

# Prescribing Patterns of Antiepileptic Drugs in Epilepsy Patients: A Picture from the Therapeutic Drug Monitoring Unit in a Medical Institute in Manipur

Ngangom Gunindro<sup>1</sup>, Sania Monica Kholi<sup>2</sup>, Yumnam Sarita Devi<sup>3</sup>, Leishangthem Joshila<sup>3</sup>, N. Hemantakumar<sup>5</sup>, Krishna Pramodini Devi<sup>6</sup>

## ABSTRACT

**Introduction:** Although epileptic seizures can be controlled with monotherapy in most cases, polytherapy is used for refractory cases. A number of studies have reported the prescription patterns of antiepileptic drugs in different parts of India. Such reports are lacking in Manipur. Therefore, the present study was planned to know prescribing patterns of antiepileptic drugs in epilepsy patients in Manipur.

**Material and Methods:** A retrospective cross-sectional analysis of prescriptions of epilepsy patients attending Therapeutic Drug Monitoring (TDM) unit in the Regional Institute of Medical Sciences, Imphal, Manipur was planned. Prescriptions of 65 epilepsy patients attending TDM unit during November, 2013 to January, 2017 were analysed with respect to demographic profiles, seizures types and number of drugs prescribed. Results were expressed in percentages.

**Results:** Out of 65 patients, 64.61% were males. Undetermined seizures were 35.38% followed by generalised tonic clonic seizure (26.15%), complex partial seizures (21.54%), secondarily generalised (12.31%) and simple partial seizures (4.61%) respectively. Two drugs combinations were found in 38.46% followed by 1 drug treatments (35.38%), 3 drugs (16.92%) and 4 drugs combinations (9.23%) respectively. Most commonly prescribed drugs were Oxcarbazepine in monotherapy (47.83%), Oxcarbazepine with Clobazam in 2 drugs combinations (36%), Oxcarbazepine, Clobazam with Levetiracetam in 3 drugs combinations and Oxcarbazepine, Phenobarbitone, Levetiracetam and Divalproex in 4 drugs combinations (33.33%).

**Conclusion:** Newer antiepileptic drugs were more frequently prescribed. Oxcarbazepine topped the list of prescriptions followed by Clobazam and Levetiracetam. Two drugs combination treatment was the commonest approach followed by monotherapy.

**Keywords:** Antiepileptic Drugs, Prescribing Pattern, Monotherapy, Polytherapy

well designed longitudinal study in a heterogeneous urban Indian population shows an age-standardized incidence rate of 27.3/100,000 per year.<sup>4</sup>

Frequent or intractable seizures often lead to poor quality of life in epilepsy patients.<sup>5</sup> In fact, epilepsy imposes substantial economic burden to the patients and their families.<sup>6</sup> The treatment of epilepsy aims at achieving seizure freedom while minimizing adverse effects of treatment. However, seizure-freedom is often over-emphasized at the expense of inducing adverse effects.<sup>7</sup>

As many as 24 antiepileptic drugs (AEDs) have been approved by the United States Food and Drug Administration (US FDA). However, despite the availability of a number of choices of AEDs for treatment, the issue that remains is how to best tailor AED choice of an individual patient.<sup>8</sup> It is reported that seizures can be adequately controlled with one drug in 80% of epilepsy patients and the risk of significant adverse effects and drug interactions increases when more than one drug is prescribed.<sup>9</sup> Usually, AED polytherapy (2 or more drug combinations) is reserved for refractory epilepsy and when such therapy is required, the lowest possible drug load i.e minimum numbers and lowest doses is desirable. While no good evidence for specific AED polytherapy exists, augmenting monotherapy with an AED offering a different or complementary mechanism of action may be considered.<sup>7</sup> There are several reasons for difficulties in choosing optimal polytherapy, the most important reason being limited data regarding favourable or unfavourable combinations.<sup>10</sup> Therefore, a serious thought must always be put at the time of institution of polytherapy.

A number of researchers have done studies to address the prescription patterns and utilization of AEDs in different parts of India. But till today, we have not come across any report of such studies in Manipur. Therefore, to provide a picture on the prescribing patterns of AEDs in epilepsy

## INTRODUCTION

Epilepsy is a condition in which a person has recurrent seizures due to a chronic, underlying process. A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. The incidence of epilepsy is approximately 0.3–0.5% in different populations throughout the world and the prevalence is estimated at 5–30 persons per 1000.<sup>1</sup> Approximately 80% of the epilepsy patients belong to resource poor and developing countries.<sup>2</sup> In India, the overall prevalence of epilepsy is reported as 5.59 - 10 per 1000.<sup>3</sup> A

<sup>1</sup>Associate Professor, <sup>2</sup>Senior Resident, <sup>3</sup>JRF, <sup>5</sup>Professor, Department of Pharmacology, RIMS, Imphal, Manipur, <sup>4</sup>Consultant, Department of Neurologist, Manipur Health Services, India

**Corresponding author:** Dr. Ngangom Gunindro, Department of Pharmacology, RIMS, Imphal, Manipur, PIN-795004, India

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patients in Manipur, we planned to evaluate prescriptions of epilepsy patients attending the Therapeutic Drug Monitoring (TDM) unit in the Department of Pharmacology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur with respect to demographic profiles, types of seizures and number of drugs used.

