



**TO EVALUATE THE PRESCRIBING PATTERN AND SAFETY PROFILE OF ANTIEPILEPTIC DRUGS IN PEDIATRIC OUTPATIENT AND INPATIENT DEPARTMENT OF GOVERNMENT MEDICAL COLLEGE AND DR SUSHEELA TIWARI GOVERNMENT HOSPITAL, HALDWANI, UTTARAKHAND**

**Pharmacology**

<b>Gupta A</b>	Post-Graduate Resident, Department of Pharmacology, Government Medical College, Haldwani-263139.
<b>Srivastava B*</b>	Professor, Department of Pharmacology, Government Medical College, Haldwani-263139.*Corresponding Author
<b>Rakholia R</b>	Associate Professor, Department of Pediatrics, Government Medical College, Haldwani-263139.
<b>Bhardwaj R</b>	Associate Professor, Department of Pharmacology, Government Medical College, Haldwani-263139.
<b>Khanchandani R</b>	Assistant Professor, Department of Pharmacology, Government Medical College, Haldwani-263139.

**ABSTRACT**

**Introduction:** Epilepsy is the most common neurological disorder in pediatric age group.[1] Due to ethical issues, data about safety and efficacy of Antiepileptic drugs (AEDs) in pediatric patients is limited. Therefore, our study was conceptualized to obtain baseline data on prescribing pattern and safety profile of antiepileptic drugs in pediatric patients.

**Material and Methods:** This was a prospective cross-sectional study, conducted from November 2016 to October 2017 in the Department of Pharmacology and Pediatrics our teaching hospital.

**Result and Summary:** Out of total 207 patients, majority was males and the most common age group affected with seizure disorders was 1-5 years. Monotherapy of antiepileptic drugs (83.1%) was significantly prescribed whereas valproate was the most commonly prescribed AED in the current study. The rate of occurrence of adverse drug reactions was lowest for valproate utilization. The WHO-UMC causality was found to be probable (53.3%) for maximum ADRs.

**KEYWORDS**

AEDs, GTCS, WHO-UMC, ADRs

**INTRODUCTION**

Epilepsy is the most common neurological disorder, causing significant morbidity and mortality in pediatric age group.[1] There are approximately 12 million persons with epilepsy (PWE) in India. Besides epilepsy, major neurological disorders affecting children includes neurocysticercosis, meningitis, migraine and cerebral palsy.[2] The cumulative lifetime incidence of epilepsy is 3%, and more than half of cases begin in childhood. Epileptic seizures have been classified as focal (originating from one cerebral hemisphere) and generalized (involving both cerebral hemisphere). This classification is important because knowing the type of seizure is essential for identifying particular etiology, selecting the appropriate therapy and predicting prognosis.[3] The overall goal of treatment is to completely prevent seizures without causing any untoward side effects. Antiepileptic Drugs (AEDs) are the mainstay of treatment. They are traditionally classified as older (conventional) and newer AEDs based on whether they have been marketed before or after 1991.[4] The conventional AEDs are generally used as first-line therapy for most seizure disorders because of their broad spectrum activity and cost-effectiveness. Most of the new drugs are used as add-on or alternative therapy, although many are now being used as first-line monotherapy. Over 80% of epileptic patients can achieve a significant reduction in seizure frequency with one drug alone.[5] In treatment of focal seizures, the success rate is higher with carbamazepine, phenytoin, or valproic acid although newer AEDs like lamotrigine, oxcarbazepine and levetiracetam are also used to treat focal seizures. For generalized or unclassified seizures, valproate is preferred in many patients.[6]

Antiepileptic drugs are known to cause adverse effects. Sodium valproate may cause severe hepatotoxicity, it was linked to 50 fatalities in USA alone.[7] Erythematous skin rash is the most common adverse effect associated with carbamazepine therapy.[7] Due to paucity of clinical trials on pediatric patients, data about safety and efficacy of many old and new antiepileptic drugs in pediatric age group is limited. Limited studies are conducted on antiepileptic drug utilization pattern in pediatric patients of uttarakhand. Drug utilization studies generate data regarding current drug prescribing pattern, which also helps concern authorities in enacting health policies. Therefore, our study is conceptualized to develop a baseline data on prescribing pattern and safety profile of antiepileptic drugs in the Pediatric Outpatient and Inpatient department of Dr Susheela Tiwari Government Hospital,

Haldwani.

