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Original Article

DRUG UTILIZATION EVALUATION OF ANTIEPILEPTICS IN THREE SELECTED MULTIDISCIPLINARY TEACHING HOSPITALS OF PAKISTAN

FAIZAN MAZHAR[1, 2], SUMBUL SHAMIM[2], SAIMA MAHMOOD MALHI[2]

[1]Dow University Hospital, Dow University of Health Sciences, OJHA Campus, Karachi, Pakistan. [2]Dow College of Pharmacy, Dow University of Health Sciences, OJHA Campus, Karachi, Pakistan.
Email: smmhej@gmail.com

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ABSTRACT

Objective: To identify the utilization pattern of antiepileptic drugs (AEDs) in a representative sample of the Pakistani population. To highlight the main risk factors associated with different forms of epilepsy.

Methods: A retrospective drug utilization review study was conducted at three teaching institutions of Karachi. During the nine months study period, epileptic and non-epileptic patients who were prescribed with AEDs were enrolled consecutively. Data were collected through the integration of computerized records and standard performa to retrieve information on age, gender, diagnosis, type of seizure and AEDs data. The results were analyzed by univariate statistics.

Results: Total 622 patients i.e., 426 epileptic and 196 non-epileptic patients who were prescribed with AED were analyzed in the study. The age ranged from 0.1 to 82 years (median, 36), there were 56% male and 44% female patients. Simple partial seizure (28%) was most common type of seizures. Monotherapy accounted for 77% of total epileptic patient. Idiopathic/cryptogenic was most common etiology of epileptic seizure (41%). CNS infections (57%) was leading cause of symptomatic epilepsy. Most prevalent utilization of AEDs for non-epileptic condition was neuropathic pain (55%). In epileptic patients, Valproate (17%) and diazepam (14%) whereas in non-epileptic patients, gabapentin (26%) and pregabalin (20%) was most commonly prescribed drugs.

Conclusion: Despite the availability of newer antiepileptics in Pakistan, the domain of classic agents were still dominated in pharmacotherapy of epileptic seizure. The utilization patterns reported here are in agreement with general guidelines except for extensive prescribing of diazepam and some drug that use off label.

Keywords: Antiepileptics, Seizures, Drug Utilization Review, Prescription.

INTRODUCTION

Epilepsy is a neurological disorder that results from recurrent, unprovoked and hyperchronous discharge of a set of neurons in brain and referred as epileptic seizures (1). It affects about 50 million people worldwide (2) while in general population of Pakistan the prevalence of disease is 9.99 per 1000 people (3) and the figure is twice in urban areas (4). Although a number of antiepileptic drugs (AEDs) are available for the treatment of epilepsy, however, the preferred approach for the management of epilepsy is monotherapy with antiepileptic drugs (5). Furthermore, about 50 % of patients can be managed successfully with the first or second antiepileptic drug (AED) that they are prescribed with (6). However, patients who do not become seizure free with monotherapy require AED polytherapy.

In neurology and psychiatry, AEDs are used extensively to treat multiple non-epilepsy disorders in addition to the epileptic reasons (7). Likewise, there are some co-morbid conditions associated with epilepsy, such as mood disorders and migraine that may often respond to treatment with AED (8). There are number of non-epileptic conditions such as neuropathic pain, migraine, essential tremor, spasticity, restless legs syndrome, bipolar disease, schizophrenia, and anxiety disorders in which both classic and newer AEDs may be used. Correspondingly, other disorders where AEDs may be of clinical importance include traumatic brain injury (that require neuroprotection) (9), Parkinson's or Alzheimer's disease, alcohol abuse and obesity (10).

Drug utilization review (DUR) is a review and assessment of the appropriateness of prescription drug use and also the prescribing patterns (11). Additionally, DUR includes healthcare provider which prescribe the drug, a dispensing pharmacist and the consumer that use the drug i.e. patient. In other words, a drug utilization study describe the users of a given drug or class of drugs and/or the conditions of use in quantitative and qualitative terms (12). As drug utilization studies serve as a mean to interpret, intervene and promote the rational prescribing, dispensing and administration of medication. Thus, the ultimate outcomes of DUR are: improved quality of patient care, better therapeutic outcomes and cost-effective pharmacotherapy. Currently, there are about sixteen classic and newer antiepileptics that are registered for the use in Pakistan but to date, there has been no study that reports their utilization patterns. This is the first description of the AEDs demographics in a Pakistani population that aims (a) to analyze and evaluate the utilization pattern of AEDs in the treatment of different types of seizure and non-epileptic disorders (b) to identify the types and etiology of seizure and to get an insight about the prevalence of off-label prescribing of AEDs.

