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Research Article

PROSPECTIVE OBSERVATIONAL STUDY ON UTILIZATION OF ANTI-EPILEPTIC DRUGS IN EPILEPTIC AND NON- EPILEPTIC CONDITIONS IN A TERTIARY CARE TEACHING HOSPITAL

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Article Received: August 2020**Accepted:** September 2020**Published:** October 2020**Abstract:**

Background: In recent years many AEDs are been prescribed for indications other than epilepsy. DUE determines the quality, standards of prescribing therapy in accordance with the guidelines and to assess its prescribing trends in various epileptic and non-epileptic populations. Pharmaco-resistant epilepsy has become major medical trouble with 5 fold higher mortality rate and awaits satisfactory management. Our study will be considered as an update that builds on & expands the findings of previous studies. **Materials & Methods:** Evaluation of 200 prescriptions of epileptic & non-epileptic patients with an emphasis on Drug refractory epilepsy presenting to the Department of Neurology, Osmania General Hospital, Hyderabad.

Aims & Objectives: To assess the AED utilization pattern in epileptic & non-epileptic conditions.

Results: The probability of patients receiving Anti-epileptic Drug therapy for epilepsy was higher (55.5%) than non-epileptic patients (45%). In epileptic patients, slight female preponderance was observed over males. The dominant age group of the study was 20-40 years and the highest numbers of AEDs were prescribed for GTCS (45.94%). Polytherapy was most commonly employed. A progressive decrease in Carbamazepine use and a gradual rise of levetiracetam use was observed. 3rd generation AEDs top the list in non-epileptic conditions. Statistical analysis comparing Monotherapy with combination therapy of gabapentin & pregabalin, we found significant p-value in different non- epileptic conditions. In our study, we found a total of 8 patients (7.20%) with drug-refractory epilepsy, of which 75% had GTCS.

Conclusion: Our study highlights the relevant differences in the utilization of older and newer generation AED. Phenytoin, the conventional AED was common in epileptic patients, while 3rd generation narrow-spectrum AEDS like gabapentin & pregabalin for non-epileptic conditions, most commonly in neuropathic pain.

Keywords: Anti-epileptic drugs, Drug-resistant epilepsy, Epilepsy, Non-epileptic conditions, Refractory epilepsy, Pregabalin, Gabapentin.

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INTRODUCTION:

WHO and its partners acknowledge that epilepsy is a major public health concern. studies. Epilepsy is responsible for high levels of suffering affecting more than 50 million people worldwide, thus making it one of the most common neurological diseases globally [1]. The International League Against Epilepsy (ILAE), The International Bureau for Epilepsy (IBE) & WHO have joined forces in the Global Campaign Against Epilepsy to bring the disease 'Out of the Shadows' to augment awareness about epilepsy, enhance care and reduce the disease impact. The risk of premature death in people within epilepsy is about 3 times higher than the general population. Nearly 80% of people with epilepsy live in low and middle-income countries and about three-quarters of people do not get the treatment they need and these patients and their families suffer from the stigma and discrimination. When properly diagnosed and treated, possibly 70% of epileptic patients can have a seizure-free life.

DUE statistics are magnificent tools with which we can evaluate the standard of prescribing in a defined setting [2]. The fundamental principle of managing epilepsy simply involves making an accurate diagnosis and selecting the most effective antiepileptic drug (AED) for the seizure type based on tolerability and drug interactions [3]. The utmost goal of antiepileptic therapy should be, to achieve a seizure-free state. Monotherapy is the conventional dictum, yet Polytherapy is needed for patients with multiple seizure types. Despite the advent of the impressive & ever-evolving armamentarium of anti-epileptics, pharmacoresistant epilepsy is associated with a higher mortality rate, waiting for satisfactory management. With 16 new AEDs having entered the market since 1990 the antiepileptic market is crowded which had an emerging theme that unifies the usage of AEDs not limited to epilepsy only. AEDs are also prescribed more frequently in neuropathic pain and psychiatric disorders.

