

## Assessment of antiepileptic drugs usage in a South Indian tertiary care teaching hospital

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### Abstract

A prospective observational study was conducted to assess the antiepileptic drugs (AEDs) usage, drug related problems and medication adherence behavior among enrolled epileptic patients in a South Indian tertiary care teaching hospital. The prescriptions from 439 patients containing AEDs were analyzed for number of AEDs prescribed and for potential drug related problems. Morisky's Medication adherence scale was applied to study the medication adherence behaviour of enrolled patients and those patients were also monitored to identify the adverse drugs reactions. Monotherapy was initiated in 61.9% patients, and when proven ineffective in controlling seizures dual therapy was initiated in 28.7% of patients and three drug therapy in 8.4% patients. Phenytoin (42.1%) was the most frequently prescribed AED followed by valproic acid (41.0%). Forty five adverse drugs reactions were reported during the study period. Phenytoin (53.3%) and valproic acid (26.7%) were the major drugs implicated for adverse drugs reactions. During the follow up visits, 96.6% of the patients were highly adherent to the prescribed medications, although less than half of the patients attended outpatient follow up.

### INTRODUCTION

Next to stroke and dementia, epilepsy is the most common neurological condition seen by Neurologists all over the world, with higher prevalence in developing countries.<sup>1,2</sup> Worldwide prevalence of the active epilepsy ranges from 4 to 5 per 1000 population<sup>3</sup> and in India, the prevalence rate of epilepsy ranges between 4.15 and 7.03 per 1000 population.<sup>4</sup> In newly diagnosed cases, 60% are partial and 40% generalized. Epilepsy adversely affect the psycho-social status and quality of life of patients.<sup>5</sup> General approaches for epilepsy management involves identification of goals and development of care plan. Treatment goals is the same for all patients irrespective of seizure types and age.<sup>6</sup> The ultimate goal is seizures freedom without adverse effects of medication and improved quality of life.<sup>7,8</sup> The choice of most appropriate antiepileptic drug (AED) depends on classification of seizures and age of patient.<sup>8,9</sup> Seizure control may be achieved by monotherapy in about 80% of the patients, with the other 20% requiring two to three AEDs.<sup>6</sup> Monotherapy is normally the first line of treatment, as it has less drug interactions and side effects; lower cost, better tolerability, medication adherence, and quality of life. When choosing an AED, factors such as mechanism

of action, ease of dosing, efficacy, long term adverse effects, neuropsychiatric profile, sedative burden, interaction with other medications, seizure types and other co-morbid conditions should be considered.<sup>10,11</sup> Usage of AEDs differs in different geographical regions, depending partly on economic development and drug availability. This is a descriptive study of the prescribing pattern of AEDs in a tertiary care teaching hospital in South India.

### METHODS

This prospective observational study was carried out in JSS Medical College Hospital, Mysore, India, It was carried out over a period of 6 months from June to December 2009. Out patients and in patients of Neurology Department and in-patient of Medicine Department with a clinical diagnosis of epilepsy meeting the inclusion criteria were enrolled in to the study. The institutional ethical committee of the hospital had approved the study. The demographic details, clinical diagnosis, seizure type, dose, frequency and dosage of AEDs, tests performed (Therapeutic Drug Monitoring (TDM), laboratory investigations, neurophysiologic and neuroradiological investigations such as CT scan, EEG) were recorded. All prescriptions were assessed for the drug related problems

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such as adverse drug reactions (ADRs), drug-drug interactions (DDI), over dosage, and sub therapeutic dosage. Morisky's medication adherence scale<sup>12,13</sup> (MMAS) was administered on patients to assess the medication adherence behavior. The MMAS have four questions of yes/no type. One point will be given to each 'Yes' answer. Higher score indicates less adherence. WHO Probability Scale and Naranjo's scale was applied to assess the causality of adverse drug reactions associated with AEDs. For control of seizures, "good control" is defined by an absence of seizure activity since prior visit; "fair control" is defined by one seizure since last visit; and "poor control" is defined by more than one seizure since last visit.<sup>6</sup>