**Materials and Methods**

This was an observational, cross-sectional, hospital based study conducted from November 2016 to October 2017 in Department of Pharmacology and Pediatrics of Government Medical College Haldwani, after taking approval from Institutional Ethical Committee. Written Informed Consent was obtained from Parents/Legal Guardians of the patients. Total 207 patients were recruited who were prescribed at least one AED.

**Statistical Analysis**

Collected data was coded appropriately, entered in Microsoft Excel (MS Excel) spreadsheet. Categorical data was presented as percentage (%). Pearson's Chi square test has been used to evaluate differences between groups for categorized variables. An association was significant if the p-value was less than 0.05.

**Results**

Our study showed more male patients 134(64.7%) were prescribed with antiepileptic drugs (AEDs) as compared to females patients 73(35.3%). (Table 1)

**TABLE 1: AGE AND GENDER DISTRIBUTION OF PATIENTS**

AGE GROUPS (YEARS)	SEX		TOTAL n(%)
	MALE n(%)	FEMALE n(%)	
0-1 year	14(6.8)	7(3.4)	21(10.1)
1-5 years	48 (23.2)	24(11.6)	72(34.8)
5 - 10 years	40(19.3)	21(10.1)	61(29.4)
10-15 years	26 (12.6)	18(8.7)	44(21.3)
15-18 years	6(2.9)	3(1.4)	9(4.3)
Total	134(64.7)	73(35.3)	207(100)

Total 113(54.6%) patients had generalized tonic clonic seizures (GTCS) whereas 20(9.7%), 52(25%), 18(8.7%) and 4(1.9%) patients were having complex partial seizures (CPS), partial seizures secondarily generalized (PSSG), simple partial seizures (SPS) and absence seizures respectively (Table 2).

**TABLE 2: ETIOLOGY OF SEIZURE CHARACTERISTICS IN PATIENTS**

S.NO	INDICATIONS	PATIENTS WITH GTCS (%)	PATIENTS WITH CPS (%)	PATIENTS WITH PSSG (%)	PATIENTS WITH SPS (%)	PATIENTS WITH ABSENCE SEIZURES (%)
1.	Idiopathic	49(55.1)	6(6.7)	27(30.3)	3(3.4)	4(4.5)
2.	Neurocysticercosis	23(42.6)	7(13)	23(42.6)	1(1.9)	-
3.	Atypical febrile convulsion	1(6.7)	3(20)	1(6.7)	10(66.7)	-
4.	Cerebral palsy	12(92.3)	1(7.7)	-	-	-
5.	Neurodevelopmental retardation	5(100)	-	-	-	-
6.	Meningoencephalitis	5(100)	-	-	-	-
7.	HIE-2	2(66.7)	1(33.3)	-	-	-
8.	Benign febrile convulsion	1(33.3)	-	-	2(66.7)	-
9.	Tubercular meningitis	3(100)	-	-	-	-
10.	Others	12(70.6%)	2(11.8%)	1(5.8%)	2(11.8%)	-
TOTAL	113(54.6)	20(9.7)	52(25)	18(8.7)	4(1.9)	

Monotherapy was prescribed in 172(83.1%) patients, of which valproate (VPA) was given in maximum 117(68%) patients. In dual therapy, combination of VPA and clobazam was given in highest number of patients i.e 14(48.3%) whereas triple therapy of VPA, phenytoin (PHT) and levetiracetam (LEV) was given maximum in 2(33.3%) patients. (Table 3)