The utilization of antiepileptic's differs in different geographical regions, depending partly on economic, development, and drug availability. Hence, we have attempted to gain a parallel insight into the utilization pattern of anti-epileptic Drugs (AED) in different types of epilepsy and the other indications of AED, in non-epileptic conditions. Both neurology and psychiatry have adopted the use of anti-epileptic drugs to treat various non-epileptic central nervous disorders. Most AEDs show multiple mechanisms of action, that include modulation of c-aminobutyric (GABAergic) and glutamatergic neurotransmission and alteration of voltage-gated ion channels or intracellular signaling pathways, elucidating the AED efficacy in managing bipolar disorder and neuropathic pain[4].

With this background, the current study was conducted at Osmania General Hospital, a tertiary care hospital of southern India. This study aimed to investigate the use of anti-epileptics, changes in prescription patterns, exposure of specific drugs to certain patients' groups, the combination of drugs, the potential for misuse, to quantify & investigate the use of antiepileptic drugs in a government health sector.

METHODOLOGY:

A prospective observational study was conducted in the telangana's apex tertiary care, Osmania general hospital. The OPD of neurology has a generous out flow with an average of 10+ epileptic patients every day, where 4-5 neurophysicians proffer prompt treatment routinely and in the IP department of General medicine for a span of 6 months. With respect to the admission status the large majority of the patients were out-patients, compared to In-Patients. Subjects from 20-75 years old who were on AEDs for epileptic & non-epileptic conditions were enrolled for the study. The study population was limited to those who were continuously eligible for the OP & IP during the entire study period. Patients were identified through case sheets; pharmacy drug prescriptions & the identification was for all patients. The data was collected in the form of a structured questionnaire and

recorded to assess the seizure type and the treatment provided, clinical utilization of AED prescribed in epileptic & non-epileptic condition who are on AED and observed for safety tolerability, efficacy, possible drug interactions, medication adherence. This study also evaluated the suspected adrs that were encountered and assessed for their causality, severity and preventability using naranjos, hartwig and shumock and thronton criteria. The statistical

hypothesis testing method employed was chi square fit test, using graph pad prism and microsoft excel.

Inclusion criteria: patients diagnosed with all types of epilepsy, patients diagnosed with non-epileptic conditions, age group 20-75.

Exclusion criteria: patients unwilling to participate, pregnant and lactating women, extensive co-morbidities, cancer patients.

RESULTS:

TABLE -1 : SOCIO-DEMOGRAPHIC PARAMETERS

TYPE OF PATIENTS	NO. OF PTS.	%
EPILEPTIC	111	55.5%
NON - EPILEPTIC	89	44.5%

Among the 200 prescriptions evaluated for the patients, 111 prescriptions hailed

epileptic cases & 89 non-epileptic cases.

TABLE-2 : DISTRIBUTION OF PATIENT POOL ACCORDING TO AGE

The productive age group 20-40 years dominated both in epileptic conditions (71.75) & non-epileptic conditions (47.19%). Least number of cases were reported in elderly age group 61-75 years in epileptic conditions (7.20%) & non-epileptic conditions (6.94%).

S.NO	AGE IN YEARS	EPILEPTIC PATIENTS		NON-EPILEPTIC PATIENTS	
		NO OF PTS	%	NO OF PTS	%
1	20-40	79	71.7%	42	47.19%
2	41-60	24	21.6%	41	46.06%
3	61-75	8	7.20%	6	6.94%

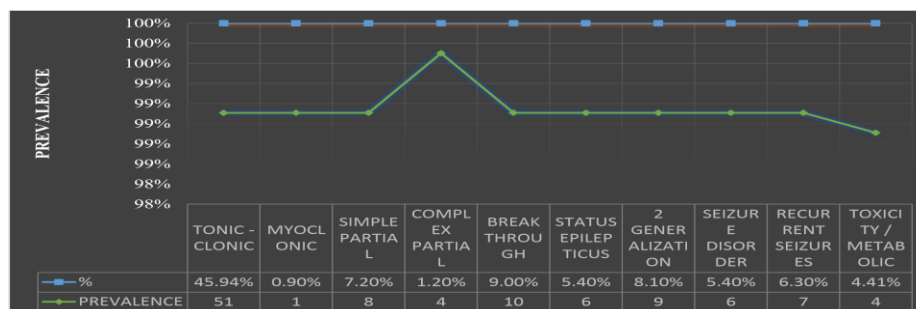
TABLE-3 : DISTRIBUTION OF PATIENT POOL ACCORDING TO GENDER

Female (51%) predominance over males (49%) was observed in epileptic patients, while in non-epileptic conditions male predominance (51.6%) over females (48.3%) was observed.