MATERIALS AND METHODS

Study site and patient population

This retrospective DUR study was conducted at in-patient and outpatient departments of three selected tertiary care teaching hospitals of Karachi namely, DOW University hospital, Civil Hospital and Jinnah Post Graduate Medical Centre which are 500, 1900 and 1000 bed hospitals, respectively. The time span of study was nine months during which the prescription data of 622 patients were audited objectively. All patients (in and out-patients) who were prescribed with AEDs were considered for analysis.

Patient identification

Data from patients admitted or visit to the three teaching hospitals during June 2012 to Feb 2013 were included in the study. Out-patients and emergency out-patients were identified through pharmacy drug prescriptions. In-patients were identified by on duty clinical pharmacist using the wards' census registers.

Data source and data collection

For out-patient and emergency out-patients a well-designed performa was filled for each prescription containing AED by a pharmacist that fill the prescription, with the integration of computerized medical records and interviews by prescribing clinician, patients and/or by their attendant where necessary. The following data were retrieved: demographic data (age and gender), diagnosis, type and etiology of seizures and prescribed AEDs.

Data collection for in-patients was done by on duty clinical pharmacist through demographics, admission notes, past medical history. Diagnosis and medications prescribed were recorded from daily reviews of clinicians' notes and treatment charts respectively. When necessary, clinicians were interviewed for clarification of their notes on the information on diagnosis and/or intended purpose for AEDs use. Where applicable, data on diagnosis or disorder for which AEDs prescribed were coded using the World Health Organization (WHO) International Statistical Classification of Diseases, 10th Revision (ICD-10) (13) in order to maintain data uniformity. WHO anatomic therapeutic chemical (ATC; www.whocc.no) system was used to classify Antiepileptic drug.

Inclusion criteria: Epileptic and non-epileptic patients of all age groups who were prescribed AEDs.

Exclusion criteria: Patients with sleep disorders (ICD10- G47) and those in-patients in which Benzodiazepine derivatives (N05BA) were prescribed for sedation purpose.

Data quality

Collected data were thoroughly reviewed by academic pharmacologist to maintain the quality of data. Transcripted data were also reviewed against data-collection performa to minimize transcription errors.

Classification of seizure

The epileptic seizures were grouped according to the classification of the International League Against Epilepsy: (a) Partial seizure (Simple partial, complex partial/focal and secondary generalized0) (b) Generalized seizure (tonic–clonic, absence, myoclonic, clonic, tonic and atonic) (c) Unclassified seizure.

Aetiologies classification of seizure

The following modified ILEA classification for aetiologies of epilepsies (12, 14) were considered: idiopathic / cryptogenic, symptomatic, status epilepticus (ICD10-G40.3) and unknown diagnosis.

Non-epileptic disorders

Three major non-epileptic indication of AEDs were identified and they were categorized into four categories: (1). Neuropathic pain (2). Psychiatric disorders (3). Cerebrovascular disease (4). Other or unknown. Whether medications were prescribed as indicated or "off-label" was assessed using the British national formulary 63 (15)

Antiepileptic drug classification

AEDs were defined as drugs with the ATC codes N03A, N05BA01 (diazepam), N05BA06 (lorazepam), N05BA09 (clobazam), N05CD08 (midazolam). As eslicarbazepine (N03AF04), felbamate (N03AX10), lacosamide (N03AX18), perampanel (N03AX22), retigabine (N03AX21), rufinamide (N03AF03), stiripentol (N03AX17), sultiame (N03AX03), tiagabine (N03AG06), zonisamide (N03AX15) are not approved for use in Pakistan therefore they were excluded from the study.

Statistical analysis

Where appropriate, data are given as median. Univariate analysis was carried out using SPSS version 20.0 (IBM Corporation, Armonk, New York). Where applicable, differences in frequency of utilization of individual AEDs between groups were compared by the X^2 test.