## MATERIAL AND METHODS

The study was conducted after approval of the protocol by the Institutional Ethics Committee (renamed as Research Ethics Board), RIMS, Imphal. A retrospective cross-sectional analysis of the medical records of epilepsy patients attending the TDM unit of antiepileptic drugs in the Department of Pharmacology, RIMS, Imphal was taken up. For a total of 65 epilepsy patients who attended the TDM unit during the period from November, 2013 to January, 2017, the prescriptions were analysed with respect to the demographic profiles, types of seizures and number of drugs used. Results were expressed as percentages.

## STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Descriptive

Age (years)	Number	%
<11	13	20
11-20	13	20
21-60	34	52.31
>60	5	7.69
Sex		
Male	42	64.61
Female	23	35.38

**Table-1:** Demographic profiles (Total number of patients = 65)

statistics like percentages were used for the analysis.

## RESULTS

Out of 65 patients attending the TDM unit, 64.61% were males and 35.38% were females. Majority of the epilepsy patients (52.31%) belonged to the age group 21- 60 years (Table 1). The types of seizures were undetermined in 35.38% of the cases followed by generalised tonic clonic seizure (26.15%), complex partial seizures (21.54%), secondarily generalised (12.31%) and simple partial seizures (4.61%) respectively. Two drugs combinations were the most frequent prescriptions (38.46%) followed by one drug treatments (35.38%). Three drugs combinations were used in 16.92% patients while 9.23% patients received combinations of four drugs (Table 2).

In totality, Oxcarbazepine was the most commonly prescribed AED (70.77%), followed by Clobazam (36.92%), Levetiracetam (27.69%), Phenytoin (23.08%), Divalproex (13.85%), Carbamazepine (9.23%) and Topiramate (9.23%). A few patients received sodium valproate, Phenobarbitone and Lamotrigine (3.08% each). Average number of AEDs prescribed per patient was 2 (Table 3).

Oxcarbazepine was the most frequent drug in monotherapy (47.83%) followed by Phenytoin (30.43%) and Carbamazepine (13.04%) respectively. Oxcarbazepine with Clobazam was the most prescribed 2 drugs combination (36%) while Oxcarbazepine, Clobazam with Levetiracetam topped the list of 3 drugs combinations. 33.33% of the 4 drugs combinations comprised of Oxcarbazepine, Phenobarbitone, Levetiracetam and Divalproex combination (Table 4).

## DISCUSSION

Seizure type	1 drug (%)	2 drugs (%)	3 drugs (%)	4 drugs (%)	Total (%)
Undetermined	10	7	4	2	23(35.38)
GTCS	6	6	3	2	17(26.15)
CPS	3	8	2	1	14(21.53)
Secondarily generalized	3	3	2		8(12.31)
SPS	1	1		1	3(4.61)
Total	23(35.38)	25(38.46)	11(16.92)	6(9.23)	65

Undetermined = Seizure disorders found unclassified, GTCS = Generalized tonic clonic seizure, CPS = Complex partial seizure, SPS = Simple partial seizure.

**Table-2:** Reported seizure types and number of drugs prescribed

Drug	Number	%
Oxcarbazepine (OCB)	46	70.77
Clobazam (CLO)	24	36.92
Levetiracetam (LEV)	18	27.69
Phenytoin (PHT)	15	23.08
Divalproex(DIV)	9	13.85
Topiramate (TOP)	6	9.23
Carbamazepine (CBZ)	6	9.23
Sodium valproate (VAL)	2	3.08
Phenobarbitone (PHB)	2	3.08
Lamotrigine (LTG)	2	3.08
	Total = 130	

Average number of antiepileptic drugs prescribed per patient (Total number of antiepileptic drugs ÷ Total number of patients) = 130 ÷ 65 = 2.

**Table-3:** Total antiepileptic drugs prescribed (Total number of patients = 65)

Regime	Drug	Number (%)	Regime	Drug	Number (%)	
1 drug	OCB	11 (47.83)	3 drugs	OCB+CLO+LEV	3 (27.27)	
	PHT	7 (30.43)		OCB+CLO+DIV	2 (18.18)	
	CBZ	3 (13.04)		PHT+CLO+LEV	2 (18.18)	
	CLO	1 (4.35)		OCB+PHT+DIV	1 (9.09)	
	VAL	1 (4.35)		OCB+TOP+LEV	1 (9.09)	
	Total = 23			OCB+TOP+CLO	1 (9.09)	
2 drugs	OCB+CLO	9 (36)		OCB+PHT+CLO	1 (9.09)	
	OCB+LEV	6 (24)		Total = 11		
	OCB+TOP	2 (8)		4 drugs	OCB+PHB+LEV+DIV	2 (33.33)
	OCB+DIV	2 (8)			OCB+CLO+DIV+LEV	1 (16.67)
	OCB+VAL	1 (4)	OCB+CLO+DIV+TOP		1 (16.67)	
	OCB+PHT	1 (4)	OCB+CLO+LTG+LEV		1 (16.67)	
	PHT+LTG	1 (4)	CBZ+CLO+PHT+LEV		1 (16.67)	
	PHT+CLO	1 (4)	Total = 6			
	CBZ+TOP	1 (4)				
	CBZ+LEV	1 (4)				
	Total = 25					