S.NO	GENDER	EPILEPTIC		NON-EPILEPTIC	
		NO OF PATIENTS	%	NO OF PATIENTS	%
1	MALES	55	49%	46	51.6%
2	FEMALES	56	51%	43	48.3%

TABLE-4 : CHARACTERISATION OF DIFFERENT EPILEPTIC PATIENTS REPORTED

Generalized tonic-clonic seizures accounted for almost 45%, followed by break through seizures (9%), and secondarily generalized epilepsy. (8%). Myoclonic seizures were reported the least (1%). Breakthrough seizures (9%) were the major cause of hospitalization, followed by toxic/metabolic seizures(4.41%). Status epilepticus, an epileptic emergency was reported the maximum (5.40%) in the intensive medical care unit of In-patient setting. In group of patients suffering from partial seizures, simple partial seizures (7.20%) were reported more than complex partial seizures (1.20%).

**TABLE-5 : UTILIZATION OF ANTI-EPILEPTICS IN EPILEPTIC PATIENTS :**

Phenytoin-the 1st generation AED (88.2%) was the highest utilized AEDs in epileptic conditions. Followed by Levetiracetam-2nd generation AED (39.6%). The 3rd gen AEDs- lacosamide was utilized in 6.30% of patients while gabapentin in 1% of epileptic patients. Chlordiazepoxide (5.4%) was prescribed in alcoholic withdrawal seizures.

	DRUG	TOTAL	%
DRUG UTILISATION IN EPILEPTIC PATIENTS	Phenytoin	98	88.2%
	Levetiracetam	44	39.6%
	Phenobarbital	4	3.60%
	Lorazepam	4	3.60%
	Midazolam	23	20.7%
	Clonazepam	1	0.9%
	Clobazam	52	13.4%
	Carbamazepine	10	3.4%
	Oxcarbazepine	11	9.9%
	Sodium valproate	25	22.5%
	Lacosamide	7	6.30%
	Chlordiazepoxide	6	5.4%
	Gabapentin	1	0.9%
Clonazepam	2	1.8%	

TABLE-6 : ANTI-EPILEPTIC DRUG USE PROFILE IN DRUG REFRACTORY EPILEPSY

The table elaborates the anti-epileptic drug regimens prescribed in the drug refractory epilepsy for different types of epilepsy with details about the seizure type, history of seizures, anti-epileptic combinations and their doses prescribed. Patients who developed DRE presented with a history of epilepsy with a minimum of 5 years and maximum 10 years. Phenytoin was prescribed as the common drug with a maximum dose of 300mg in two divided doses. Levetiracetam 500mg was prescribed for twice daily doses. Carbamazepine -controlled release was prescribed at a maximum dose of 300mg. sodium valproate was prescribed at a maximum daily dose of 300mg . Although phenobarbital is not prescribed now, it was observed in two cases for a maximum dose of 60mg in two divided doses. Phenobarbital was only utilized as a continuation of therapy who were already prescribed (i.e, since 10years). Newer generation anti-epileptics clobazam 10mg twice daily & lacosamide 100mg twice daily was also observed in drug refractory epilepsy.

S.NO	SEIZURE TYPE HISTORY OF SEIZURE	HISTORY OF	AED COMBINATION IN USE	DOSE OF AED
1	CPS	10 yrs	Phenytoin + levetiracetam	300 mg + 500 mg (BD)
2	GTCS	5 yrs	Phenytoin + valproic acid + clobazam	300 mg + 750mg (BD)+ 10mg
3	GTCS	5 yrs	Phenytoin + valproate carbamazepine-CR + phenobarbital	300mg + 500(BD) + 300mg + 60mg (BD)
4	CPSWITH SEC.GENERALISED	10 yrs	Phenytoin + levetiracetam + Clobazam	300mg 500mg (BD) + 10mg (OD)
5	GTCS	childhood	Sodium valproate + levetiracetam	300mg (OD) + 500mg (BD)
6	GTCS	7 yrs	Sodium valproate+ lacosamide	500mg (BD) + 100mg (BD)
7	GTCS 9 yrs		Phenytoin + valproic acid	300mg + 500mg (BD)
8	FOCAL SEIZURES WITH SEC.GENERALISATION	10 yrs	Phenytoin + sodium val + levetiracetam + clobazam	300mg + 300mg + 250mg (BD) + 10mg (BD)