RESULTS

Patient demographics

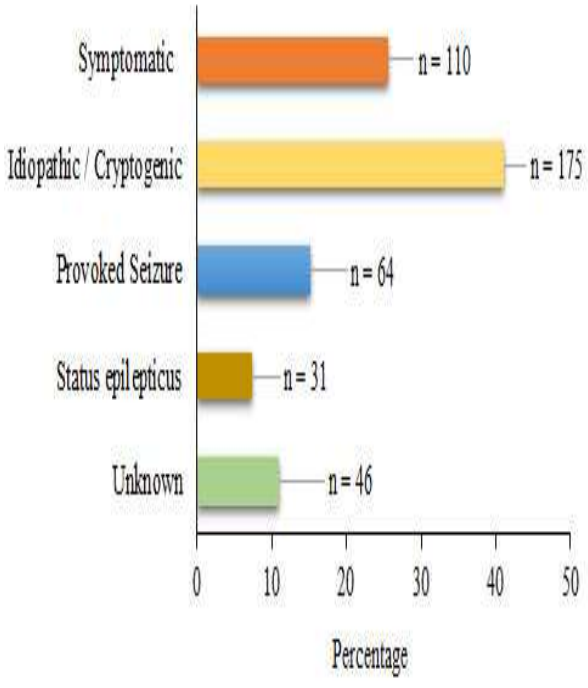
Among 622 patients prescriptions, 426 were epileptic patients (55.9 % male, 44.1 % female) and 196 were non-epileptic patients (55.6 % male, 44.4 % female) Table 1. The age ranged from 0.1 to 88 years (median, 36 years) with 24.75 % of patients being younger than 19 years of age. At the time of the survey, among the 622 patients in which AEDs were prescribed, 279 patients (44.9 %) were treated as in-patients, 242 (38.9 %) and 101 (16.2 %) were seen on out-patient and emergency out-patient basis respectively.

Classification of epileptic seizure and mode of treatment

The types of epileptic seizure as well as the mode of treatment are summarized in Table 2. Out of 426 epileptic patients, seizure types were identified in 417 patients. Among all seizure types, simple partial seizures were accounted for 28.1% followed by generalized tonic–clonic seizures (23.5 %). Of the 426 AED users, three hundred and twenty three patients were on monotherapy (77.5 %) and seventy of them were on combination of two AEDs (17.1 %). Combination of more than two AEDs (polytherapy ≥ 3 AEDs) was used in 24 patients (5.8 %). Monotherapy were significantly higher ($P < 0.001$) in generalized seizure (n=155, 60.3%) in contrast to focal (n=102, 39.7%).

Etiological Classification of seizure

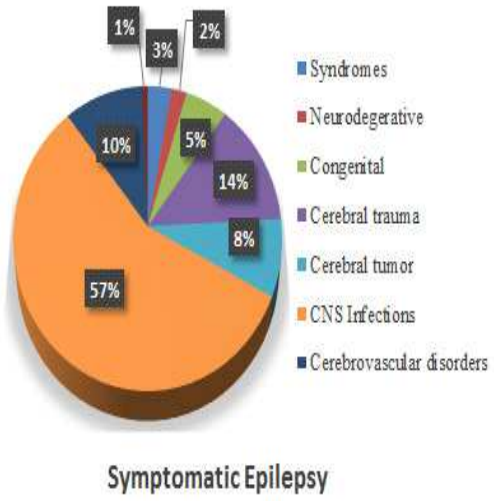
Four major types of seizure etiology were identified, the etiology or diagnosis were categorized accordingly (Fig. 1). Of the 426 epileptic patient, there were 380 (89.2%) patient in which seizure etiology or diagnosis were identified. In remaining 46 (10.8%) patient the seizure etiology or diagnosis were un-identified. The cryptogenic/idiopathic were accounted for most common cause of epileptic seizures (n=175, 41.1 %). Symptomatic epilepsy was found in 110 (25.8%) patients which is followed by provoked epilepsy (n=64, 15 %). Among the symptomatic epilepsy, the proportion of CNS infection (n=62, 62.2%) was significantly high ($P < 0.05$) in comparison to other causes (n=37, 37.4%; Fig. 2). High grade fever (n=42, 9.9%) was the most common cause of provoked epilepsy.



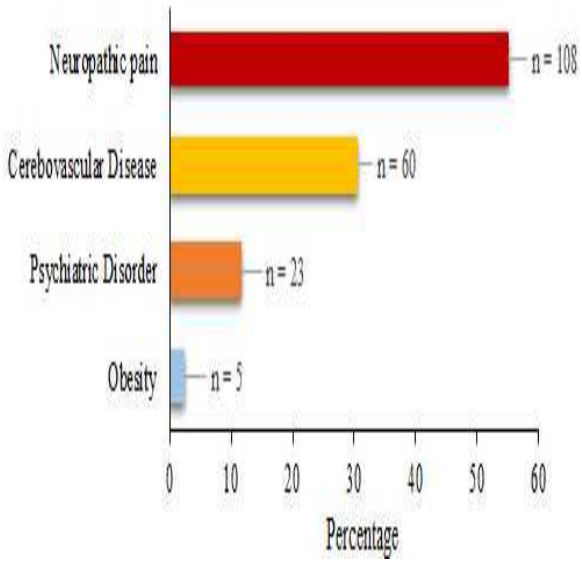
Fig, 1: Etiological classification of seizures.