**Table-4:** Antiepileptic drug regimes prescribed

In our study, Phenytoin, Carbamazepine, Sodium valproate and Phenobarbitone were the conventional (older) antiepileptic drugs found prescribed. Prescriptions of a number of newer AEDs were also present and these drugs included Oxcarbazepine, Clobazam, Levetiracetam, Divalproex, Topiramate and Lamotrigine. Independent of drugs prescribed either as monotherapy or combination therapy, Oxcarbazepine constituted 70.77% of all the prescriptions followed by Clobazam (36.92%) and Levetiracetam (27.69%) respectively. This observation was in contrast to some study reports where the older drugs were more frequently prescribed.<sup>11,12</sup> Out of the 65 patients, 64.61% were male patients and similar pattern were also reported in some Indian studies.<sup>13,14</sup>

Although the use of Phenytoin had declined due to more adverse effects as compared with either Carbamazepine or Valproate, we observed more prescriptions of Phenytoin among the older drugs in our study (Table 3). This could have been because of higher efficacy and low cost of phenytoin to control epileptic seizures.<sup>14</sup>

Oxcarbazepine, is an analogue of Carbamazepine with comparable spectrum of efficacy and side effects to Carbamazepine. More prescriptions of Oxcarbazepine could have been because of its advantages over Carbamazepine in terms of lack of induction of hepatic enzymes, no auto-induction of metabolism and fewer pharmacokinetic interactions. In addition, two-thirds of the patients who are allergic to Carbamazepine can tolerate Oxcarbazepine.<sup>15</sup> We observed that combination drug treatments constituted majority of the prescriptions. Two drugs combinations topped the list followed by monotherapy, three and four drugs combinations respectively. This observation was in contrast to several other studies where a higher percentage of patients were prescribed monotherapy.<sup>16,17,18</sup>

The newer AEDs – Clobazam, Levetiracetam, Topiramate, Divalproex and Lamotrigine were mostly used as add-on drugs. Clobazam is a non-sedating, well tolerated

benzodiazepine with low cost and good efficacy in most seizure types.<sup>19</sup> Levetiracetam, a newer broad spectrum AED with excellent safety record, with essentially no medically dangerous side effects is used widely as add-on and monotherapy. Topiramate has proven efficacies against partial and generalised seizures while Lamotrigine is clearly effective against all seizure types, including absence seizure. The near absence of sedative and cognitive side effects make Lamotrigine a unique drug among the AEDs.<sup>20</sup> Both Topiramate and Lamotrigine are not associated with clinically significant interactions with other AEDs, although hepatic enzyme inducers can accelerate their metabolisms. The decline in number of prescriptions of Sodium valproate, a drug effective for various seizure types could be due to problematic drug interactions with other AEDs.<sup>15</sup> More frequent prescriptions of Divalproex than Valproate might be related to its enhanced tolerability. If this could be the reason, then a serious consideration should be given to the low peak Valproate concentration associated with Divalproex which could reduce its effectiveness.<sup>21</sup>

In recent years, the drugs approved for epilepsy are increasing and newer AEDs provide the clinicians with a wider choice to help patients achieve therapeutic goals for cases not responding to a conventional AEDs.<sup>14</sup> The aim of epilepsy treatment is to achieve the complete seizure control, or if not possible, to reduce the seizure frequency and severity with minimal adverse effects of treatment. Therefore, optimal use of AEDs is the key to standard treatment. One must remember that the choice of drugs depends on many factors e.g. seizure type and severity, drug availability, efficacy, adverse effect profile, ease of use, affordability, age, sex, compliance, pregnancy, concurrent systemic diseases etc.<sup>22</sup> Our study has limitations. Being a retrospective cross-sectional study, there is restraint on data acquisition. As the study confines exclusively to the records of patients attending the TDM unit, the sample size is small, and hence, the percentages might not be the true representations of

the evaluated parameters. Nonetheless, the study shows some ideas on the common types of epilepsy, demographic parameters and patterns of AED prescriptions in patients with epilepsy in Manipur.

## CONCLUSION

Newer AEDs were more frequently prescribed and Oxcarbazepine topped the list of prescriptions followed by Clobazam and Levetiracetam. Among the older drugs, Phenytoin was most frequently prescribed. Two drugs combination treatment was the commonest approach followed by monotherapy.

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