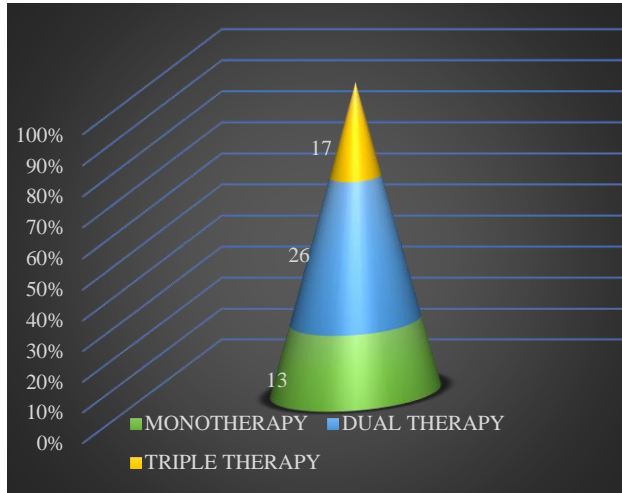
TABLE-7 : THE ASSOCIATION OF INDIVIDUAL AED WHEN USED IN DIFFERENT COMBINATIONS TO TREAT DRUG RESISTANT EPILEPSY

The prescription evaluation of different antiepileptic regimens utilized in drug refractory epilepsy showed different combinations (combination of newer & older AEDs). AED utilization and seizure retention was observed. the response was documented. The p-value obtained was 0.097 depicting that there is no significant association between AED different AED regimens prescribed.

		CBMZ	CBZ	LEV	LACO	V.A	Phenytoin	Total	Chi-square value	P-value
AE D	Phenytoin		4	1	1	6		12	40.43	0.097
	Val.acid						6	6		
	Lacosamide						1	1		
	Clobazam						4	4		
	Levetiracetam		1			1	2	4		
	Phenobarbital	1					1	1		
	Carbamazepine						1	1		
	Chlordiazepoxide							0		
	Oxcarbamazepine							0		
Total		1	5	1	1	7	15			

TABLE -8: STATUS OF THERAPY

Chi 1-square goodness of fit was applied to test the co-relation between polytherapy and duration of history of seizures. The result indicated that there is no significant difference ($P > 0.05$) between the polytherapy and of history of seizures.



History of Seizures	No. of PT's on POLY THERAPY
1-5 years	11
6-10 years	3
11-15 years	1
16-20 years	2
21-25 years	3
25-30 years	2

TABLE-9 : FREQUENCY OF NON-EPILEPTIC CONDITIONS PRESCRIBED WITH AEDs

In non-epileptic patients AEDs were prescribed for different types of neuropathic pain, movement disorders, headache, psychiatric disorder.

NON – EPILEPTIC CONDITION	NO. OF. PTS	%
Neuropathic pain / neuralgia	40	44.94%
Movement disorders	3	3.37%
Neurofibromatosis	1	1.12%
NMO	2	2.2%
PSE	5	5.61%
Headache	7	7.8%
Cervical spondylosis	8	8.9%
Psychiatric disorder (mania)	1	1.12%

TABLE-10 : CATEGORISATION OF NEUROPATHIC PAIN PRESCRIBED WITH AEDs :

Among the 89 non-epileptic patients 49.94% patients reported with different types of neuropathic pains. Among neuropathic pain 31.57% patients presented with parasthesias, 19.29% presented with sciatic pain, 7% with generalized weakness, 5% people presented with peripheral neuropathy, 2% with alcoholic neuropathy, LBA, varicose veins. 1% accounted for other types of neuropathies.

S.NO	NEUROPATHIC PAIN	NO OF PATIENTS	%
1	Parasthesias	18	31.57%
2	Diabetic neuropathy	1	1.75%
3	Alcoholic neuropathy	2	3.50%
4	Peripheral neuropathy	5	8.77%
5	Sciatic pain	11	19.29%
6	Lower back pain	2	3.50%
7	Post-herpetic neuralgia	1	1.75%
8	Generalized weakness	7	12.2%
9	Varicose veins	2	3.50%
10	Radial nerve palsy	1	1.75%
11	Neck pain	4	7.01%
12	Cranial nerve palsy	1	1.75%
13	Sensory neuropathy	1	1.75%
14	Radulopathy	1	1.75%

TABLE-11 : DRUG UTILISATION IN NON – EPILEPTIC CONDITIONS.