Table 1: Patient Demographics (N=622)

SEX	Epileptic patients		Non-Epileptic patients		Total
	n	*%*	*n*	*%*	
Male	238	55.9	109	55.6	
Female	188	44.1	87	44.4	
AGE					
<1	19	4.5	0	0	**19**
1-4	20	4.7	0	0	**20**
5-9	31	7.3	4	2	**35**
10-19	82	19.2	21	10.7	**103**
20-29	70	16.4	27	13.8	**97**
30-39	68	16.0	24	12.2	**92**
40-49	38	8.9	28	14.3	**66**
50-59	40	9.4	33	16.8	**73**
60-69	38	8.9	39	19.9	**77**
>70	20	4.7	20	10.2	**40**
TOTAL	**426**		**196**		**622**
In-Patient	236	31.2	43	21.9	**279**
Out-Patient	133	13..4	109	55.6	**242**
Emergency	57	13..4	44	22.4	**101**
Out-Patient					



Fig, 2: Etiology of symptomatic epilepsy.



Fig, 3: Distribution of non-epileptic AED users according to indication/diagnosis

Distribution of non-epileptic AED users according to indication/diagnosis

Distribution of non-epileptic AED users according to indication/ diagnosis are summarized in Fig. 3. In a total population of non-epileptic AED user (n=196), one-hundred-eight patients were found to use AEDs for neuropathic/neurological disorders (55.1%), twenty three for psychiatric disorders (11.7%) and sixty for cerebrovascular disease (30.6%) and remaining 2.5 % were treated for obesity. Most common non-epileptic conditions in which AEDs were used are traumatic brain injury (n=39, 19.9%) followed by diabetic neuropathy (n=35, 17.9%) and migraine (n=21, 10.7%).

Overall utilization of AEDs in epileptic and non-epileptic patients

Table 3 summarizes the overall utilization of AEDs in epileptic and non-epileptic patients. Regardless of AED mode of treatment (monotherapy, dual or poly-therapy), in epileptic patients valproate accounted highest utilization rate (16.8 %) followed by diazepam (14.4 %) and Phenytoin (13%). In non-epileptic patients most frequently prescribed AED was gabapentin (10.2%). However pregabalin (8%) accounted for second most commonly used AED in non-epileptic patients.

During the period of study about 82% AEDs were prescribed according to labeled indication and 18.1% prescribed for off-label use.

Anti-epileptic abbreviated as CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; DZ, Diazepam; GBP, Gabapemtin; LTG, lamotrigine; LEV, Levetiracetam; LZP, Lorazepam; MDZ, Midazolam; OCBZ, Oxcarbazepine; PHE, Phenobarbital; PHT, Phenytoin; PGB, pregabalin; TPM, Topiramate; VPA, valproate ; VGB, Vigabatrin.

Seizure specific utilization frequency of AED as monotherapy

Monotherapy was used in 323 (77.2%) epileptic patients. Most frequently used AEDs as monotherapy in focal seizure was lamotrigine (n=26, 20 %) and topiramate (n=16, 12.3%). Whereas valproate (n=33, 21.3%) and diazepam (n=26, 16.85%) was the most common AEDs used in monotherapy of generalized seizures. Utilization pattern of different AEDs monotherapy in different type of seizures are highlighted in Table 4.

Table 2: Classification of Epileptic Seizure and Mode of Treatment (N=417)

Seizure Type		Monotherapy	Dual Therapy	Poly-Therapy	n	%
Focal	Simple Partial seizure	103	10	4	117	28.1
	Complex partial seizures	24	19	2	45	10.8
	Secondarily generalized	3	1	1	5	1.2
	Atonic seizures	3	2	0	5	1.2
Generalized	Atypical Absence seizure	0	1	0	1	0.2
	Clonic seizures	40	6	2	48	11.5
	Myoclonic	10	4	0	14	3.4
	Tonic seizures	27	4	2	33	7.9
	Tonic–clonic seizures	70	18	10	98	23.5
	Typical Absence seizure	5	0	0	5	1.2
	Unclassified	38	5	3	46	11.0
	n	323	70	24		
	%	77.5	17.1	5.8		

Table 3: Overall utilization of aeds in epileptic and non-epileptic patients

Anti-epiletic	Epileptic patients		Non-Epileptic Patients	
	n	%	n	%
CBZ	20	3.7	3	1.4
CLB	11	2	1	0.4
CZP	27	4.9	5	2.3
DZ	79	14.4	7	3.3
GBP	9	1.6	56	26
LTG	43	7.9	15	7
LEV	46	8.4	17	8
LZP	26	4.8	-	-
MDZ	9	1.6	-	-
OXCBZ	17	3.1	3	1.4
PHE	30	5.5	1	0.5
PHY	71	13	18	8.4
PGB	3	0.5	44	20.5
TPM	49	9	14	6.5
VPA	92	16.8	30	14
VGB	15	2.7	-	-