## RESULTS

### *Patient characteristics*

The data of 439 patients was reviewed, 404 (92.2%) were inpatients and 35 (7.9%) outpatients. The maximum number of patients enrolled was

in the age group of 11 to 20 years and the age of onset of seizures was found to be less than 10 years in 33.5% patients. Generalized seizures accounted for almost 82.0% followed by partial seizures (15.3%) The demographic details of the study population, types of the seizures are presented in Table 1.

### *AED utilization pattern*

A total of 646 AEDs were prescribed during the study period, corresponding to an average of 1.5 AEDs per patient. Table 2 summarizes the AED utilization pattern among the study population. In the study population, 274 (62.4%) patients received monotherapy, 126(28.7%) patients received dual therapy, 38 (8.7%) patients received three drug therapy and only one patient was prescribed four drugs for the management of epilepsy.

### *AED usage as monotherapy*

Independent of the AED use pattern (either monotherapy or combination therapy) phenytoin

**Table 1: Demographic and clinical characteristics of the study population (n=439)**

Characteristics	Number	Percentage (%)
<i>Gender</i>		
Male	269	61.3
Female	170	38.7
<i>Age group</i>		
1 to 10 years	87	19.8
11-20 years	131	29.8
21 to 30 years	107	24.4
31 to 40 years	57	12.9
41 to 50 years	24	5.5
51 to 60 years	18	4.1
Above 60 years	15	3.4
<i>Age of onset of seizures</i>		
Since birth	13	2.9
1 to 10 years	134	30.5
11-20 years	113	25.7
21 to 30 years	89	20.3
31 to 40 years	50	11.4
41 to 50 years	16	3.6
51 to 60 years	16	3.6
Above 60 years	8	1.8
<i>Type of seizures</i>		
Generalized seizures	360	82.0%
Partial seizures	67	15.3%
Hot water epilepsy	12	2.7%

**Table 2: AED utilization pattern**

Type of seizures	Mono therapy (n=274)	Dual therapy (n=126)	Three Drugs Therapy (n=38)	Four drugs therapy (n=1)	Total number (n=439)
Generalized seizures	224 (81.8%)	105 (83.3%)	30(78.9%)	1(100%)	360(82.0%)
Partial Seizures	38 (13.9 %)	21(16.7%)	8 (21.1%)	-	67(15.3%)
Hot water epilepsy	12 (4.3%)	-	-	-	12(2.7%)
<b>Total</b>	<b>274</b>	<b>126</b>	<b>38</b>	<b>1</b>	<b>439</b>

(42.1%) was the most frequently prescribed AED followed by valproic acid (41.0%), carbamazepine (25.1%), phenobarbitone (16.6%), clobazam (14.4%). Both phenytoin (23.0%) and valproic acid (21.9%) were the highly used AEDs as monotherapy followed by carbamazepine (10.5%) and phenobarbitone (4.3%). The details of the AED monotherapy are presented in Table 3.

The most commonly prescribed combination therapy of AED consists of phenytoin/phenobarbitone (23%), Valproic acid/clobazam (16.6%), valproic acid/carbamazepine (11.9%), carbamazepine/clobazam (8.7%) and valproic acid/phenytoin (5.5%). For generalized seizures, phenytoin was the highly prescribed AED followed by valproic acid and carbamazepine. For partial seizures, valproic acid was the widely prescribed AED followed by phenytoin and carbamazepine. whereas for hot water epilepsy, valproic acid was the widely used AED followed by clobazam, phenytoin and phenobarbitone. The details of AED usage in different types of seizures are presented in Table 4.

One patient with mentally retardation was treated with epilepsy surgery as the patient's seizures were not controlled with the use of 4 AEDs, though he was highly adherent to the AED treatment. Three pregnant patients were on phenytoin monotherapy along with folic acid 5 mg once daily. They were on phenytoin prior to pregnancy.