**TABLE 3: PRESCRIPTION OF ANTIPILEPTIC DRUGS ACCORDING TO SEIZURE CHARACTERISTICS AS MONO, DUAL AND TRIPLE THERAPY**

AED THERAPY	GTCS (%)	CPS (%)	PSSG (%)	SPS(%)	ABSENCE SEIZURES (%)	Total (%)
Mono Therapy						
VPA	65(74.7)	4(21.1)	37(82.2)	8(44.4)	3(100)	117(68)
PHT	8(9.2)	3(15.8)	5(11.1)	3(16.7)	-	19(11.1)
PB*	9(10.3)	3(15.8)	-	2(11.1)	-	14(8.2)
Others	5(5.7)	9(47.4)	3(6.7)	5(27.8)		22(12.8)
Total	87(100)	19(100)	45(100)	18(100)	3(100%)	172(100)
Dual Therapy						
VPA + Clobazam	9(42.9)	-	5(83.3)	-	-	14(48.3)
VPA+LEV	3(14.3)	1(100)	1(16.7)	-	1(100%)	6(20.7)
Others	9(42.9)	-	-	-	-	9(31)
Total	21(100)	1(100)	6(100)	-	1(100)	29(100)
Triple Therapy						
VPA + PHT+ LEV	1(20)	-	1(100)	-	-	2(33.3)
Others	4(80)	-	-	-	-	4(66.7)
Total	5(100)	0	1(100)	0	0	6(100)

\*PB- Phenobarbitone

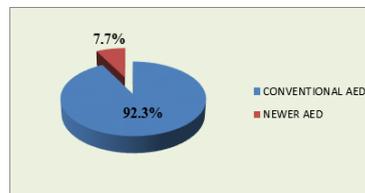
Monotherapy was significantly prescribed in 172(83.1%) patients whereas in monotherapy, valproate 117(68%) was significantly prescribed to patients. (Table 4)

**TABLE 4: SIGNIFICANCE OF MONOTHERAPY AND VALPROATE MONOTHERAPY PRESCRIPTION**

AED PRESCRIPTION	NO. OF PATIENTS (%)	p-value*
Monotherapy	172(83.1)	0.036
Valproate	117(68)	0.001

\*p-value < 0.05 is significant

Conventional AEDs were prescribed in 92.3% patients whereas newer AEDs were prescribed in 7.7% patients. (Figure 1)



**FIGURE 1: COMPARISON OF CONVENTIONAL AND NEWER ANTIPILEPTIC DRUGS UTILIZATION**

Valproate caused 18(60%) ADRs while phenytoin and carbamazepine caused 10(33.3%) and 2(6.7%) ADRs respectively. (Table 5)

**TABLE 5: ADVERSE DRUG REACTIONS ASSOCIATION WITH ANTIPILEPTIC DRUGS**

S. No	SYSTEMS (n)	REACTION	NUMBER (%)	VPA n(%)	PHT n(%)	CBZ n(%)
1.	CNS (8)	Drowsiness	1(3.3)	1(3.3)	-	-
		Excessive Lethargy	1(3.3)	1(3.3)	-	-
		Irritability	1(3.3)	-	1(3.3)	-
		Headache	4(13.3)	4(13.3)	-	-
		Memory Impairment	1(3.3)	1(3.3)	-	-
2.	Dermatological (2)	Papular Rash	2	1(3.3)	1(3.3)	-
3.	Endocrine (2)	Facial Hair	1(3.3)	1(3.3)	-	-
		Gynaecomastia	1(3.3)	1(3.3)	-	-
4.	GIT (11)	Anorexia	4(13.3)	3(10)	1(3.3)	-
		Dyspepsia	1(3.3)	1(3.3)	-	-
		Gum Hypertrophy	5(16.7)	-	5(16.7)	-
		Increased Appetite	1(3.3)	1(3.3)	-	-
5.	Hepatic (1)	LFT Dearranged	1(3.3)	-	1(3.3)	-
6.	Metabolic (5)	Weight Gain	4(13.3)	3(10)	-	1(3.3)
		Weight Loss	1(3.3)	-	1(3.3)	-
7.	Musculoskeletal(1)	Arthralgia	1(3.3)	-	-	1(3.3)
	TOTAL (%)		30(100)	18(60)	10(33.3)	