Table 4: Utilization pattern of aeds monotherapy in different type of seizures

AEDs	Simple Partial seizure				Generalized						
	SP	CP	SG	Total	AS	CS	MCS	TS	TCS	TAS	Total
CBZ	4	1	0	5 (3.8%)	0	1	0	3	2	0	6 (3.9%)
CLB	1	0	0	1 (0.8%)	0	0	2	1	2	0	5 (3.2%)
CZP	4	0	0	4 (3.1)	0	4	0	3	3	2	12 (7.7%)
DZ	12	3	0	15 (11.5%)	0	11	2	2	11	0	26 (16.8%)
GBP	-	-	-	-	0	0	2	0	0	0	2 (1.3%)
LTG	24	2	0	26 (20%)	2	0	0	0	1	1	4 (2.6%)
LEV	2	3	1	6 (4.6%)	0	2	0	1	0	0	3 (1.9%)
LZP	2	0	0	2 (1.5%)	0	2	0	1	3	0	6 (3.9%)
MDZ	3	0	0	3 (2.3%)	0	1	0	0	1	0	2 (1.3%)
OCBZ	7	0	0	7 (5.4%)	0	0	1	4	1	0	6 (3.9%)
PHE	10	0	1	11 (8.5%)	0	1	0	2	10	1	14 (9.0%)
PHY	12	2	1	15 (11.5%)	0	5	0	5	11	0	21 (13.5%)
PGB	0	0	0	-	0	0	1	0	0	0	1 (0.6%)
TPM	10	6	0	16 (12.3%)	1	1	0	0	11	0	13 (8.4%)
VPA	9	6	0	15 (11.5%)	0	12	2	5	13	1	33 (21.3%)
VGB	3	1	0	4 (3.1%)	0	0	0	0	1	0	1 (0.6%)

Where: SP, simple partial; CP, complex partial; SG, secondary generalized; AS, atonic seizure; CS, clonic seizure; MCS, myoclonic-seizure; TS, tonic seizure; TCS, tonic-clonic seizure; TAS, typical absence seizure. Refer table 3 for AED abbreviations.

Table 5: Age specific distribution of AEDs

AEDs	Age									
	< 1	**1 - 4**	**5 - 9**	**10 - 19**	**20 - 29**	**30 - 39**	**40 - 49**	**50 - 59**	**60 - 69**	**>70**
CBZ	0	1	1	6	6	1	0	5	2	1
CLB	0	0	0	5	2	2	1	0	1	1
CZP	1	4	1	8	5	3	0	5	4	1
DZ	0	3	10	19	15	21	8	3	7	0
GBP	0	0	1	2	10	12	9	14	11	6
LTG	0	2	3	4	10	2	7	15	10	5
LEV	1	0	0	9	8	13	11	4	11	6
LZP	0	1	0	0	7	6	9	2	1	0
MDZ	0	0	3	2	3	1	0	0	0	0
OCBZ	0	0	1	3	4	2	1	2	4	3
PHE	7	2	2	12	2	0	1	2	2	1
PHY	6	0	7	18	14	11	5	13	8	7
PGB	0	0	0	5	9	3	9	6	9	6
TPM	2	2	5	11	4	11	8	10	5	6
VPA	3	7	5	17	19	33	12	7	16	4
VGB	0	1	1	2	2	2	0	1	4	3

Refer table 3 for abbreviations

Table 6(a,b): Gender specific distribution of AEDs

AEDs		CBZ	CLB	CZP	DZ	GBP	LTG	LEV	LZP	VGB
Female	**n (%)**	11 (47.8)	1(8.3)	14 (43.8)	57 (66.3)	40 (61.5)	28 (48.3)	30 (47.6)	13 (50)	7 (46.7)
Male	**n (%)**	12 (52.2)	11 (91.7)	18 (56.3)	29 (33.7)	25 (38.5)	30 (51.7)	33 (52.4)	13 (50)	8 (53.3)

AEDs		MDZ	OCBZ	PHE	PHY	PGB	TPM	VPA
Female	**n (%)**	2 (22.2)	8 (40)	18 (58.1)	24 (27)	24 (51.1)	35 (54.7)	47 (37.9)
Male	**n (%)**	7 (77.8)	12 (60)	13 (41.9)	65 (73)	23 (48.9)	29 (45.3)	77 (62.1)

Refer table 3 for abbreviations

Gender specific distribution of AEDs

The utilization of all AEDs in male and female were almost equal except diazepam, valproate, and phenytoin. Valproate and phenytoin is found to use more often in men than women ($P < 0.05$) Table 6(a,b). Diazepam was found to use more in female than males ($P < 0.01$).