Gabapentin in combination with nortriptyline (12.2%) was the most common AED prescribed, followed by the combination of pregabalin with nortriptyline. Gabapentin (7.6%) and pregabalin (9.32%) was also commonly prescribed over other AEDs. Newer generation AEDs like oxcarbamazepine (2.11%) was prescribed in few patients, followed by lorazepam (1.69%). Older AEDs like phenytoin & carbamazepine was less prescribed (1.27%). Valproate & levetiracetam was the least prescribed (1%).

	DRUG	TOTAL	%
DRUG UTILISATION IN NON – EPILEPTIC CONDITIONS	Valproate	1	0.4%
	Levetiracetam	1	0.4%
	Clonazepam	2	0.84%
	Phenytoin	3	1.27%
	Lorazepam	4	1.69%
	carbamazepine	3	1.27%
	Oxcarbamazepine	5	2.11%
	Pregabalin	22	9.32%
	Gabapentin	18	7.62%
	Pregabalin + amitriptyline	2	0.84%
	Pregabalin + nortriptyline	16	6.77%
	Gabapentin + nortriptyline	29	12.2%

TABLE-12 : Association of monotherapy & combination therapy of pregabalin & gabapentin in Nonepileptic patients: There is significant association between the use of monotherapy & combination therapy of the anti-epileptics pregabalin & gabapentin in non-epileptic condition. These AEDs were more commonly prescribed in combination with TCA amitriptyline & nortriptyline in non-epileptic conditions. Its use includes in various neuropathies like LBA, generalized weakness etc. Combination therapy of gabapentin (gabapentin + nortriptyline) the most commonly observed in conditions like low back pain followed by parasthesias.

<i>Non-epileptic condition</i>	<i>Pregabalin monotherapy</i>	<i>Pregabalin combination</i>	<i>Gabapentin monotherapy</i>	<i>Gabapentin combination</i>	<i>Total</i>	<i>Chisquare value</i>	<i>P-value</i>
<i>Paresthesias</i>	5	3	2	7	17	109.1	0.021
<i>Cervical spondolysis</i>	3	1	1	4	9		
<i>Tremors</i>		1			1		
<i>Lower back pain</i>	1	2		9	12		
<i>Diabetic neuropathy</i>			2		2		
<i>Sciatica</i>					0		
<i>Radulopathy</i>		1			1		
<i>Radial nerve palsy</i>					0		
<i>Hemiparesis</i>		1			1		
<i>Neck pain</i>	1	3		2	6		
<i>Neuromyelitis Optica</i>	1				1		
<i>Alcoholic neuropathy</i>				1	1		
<i>Gait disturbances</i>				1	1		
<i>DSPN</i>			1		1		
<i>Cellulitis</i>			1		1		
<i>Paraparesis</i>	1				1		
<i>Lumbar compressive myelopathy</i>			1		1		
<i>DVT</i>	1			1	2		
<i>Lumbar spondolysis</i>	1		1		2		
<i>3rd Cranial nerve palsy</i>	1				1		
<i>sSensory neuropathy</i>	2				2		
<i>Post herpatic neuralgia</i>		1	1		2		
<i>Neurofibromatosis</i>		1			1		
<i>Varicose Veins</i>			1		1		
<i>Reynauld's phenomenon</i>		1			1		
<i>L2- wedge compression</i>					0		

<i>Generalized weakness</i>	3	2	3	3	11		
<i>Post-surgery</i>			2		2		
<i>Holocranium</i>		3			3		
<i>Myasthenia Gravis</i>		1			1		
<i>Ulnar neuralgia</i>		1			1		
Total	20	22	16	28	86		

TABLE-13: ADRs ENCOUNTERED

Among the utilisation of 331 AEDs a total of 5 ADRs were encountered among 111 epileptic patients. The most severe being Stevens-johnsons syndrome induced by carbamazepine. The offending AEDs were stopped and alternate AEDs were prescribed. On evaluation of causality of ADRs, majority were found to be possible (60%) .