#### *Drug related problems*

*Adverse drug reactions (ADR):* A total of 45 ADRs were reported from 35 patients. Some patients developed more than one ADR (6 patients developed 2 ADRs and 2 patients developed 3 ADRs). In most of the ADRs, the organ system affected was gastrointestinal system and central nervous system. The most common drugs implicated for ADRs were phenytoin (53.3%), valproic acid (26.7%), and carbamazepine (8.9%). There were 23 ADRs with phenytoin. They were: Gum hyperplasia (9), rash (3), 2 each for somnolence, ataxia, dizziness and somnolence; one each for asthenia, fixed drug eruptions, and

**Table 3: AED usage as monotherapy**

Antiepileptic Drugs	Total number (Percent) (n=439)	Monotherapy (Percent) (n=439)
Phenytoin	185 (42.1)	101 (23.0)
Valproic acid	180 (41.0)	96(21.9)
Carbamazepine	110 (25.1)	46(10.5)
Phenobarbitone	73 (16.6)	19(4.3)
Clobazam	63 (14.4)	5(1.1)
Others	35 (7.8)	7(1.6)
<b>Total</b>	<b>646</b>	<b>274</b>

**Table 4: Utilization of various AEDs in different type of seizures.**

Drugs	Types of seizures			Total no.
	Generalized seizures	Partial seizures	Hot water epilepsy	
Phenytoin	160	25	1	185
Carbamazepine	86	24	-	110
Valproic acid	139	33	8	180
Phenobarbitone	62	10	1	73
Clobazam	55	6	2	63
Diazepam	4	-	-	4
Clonazepam	9	5	-	14
Levetiracetam	6	-	-	6
Oxcarbazepine	2	-	-	2
Topiramate	2	1	-	3
Zonisamide	5	1	-	6

insomnia. There were 13 ADRs with valproic acid. They were: weight increase (5), 2 each for abnormal behavior and somnolence; and one each for fatigue, menstrual disorder, dizziness, and liver function test abnormality. There were 4 ADRs with carbamazepine. They were ataxia (2), and one each for dizziness and lethargy. There were 2 ADRs with phenobarbitone, one each for abnormal behavior and gum hyperplasia. Tremor was seen in one patient while increasing the dose of levetiracetam. A patient presented with anticonvulsant hypersensitivity syndrome with the combined use of phenytoin and phenobarbitone (Figure 1) Causality association between drug and reaction was probable in 73.33% (n=33) and 48.88% (n=22) as assessed by using WHO probability scale and Naranjo's algorithm respectively. Medications were discontinued in 13 cases and the dose was altered in 5 cases. No change was made in 60% (n=27) of cases, as these ADRs were mild. Some patients did not agree to change their medications inspite of medical advice as they were getting the AEDs free.

*Over dosage:* Four patients (0.5%) had overdose of AEDs. All were using phenytoin.

*Medication adherence:* Based on MAS, 6 patients (1.4%) were non adherent to medication and scored 3-4 points of 4 questions, and 433 patients (98.6%) were adherent to AEDs and scored  $\leq 2$

points of 4 questions. At the end of the study, only one patient was found to be highly non adherent to AED therapy scoring 4 points.

#### *Control of seizures*

Good control of seizures was observed in 262 (59.7%) patients, fair control in 98 (22.3%) patients, and poor control in 79 (17.9%) patients at the beginning of the study. A total of 206 (46.9%) patients visited the outpatient department for follow up. During the follow up, 160 patients (77.7%) had good control of seizures, 17 patients (8.3%) had fair control and 29 patients (14.1%) had poor control. Compared to the time of enrollment, proportion with good control improved by 15.9% and adherence to medications improved by 7.1% (from 89.5 to 96.6%). The improvement in outcome and medication adherence was attributed to the counseling provided. Eighteen patients with seizure freedom of 3 years were tapered off medications.