Most frequent combinations of AEDs

In epileptic patients most frequently prescribed dual combinations of AEDs were diazepam/phenytoin (11.4%) and levetiracetam/valproate (10.5%). In triple AEDs regimen most common AEDs combination was diazepam/phenytoin/valproate. In non-epileptic patients combination of pregabalin/lamotrigine was most frequent.

Age specific distribution of AEDs

Phenobarbitone was found to use more commonly in children's (n=23, 74.2%) which is statistically significantly ($P < 0.01$). Conversely, the utilization rate of phenytoin in adults age groups were significantly high ($P < 0.001$; n=66, 74.2%). Table 5 reports the utilization pattern of AEDs in different age groups of epileptic and non-epileptic patient.

DISCUSSION

Despite the availability of newer antiepileptics in Pakistan, the domain of classic agents were still dominated in pharmacotherapy of epileptic seizure. The utilization patterns reported here are in agreement with general guidelines except for extensive prescribing of diazepam and some drug that use off label.

The present study reports that the proportion of male epileptic patients is more than women in Pakistani patient population that is in consistency with several other studies (16-18). Greater exposure of male gender to risk factors for lesional epilepsy and acute symptomatic seizures were account for this difference. Moreover, about 50% of the epileptic patients who were prescribed with AEDs are younger than 29 years of age. Conversely, in non-epileptic patients the proportion of younger age groups (<29) are smaller (26.5%). Generally, epilepsy affect all age groups but it is presumed that epilepsy is more common in two extremes of ages. And our finding is consistent with previous studies that epilepsy is more prevalent between the ages of 20-40 years (4, 17). Lack of peak in higher age was probably due to lower general population of geriatrics as well as higher younger population of study.

We have found that the most common seizure type was generalized seizures, which is in accordance with the findings of previous epidemiological studies of epilepsy in Pakistan (17). In our study simple partial seizure accounted for 28%, which is highest among all types of partial seizures which has also been reported by Lakhair, *et al.* 2012 and Usman, *et al.* 2007 (17, 18). Correct recognition of seizure type is crucial in pharmacotherapy of epileptic seizures because the effectiveness of AED is greatly influenced by the type of seizure in addition to other factors such as, general medical condition and drug adverse effect profile.

Our data indicated that monotherapy (77.5%) was most frequently use treatment mode in all types of seizure (Table 2). This is in agreement with the findings of previous studies (18-21) that mention that seizure control by use of AEDs in monotherapy is always preferred over dual or polytherapy. Accordingly, monotherapy permits patient compliance, cost minimization and it is associated with lower risk of toxicity profile and drug-drug and drug disease interactions. Our data further demonstrates that dual and poly-therapy was used in 16.8% and 5.8% patients, respectively. Since, some patients did not achieve seizure freedom with one AED and they required two or more AED for seizure control. The failure of AED monotherapy could be associated with multiple factors e.g. pharmacogenetic factors, misinterpretation of seizure type that leads to ineffective AED choice, non-compliance due to adverse effects.

Concerning pharmacotherapy, duration of AED treatment is mainly determined by etiology of seizures. In most epileptic patients the underlying cause is of unknown origin (4) and similar finding was observed in our study. If there is identifiable cause it usually involves some form of brain damage. Head trauma and stroke are

the two most commonly recognized causes. In our study cryptogenic/idiopathic epilepsy were noted in 41% patients, 25.8% had symptomatic epilepsy and provoked epilepsy was found in 15% patients. Singhi reported that in the developing countries, CNS infections are the main culprit of acquired epilepsy (22) .While, our data showed that CNS infections were the most common cause of symptomatic epilepsy (n=62, 62.2%), meningitis and neurotuberculosis being two most recognized CNS infections. Nonetheless, several studies describe that more than 400,000 people in Pakistan are suffering from the tuberculosis every year which is the fifth largest in the world. Also, it has been estimated that approximately 10% of all patients with tuberculosis have CNS involvement and in general, the incidence of CNS tuberculosis is proportional to the prevalence of tuberculous infection (23, 24). Beside this, other CNS infectious disorders include meningitis (both viral and bacterial), malaria and neurocysticercosis. In conjunction, high grade fever was common cause of provoked seizure in children (<18 year, n=33) which was also reported by Tahir (25)while febrile seizure is one of the most common seizure in children's (26, 27).