ADRS ENCOUNTERED						
NO. OF PTS	ADR REPORTED	SUSPECTED DRUG	CASUALTY ASSESMENT	AED STOPPED/ CONTINUED	CHANGE OF DRUG	
1	Maculopapular rashes, itching, skin lesions	Phenytoin	Probable	stopped	levetiracetam	
1	SJS	Carbamazepine	Probable	stopped	clobazam	
1	Respiratory arrest with respiratory depression	Midazolam	Possible	stopped	Phenytoin	
1	Gum hyperplasia	Eptoin	Possible	Stopped	Enchorate lacosam	
1	Cerebellar ataxia	Eptoin	possible	Stopped	Levipril	

TABLE-14: FREQUENCY OF ADVERSE DRUG EVENTS

Of the 111 epileptic patients, phenytoin was the primary offending drug causing adverse drug events like generalized weakness (18.0%), giddiness (10.8%), tremors (4.5%), rashes (1.8%). Valproate caused headache in 7.2%. Neutropenia/pancytopenia (4.5%) due to levetiracetam was observed. phenytoin induced side-effects were reported the highest. Valproate & levetiracetam adverse effects were also encountered & monitored.

ADE	Suspected drug	Stopped/ continued	frequency	% of patients
giddiness	Phenytoin	continued	12	10.8%
tremors		continued	5	4.5%
rashes		Stopped & continued	2	1.8%
Generalised weakness		stopped	20	18.0%
Headache	Valproate	not stopped	8	7.2%
Neutropenia, pancytopenia	Levetiracetam	stopped	5	4.5%

DISCUSSION

Anti-epileptic treatment is the mainstay in therapeutic approach for managing epilepsy, pleotropic uses of anti-epileptics in non-epileptics have been unfolding. In the recent years many AEDs have been increasingly prescribed for neurological conditions other than epilepsy, albeit off-label, such as neuropathic pain, migraine prophylaxis, psychiatric disorders and movement disorders. Traditionally AEDs are classified as 1st generation, 2nd generation & 3rd generation based on whether they have been marketed before or after 1991. All the 3 generations are heterogeneous in terms of mechanism of action and pharmacological parameters, but the latter generally exhibit better tolerability.

In light of these considerations, our study was carried out with the objective to evaluate and provide a temporal insight on the pleotropic uses of AEDs among the patients attending Neurology OPD & in-patient of general medicine in OGH, Telangana's apex tertiary care hospital. To the best of our knowledge our study is the first of its kind in the Indian clinical setting to depict the utilisation pattern of anti-epileptic drug use in patients with epileptic & non-epileptic conditions.

Demographic details of patients are depicted in table-1. We observed a slight preponderance of females over males which was in congruence with **Parajuli et.al (2018)[5]** while inconsistent with study conducted by **Ahsan Hahroon et.al (2012)[6]**, however a 1:1 male : female ratio was reported by **Kariyaswami SH et.al (2004)[7]**. As observed widely males have a higher incidence of focal epilepsy, while women are influenced by genetic factors or hormones leading to a higher incidence of generalized epilepsy. Dominant age groups in epileptic patients was 20-40 years (71.71%), followed by 40-60 (21.62%) and 60-75 (7.20%), the findings which were in concordance with an earlier study by **Ngangom Gunindro et.al (2018)[8]**. Highest number of AEDs were prescribed for GTCS 45.94% (51 cases), followed by secondary generalized seizures 8.1% (9 cases), simple partial seizure 7.20% (8 cases), seizure disorder 5.40% (6 cases), complex partial seizures 1.20% (4 cases) and myoclonic seizures accounted the least. In contrast, another study carried out in southern India by **Pragna M Patel et.al (2016)[9]** reported Partial seizures to be the most common type. However, this may be due to the difference in the pattern of admission or referral service. Newer AEDs provides clinicians with a wider choice to help patients achieve therapeutic goals even for those not responding to a conventional AED. The main reason for utilization of newer AED is the persistence in seizure activity.

