogenic and cognitive ones) [33]. We also found that the ADRs in the non-seizure cases were much less compared to the ones present in the seizure related cases. This could probably be due to a result of the decreased drug dose in the non-seizure related case.

Matters related to cost, we got to dig deep into several brands of all the various drugs that we encountered during the study period. In this, we took the daily recommended dose of each of the drugs and multiplied it by the cost per tablet of the individual drug. In so doing, we gained a clear perspective into just how much goes into the use of AEDs per day. This is vital in getting to know just how much of a burden this is because as is in most cases, AEDs tend to be taken over a period of time. For instance, in the US, the burden of AEDs amounts to averagely 15.5 billion dollars [34].

In our study we got to compare the costs of both the older generation tablets versus the newer. The older generation were far much cheaper compared to the new. For instance, taking phenytoin seeing as it was the most prescribed of the old drugs in the course of the study, had an average daily cost of around 4 rupees while still maintaining a thrice daily dose. The newer drugs on the other hand portrays a totally different picture. Here we take the cost of levetiracetam which was received by 126 patients out of the 213. Taking a twice daily dose, we see the average cost going to around 35 rupees per day. This is relatively a high cost. On a different dimension, we could take the injection costs. Phenytoin costs average at around 173 per day at a three times daily dose (though this could be as a result of use of fosphenytoin which is relatively more expensive.) However, even as this is the case, it came nothing close to the average daily cost of levetiracetam which is around 400 rupees for a 750 mg twice daily dose. In terms of maximum daily dose, levetiracetam had an average of 236 rupees. Levipil injection had 665.28 rupees while keppra was 1194 rupees while phenytoin had an average of 32 rupees per day. This shows that newer AEDs are much expensive as compared to older AEDs. Comparing the two in terms of cost is indeed a myriad. This cost in turn means that the burden is passed on to the individual and their families. According to prior studies, there is uncertainty as to the degree to which private health insurance or social health insurance coverage covers this costs [35]. Thus it is much necessary in future research to examine the role of different models of insurance programs in protecting against economic hardship for this cases, especially in low and middle income settings.

Conclusion
In conclusion, AEDs are still much in use and newer AEDs are indeed catching on as was seen in the study. Newer drugs had more cases of ADRs while comparing to older generation drugs. Matters cost, we see that the newer generation drugs

had a higher cost compared to the older ones. Considering that the use of AEDs is a recurring process, this leads us to the conclude that the burden is passed on to the individual as studies show that it is unclear as to how far the insurance companies will go to help with the burden. More studies need to be done on this to show the various seizure retention rates and burden borne by the individual. In our study we also noted that even if there are set guidelines set by the National Institute for Health and Care Excellence (NICE) on the treatment of AEDs, most are not being followed. Our main limitations were not being able to carry out the pharmacokinetics to be able to show drug safety of the drugs. We also did not come across any pregnant women during the period of study hence could not study effect or outcomes of the drug during pregnancy. We recommend that a study of the same to be done over a period of a few years, also both prospective and retrospective so as to see how the results will vary.

Overall, if DUE is carried out more frequently, will help shed more light on the progress made in various aspects. This will in turn help educate healthcare providers, create patient awareness and compliance which ultimately will lead to enhanced therapeutic outcomes and ultimately, the improved quality of life for the patient.

Summary

The purpose of this research was to analyze the usage of AEDs, the cost of treatment, to find out any drug related issues with the treatment given (drug induced seizures, pregnancy, interactions, side effects or adverse effects, drug safety and effect of drug) and to study the effect of the old and newer AEDs in terms of effect, side effects, adverse drug reactions (ADRs.). This study revealed that newer drugs had more cases of ADRs while comparing to older generation drugs and also that the newer generation drugs had a higher cost compared to the older ones. This means that the individuals are overburdened because insurance companies cannot fully cover for them. The study is helpful in opening up investigations into how the situation can be approached, to help enhance the therapeutic outcomes and effects of AEDs on the patients in order to better their health standards.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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