Interestedly, we found that neuropathic pain disorder is a common non-epileptic condition for which AEDs are mostly prescribed. In our study among non-epileptic AEDs users, the proportion of diabetic patients was high (n=35, 18%). This high proportion is possibly linked with high prevalence of diabetes in Pakistan. It is estimated that the prevalence of neuropathy in diabetes patients is approximately 20% (28). Cerebrovascular disorder accounted for 31% in which patients with traumatic brain injury was most frequent. We found that the use of AEDs for the prophylaxis of posttraumatic seizure was common (20%, n=39). For early pharmacoprophylaxis after severe traumatic brain injury (TBI) phenytoin or valproic acid or carbamazepine is recommended by American Academy of Neurology (AAN) [30] and the Brain Trauma Foundation (29). In practice, phenytoin and valproate were two most frequently used AEDs in TBI, this may be due to their convenient loading by intravenous route and lack of sedative action. Multiple evidences suggest the use of levetiracetam for the prophylaxis of posttraumatic seizure (30, 31) however in our study only 6 patients were prescribed with levetiracetam for prophylaxis of posttraumatic seizure. Recently, Kruer *et al.* reported that their findings favor the shift from phenytoin to levetiracetam for the prophylaxis of posttraumatic seizure (32).

Over the period of study the most frequently prescribed AED in epileptic patients was valproate (16.8%). Valproate has wide spectrum of anticonvulsant effect and relatively it is very effective in the treatment of focal and in particular generalized seizures. Diazepam was the second most frequently used AED. Our study includes other benzodiazepines such as clobazam, lorazepam, clonazepam and midazolam that share similar mechanism of action but differ in pharmacokinetic profile which accounts for their clinical difference. Although diazepam is associated with serious troublesome side effects of sedation that affects the individual daily life. Its long term use also associated with cognitive side effects. One of its main advantage over other benzodiazepines is the availability of its rectal form. Nevertheless, diazepam is still among the AED of choice in emergency treatment of acute seizures, status epilepticus and febrile seizures. Some reports suggest that lorazepam is superior over diazepam but in most South Asian countries including Pakistan, intravenous form of lorazepam is not available. Phenytoin was the third most frequently prescribed drug in epileptic patients. Its main mechanism of action include blocking of voltage-dependent neuronal sodium channels that results in limiting repetitive firing of action potentials. Major disadvantages of phenytoin includes its side effects and drug interactions. Gingival hyperplasia, hirsutism, and ataxia are adverse effects of phenytoin that affects the quality of life, its long term use may also lead to development of peripheral neuropathy and osteoporosis (33, 34). DUR among non-epileptic patients exhibited that gabapentin (10.2%, n=56) and pregabalin (8%, n=44) were most commonly prescribed AEDs. Pregabalin is FDA approved for neuropathic pain whereas gabapentin is approved for postherpetic neuralgia in adults. In addition, gabapentin is extensively use off label for management of neuropathic pain associated with various disorders. In epilepsy, both gabapentin and pregabalin are approved as an adjunctive therapy in focal seizures. Lack in drug-drug interaction and low degree of protein binding makes them desirable AEDs for adjunct treatment.

For the treatment of generalized seizures, Valproate (n=33, 21.3%) was the dominating AED of our study that was prescribed as monotherapy. Due to its broad spectrum of activity valproate is used as first line or add-on for both partial and generalized seizures in both adults and children. In our study the valproate monotherapy was mostly used in patients with generalized tonic-clonic seizure (21.7%), clonic seizure (20%) and simple partial seizure (15%). Most clinicians preferred valproate as the first choice for treating generalized tonic-clonic seizures as sodium valproate inhibits epileptiform activity at multiple foci or levels (35). Valproate has multiple mechanisms of action. It augments GABAergic neurotransmission, halt repetitive spike firing by inhibition of voltage gated sodium channels and blocks calcium currents (T-type) to encounter generalized absence seizures. In partial seizures, lamotrigine was the preferred agent. Lamotrigine was prescribed in 67% of patient with simple partial seizures. Although the preferred first line AED for partial seizures is carbamazepine, however lamotrigine is well tolerated when compared to other AEDs, it lacks cognitive side effects that are associated with carbamazepine (36) and have better pharmacokinetic and adverse effect profile.