Of the study population, 81 patients had co morbid conditions. Of these, hypertension (15, 18.5%) was the most common, followed by headache (11, 13.5%), and neurocysticercosis (10, 12.3%). A total of 185 patients were receiving 311 concomitant medications including multivitamins, antacids and hematinics.



Figure 1. The photo of patient who developed anticonvulsant hypersensitivity syndrome with phenytoin and phebobarbitone

## DISCUSSION

According to the literatures, the incidence of epilepsy has a bimodal distribution with a peak in the first decade and a second peak in the elderly.<sup>2,14,15</sup> In the present study, the peak was observed at the age group of 10 to 20 years (29.8%). This may be because most of the Pediatric patients receive epilepsy management at Pediatric Department and this study was done in Neurology Department.

Various epidemiological studies on epilepsy are unable to explain a difference in gender distribution in their study population<sup>6,11,16</sup> and some studies describe a female predominance.<sup>6,17</sup> In our study we found the males (61.3%) to be almost two folds greater than the females (38.7%).<sup>18</sup> The lesser number of females may be due to higher illiteracy, poorer understanding of the disease and treatment, social stigma, and the need for male relative to consent and accompany the females for hospital visit. There

was disproportionate large number of generalized seizures among our study subjects. This was likely due to incomplete clinical information, EEG and imaging.

Most of the epileptic patients were effectively managed with conventional AEDs like carbamazepine, phenytoin, phenobarbitone and valproic acid, as observed in the earlier studies.<sup>6,15-21</sup> The highly used AED among the study population was phenytoin<sup>23,24</sup> (41.7%) patients and valproic acid (41.0%), both were mainly used for generalized seizures. The reason for high use of phenytoin was lower cost with free supply at government hospitals. For partial seizures the highly used AEDs was valproic acid followed by carbamazepine. Valproic acid was also the most commonly highly used AED for hot water epilepsy followed by clobazam. Clobazam was mainly used as an add-on therapy with valproic acid in generalized seizures. Phenobarbitone was prescribed for generalized seizures followed by partial seizures. Some of the patients with hot

water epilepsy received clobazam just before the head bath to prevent the seizure attack. The newer AEDs like clonazepam, levetiracetam, zonisamide, oxcarbazepine and topiramate were used in few cases. Valproic acid was widely used in this study population because of its broad-spectrum of activity, particularly because many of our patients' seizure type could not be clearly determined. .

Monotherapy was practiced in 62.4% of our patients, as in many previous studies<sup>6,9,16-20,23-26</sup>, with its many advantages.<sup>27</sup> Nevertheless, multiple drug therapy is unavoidable in some patients, though polytherapy adversely affect the quality of life.<sup>28-30</sup> In 28.7% of patients, seizures were managed with dual therapy. The commonly prescribed AED combination was phenytoin/phenobarbitone, as these drugs are available as combination tablets, and of low cost. Valproic acid/phenytoin and valproic acid/carbamazepine are our other commonly used combinations. The later combination is also commonly used in Nepal.<sup>20</sup>

Hypertension, headache and neuro-cysticercosis were common comorbidity in our patients, as compared to cerebrovascular accident, dementia, and intra cerebral hematoma in a German study.<sup>23</sup>

Overall, the medication adherence of our patients is good. Factors for medication non adherence are polytherapy, unclear instruction, forgetfulness, adverse drug reactions, inadequate patient counseling, illiteracy, poverty, high cost of treatment, and long term use of drugs.<sup>30</sup> However, only less than half of our patients attended outpatient follow up.

In conclusion, our study on AED usage in a South Indian teaching hospital shows monotherapy was used in about two thirds of patients. Phenytoin and valproic acid were the commonly used monotherapy followed by phenytoin/phenobarbitone in combination therapy. Gum hyperplasia from phenytoin was the most common ADR.

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