Polytherapy was the most commonly employed and such Prescriptions were significantly higher in patients with an early age of onset of seizures as compared to monotherapy. The age of onset of seizures has a significant impact on determining the treatment, probability of reduction of seizures and cognitive side effects. To determine this, we performed a statistical analysis 'chi-square goodness of fit', to test the correlation between polytherapy and history of seizures. The result indicated that there is no significant difference ($P > 0.05$) between polytherapy and duration of history of seizures (i.e, long standing/de novo/ new-onset epilepsy). A similar higher incidence of polytherapy has been reported by **Rupa Joshi et.al (2017)[10]** and **Ngangom Gunindro et.al (2018)[8]**. The reason could be due to an increase utilization of second-generation AEDs, most of which are approved as add-ons therapy. Our observations are in contrast to several other studies where a higher percentage of patients were prescribed monotherapy (70-0%) in India **Pragna M Patel et.al (2016)[9]** and **K.S.G Arul Kumaran et.al (2009)[11]**

The wide use of polytherapy have been linked to decrease QOL and increases risk of drug-drug interaction. Nevertheless rational polytherapy was observed. A concept that a combination of AEDs with complementary MOAs will work synergistically to maximize efficacy and minimize the potential for adverse events[12]. Drug combinations with different MOAs are efficacious over combination drugs with similar MOAs as it renders synergistic efficacy[12]. Paradoxically, over-treatment with AEDs can occasionally result in an increase in seizure activity and there is no evidence from randomized controlled studies that shows polytherapy is superior to monotherapy in achieving seizure control. Use of a single drug at optimal tolerated serum concentrations produces excellent therapeutic results and minimal side effects in most patients [13]. Successful monotherapy may require higher-than usual AED doses or serum concentrations greater than the upper limit of the usual therapeutic range [14].

Phenytoin 'the conventional AED' was commonly prescribed (88%) due to its higher efficacy in controlling seizures. Among newer agents, Levetiracetam (39.6%) was routinely prescribed followed by clobazam (45.61%) (even higher than carbamazepine), oxcarbamazepine (9.9%) and narrow spectrum AED lacosamide (6.30%). A higher use of clobazam, a non-sedating, well tolerated benzodiazepine with lost cost and good efficacy has been reported earlier both as monotherapy and add-on therapy. Moreover, we noticed a progressive decrease

in incident of carbamazepine use and gradual rise of broad-spectrum AED levetiracetam. This could be due to the fact that both drugs have a common indication, i.e. partial seizure, with the latter exhibiting higher tolerability, excellent safety record and essentially no medically dangerous side effects when prescribed as add-on or monotherapy. The prevalence of first-generation AED use among middle age group was higher during the whole study period.

With respect to the use of AEDs for non-epileptic condition third generation AEDs top the list followed by first generation and second generation. Conventional AEDs were commonly prescribed for epileptic condition, newer AEDs were frequently prescribed for non-epileptic conditions. **Hsieh et.al study Taiwa (2011)[15]** and stated that newer AEDs were used primarily to treat pain disorder and the primary class of drugs used to treat epileptic disorders was conventional AEDs. It was found in **Arulkumaran et.al (2009)[16]** study in Coimbatore that older AEDs were the most frequently used (77.72%) when compared to newer AEDS for epilepsy. our study recounted the use of Pregabalin and Gabapentin, both as monotherapy as well as in combination therapy with TCAs. Table – 12 chronicles the dramatic shift in utilization of these newer AEDs. Combination of Gabapentin with Nortriptyline accounted for about (12.2%) use followed by pregabalin (9.32 %), gabapentin (7.62%), Pregabalin with Nortriptyline combination (6.77%), oxcarbamazepine (2.11%) lorazepam (1.6%) phenytoin and carbamazepine (1.27%) clonazepam and Pregabalin and Amitriptyline combination (0.84%). We also performed statistical analysis comparing monotherapy with combination therapy of gabapentin and pregabalin and it was statistically significant (P value 0.021). Generally, pregabalin is preferred to gabapentin as a first-line medication because of the availability of higher quality studies on its effects, more predictable pharmacokinetics, shorter titration periods, and the option for twice-daily dosing. Whereas gabapentin is cost-effective and has fewer drug-drug interactions.

Compared to the other studies carried out in the same setting by **Syeda Rana Nikhat et.al (2017)[17]**, that reported a total of 6 cases of ADR with phenytoin and Carbamazepine each, our study reported only 5 cases of ADR which reflects the rational use of culprit drugs i.e. phenytoin accounted for 3 cases where as carbamazepine and midazolam accounted for one case each.