Those patient who do not achieve seizure freedom with monotherapy are eventually treated with combinations of two or more AEDs for seizure control, improvement of efficacy and tolerability. Our study revealed that the utilization pattern of diazepam/phenytoin (11.4%) and levetiracetam/valproate (10.5%) combination was high among epileptic patients. Rational combination of AEDs should be based on the evidence of synergism and safety. Several evidence suggest that combination of diazepam/phenytoin (i.e. enhancer of GABAergic inhibition/a sodium channel blocker) appears to be advantageous (37, 38). Levetiracetam has unique antiepileptic profile because of its novel mode of action. It has been reported that combination of levetiracetam with other AEDs, in particular valproate shows synergistic effect (39, 40)which justify the rational for the use levetiracetam/valproate combination. Furthermore, when the patient is maintained on an AED that possess enzyme-inhibiting (valproate) or enzyme-inducing activity (phenytoin), levetiracetam is desirable option because of its low risk of pharmacokinetic interactions (41).

Our study revealed that utilization of Phenobarbitone was common in children than in adults. Increase in prescription rate of phenytoin and valproate with age may be linked with increased incidence of symptomatic epilepsy in adult because of greater exposure to risk factors (such as stroke, traumatic brain injury). Moreover, this frequent utilization in adult population might also be justified by the fact that phenytoin and valproate were routinely used in management of acute seizure attacks and pharmacoprophylaxis of post traumatic seizure. We found that there is a decline in diazepam prescription in older adult population (>60 years) which could be explained by its slow metabolism, cognitive side effects and greater risk of apnea and falls in geriatrics (42).

Compared with male, female were prescribed with valproate and phenytoin less frequently, and more frequently with second antiepileptics. Both, phenytoin and valproate are known teratogens and categorized in FDA pregnancy risk category D for treatment of epilepsy however, very recently base on the findings of Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study; FDA advised to change valproate labeling from Category D to category X for the indication of migraine prophylaxis in pregnant women (FDA Medwatch). In addition to their teratogenicity, phenytoin also associated with cosmetic side effects (hypertrichosis, hirsutism, and coarsening of facial features, gingival hyperplasia). These adverse effects and teratogenic potential could explain lower utilization of phenytoin in female population.

Finally, we have also compared the pattern of AEDs utilization of the present study with other countries (Table 7). Classic anticonvulsant such as phenytoin and valproate are still considered as first line treatment for certain types of epileptic seizures. One difference that

observed in utilization pattern of AEDs of present study is high utilization rate of diazepam. Despite the availability of newer AEDs such as pregabalin, gabapentin and vigabatrin, they were not often used as compared to classic AED.

Table 7: Comparison of AED utilization pattern with other countries

Country	Year of study	Most frequently used AED (%)	Ref.
India	2011	PHE (56), PHY (35), VPA (22)	(43)
India	2013	PHY (43), PHE (41), CBZ (16)	(44)
India	2008	VPA (24), CBZ (23), PHY (17)	(45)
Germany	2009	VPA (30), CBZ (26), LTG (21)	(46)
India	2011	CBZ (44), PHE (25), VPA (21)	(47)
India	2013	PHY (42), VPA (41), CBZ (25)	(48)
Italy	1986	PHE (77), PHY (31), CBZ (29)	(49)
Australia	2007	VPA (35), CBZ (17), PHY (15)	(50)
U.K	1998	VPA (36), CBZ (37), PHY (30)	(51)
U.K	2000	CBZ (30), PHY (30), VPA (25)	(52)
Italy	2007	OXCBZ (25), CBZ (17), LTG (12)	(53)
Taiwan	1999	CBZ (57), PHY (32), VPA (31)	(54)
U.S.A	1993	PHY (48), CBZ (31), PHE (18)	(20)
Oman	2000	VPA (49), CBZ (44), PHY (12)	(55)
Present Study	2012	VPA (17), DZ (14), PHY (13)	-

Refer table 3 for abbreviations

CONCLUSION

Despite the availability of newer AEDs, use of classic AEDs is still prevalent. Most prominent type of seizure were generalized tonic-clonic. Our data indicate that CNS infections are main offender of symptomatic epilepsy. Epilepsy is more prevalent in male gender. Monotherapy was most frequently used in all types of epileptic seizures. Valproate, diazepam and levetiracetam are most frequently utilized AEDs in epileptic patient. Most common non-epileptic problem for which AEDs utilized is neuropathic pain. Most commonly prescribed AED in non-epileptic population is gabapentin followed by pregabalin. Phenytoin and valproate were predominantly used in male patients. The present study provides valuable data of utilization patterns of AEDs that may be utilized in updating the current treatment guidelines.

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CONTRIBUTIONS OF AUTHORS STATEMENT

1. **FAIZAN MAZHAR**: literature search, study design, data collection, data analysis, data interpretation, writing
2. **SUMBUL SHAMIM:** data interpretation and manuscript review.
3. **SAIMA MAHMOOD MALHI:** study design, data analysis, manuscript review and discussion writing.

CONFLICT OF INTEREST STATEMENT

We have no conflict of interest to declare

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