As confirmed by **Landmark CJ et.al (2011)[18]** AEDs are gradually becoming the primary indication

for neuropathic pain, which could explain the increasing use of newer AED as found in our study. During our study period there was no single ADR encountered with the use of third generation AEDs which proves they efficacy and tolerability. To our knowledge at present, data on the new AEDs for non-epileptic conditions are inconclusive.

Upon oral history two female patients complained of increased seizure frequency during menstrual cycle. For whom no adjunctive therapy was used. Two women were on Oral Contraceptive (OCs) where the dose of phenytoin was reduced in one case and in other case phenytoin was replaced with levetiracetam.

We found a total of 8 patients (7.20%) with intractable epilepsy of whom 75% of patients had GTCS type of seizures. In decreasing order PHT, VPA, LEV, CLB, LAC, and CBZ were the most commonly prescribed AED, this findings are in contrast with the studies conducted by **Priscila de Freitas-Lima et.al (2013)[19]**. According to ILAE guidelines CBZ and PHT are considered to have the highest evidence for use as initial monotherapy in treating refractory epilepsy. But in our study there was not a single case prescribed with monotherapy, moreover the use of carbamazepine was found to be the least. These may be due to the high profile of AEs compare to newer drugs and also due to the high efficacy and tolerability. **French JA, et.al (2004)[20]** concluded that newer AEDs are adequate for use as adjunctive therapy in adults with intractable partial epilepsy.

Among 8 cases of refractory epilepsy 50% of patients were on Dual therapy and 25% of patient on triple therapy and another 25% on Quadrapule therapy. In present study Second generation AED constituted an important part of the most prevalent polytherapy. However, the combinations that were prescribed contradicted ILAE guidelines. A study conducted by **Nicholas P Poolos et al (2018)[21]** concluded that for treating refractory epilepsy with monotherapy the best response was observed in the lowest quartile of dosage range. In our study there was no patient on monotherapy and the patients on polytherapy i.e. 87.5% were started on low dose. Of whom 62.5% of them responded well. P value (0.097) calculated showed no significant association of individual AED when used in different combinations to treat drug Refractory epilepsy.

CONCLUSION:

Our study provides an insight in the prevalent utilization and the relevant differences in the use of older and newer generation Anti-epileptics for

epileptic & non-epileptic neurological conditions. 1st generation & 2nd generation AEDs were more commonly prescribed in epileptic conditions, while non-epileptic conditions were frequently prescribed with 3rd generation AEDs. Females were more prevalent over male, GTCS was the most common diagnosis in both the genders. Unlike previous studies majority of epileptic patients were prescribed with 1st generation narrow spectrum AED phenytoin followed by levetiracetam, a broad-spectrum AED. Clobazam was commonly used as an adjunctive therapy. Nevertheless, rational Polytherapy was more frequently adopted over monotherapy. Newer 3rd generation AED lacosamide was prescribed as an additional adjunctive treatment in partial & secondarily generalized seizures who have not been adequately controlled with 1-3 concomitant AEDs. Prescribing patterns in non-epileptic conditions depicted the use of 3rd generation AEDs gabapentin & pregabalin. Maximum utilization of Gabapentin monotherapy followed by pregabalin was observed. There was a rising trend in prescribing pattern of anti-epileptics (pregabalin & gabapentin) in combination with tricyclic anti-depressants (amitriptyline & nortriptyline) for different types of neuropathic pains. The current and the future design of prescriptions for newer AEDs harbours potentiality new AEDs also include a potential in the treatment of nonepileptic CNS disorders like bipolar disorder and various neuropathic pains. The global market size of each of these two indications is similar to that of epilepsy, whereas they both have fewer approved drugs for treatment than epilepsy. therefore, a new AED with additional indications in bipolar disorder and neuropathic might have a potent market size 3 times larger than epilepsy alone. Antiepileptic regimens utilized in drug refractory epilepsy showed different combinations of newer & older generation the most frequent combination being phenytoin with sodium valproate & levetiracetam. Use of lacosamide & controlled release carbamazepine was also observed. Albeit not cost effective, these formulations offer ease of administration due to less frequent dosing and better compliance. However, there is a need for new pharmacological paradigms to tackle the problem of intractable epilepsy.

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