**DISCUSSION**

Drug utilization is defined as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[5] There is paucity of clinical trials in pediatric patients due to ethical issues so data about safety and efficacy of AEDs is limited in this population. This difficulty can be overcome by drug utilization studies. Therefore, present study was conceptualized to develop a baseline data on prescribing pattern and safety profile of antiepileptic drugs in the pediatric department of our institution.

Incidence of epilepsy is highest during childhood, with maximum cases reported in children below 3 years of age.[8] In our study, maximum patients 72(34.8%) of seizure disorder were from 1-5 years

age group and the majority were males (Table 1). These findings were similar to N Maity et al and Bhatt KM et al but were in contrast to Hasan SS et al, where maximum patients belong to 6-10 year age group with predominance of male patients.[9,10,11] Poor reporting of female patients to the health care facilities due to the lack of care and orthodox cultural practices may be the reason for predominance of male patients.[12] Besides, to some extent female sex hormones (progesterone, estrogen) also tend to inhibit seizure occurrence.[13] In our study, most common etiology was idiopathic seizures 89(43%) and most frequently occurred seizures were GTCS 113(54.6%) followed by PSSG 52(25%) and CPS 20(9.7%) (Table 2). Similarly, Henry Daniel Raj T et al and Rishe W et al found GTCS (70% and 48.6% respectively) to be the most common type of seizures in their studies.[1,5] Contrary to this, Hasan SS et al found majority of patients having partial seizures followed by generalized seizures.[11] Monotherapy 172(83.1%) was most commonly prescribed in our study irrespective of seizure type and the association of monotherapy with various seizure types was significant ( $p = 0.036$ ) (Table 3,4). Rishe W et al and Khan PM et al also found utilization of monotherapy in 78.6% and 72% patients respectively.[11] Contrary to our study, in some studies considerable number of patients were prescribed with dual and triple therapy.[11] The current guidelines recommends that patients with epilepsy should be treated with monotherapy of first line drugs unless patient does not respond to it, were adhered in our study.[6] In patients receiving monotherapy 172(83.1%), valproate 117(68%) was significantly prescribed in various seizure types ( $p < 0.05$ ) (Table 3,4). Similar to our study, valproate (43%) was the most common monotherapy in all the seizures types in a study by Khan PM et al.[14] Contrary to this, carbamazepine (52.6%) was used mainly as monotherapy in study done by Hasan SS et al.[11] Overall in mono or combination therapy, valproate 147(71%) was the most commonly prescribed AED in our study (Table 3). In the current study, newer AEDs such as levetiracetam, oxcarbazepine were used in 7.7% patients (Figure 1). These were mainly used as combination therapy contrary to conventional AEDs which were prescribed more commonly as monotherapy. The overall rate of adverse drug reactions was 30(14.5%) (Table 6). Most of the ADRs in our study belong to the Type A category i.e. they were predictable and can be explained by the pharmacological actions of the drug.[3] Gum hypertrophy 5(16.7%) was the most common ADR. The rate of occurrence of adverse drug reactions was lowest with valproate utilization (12.2%), similar to study done by Henry Daniel Raj T et al.[1] These results indicates that safety profile of valproate is better. All the reported ADRs were analyzed using WHO-UMC causality assessment scale. It was found to be probable in 16(53.3%) and possible in 14(46.7%) patients.

## Conclusion

In the current study, most common affected age group was 1-5 years and GTCS were most commonly encountered. Monotherapy of valproate was significantly prescribed to treat epilepsy irrespective of seizure types. Newer AEDs were prescribed more often as combination therapy contrary to conventional AEDs. The rate of occurrence of adverse drug reactions was lowest with valproate utilization. For further confirmation of its efficacy, more studies are required on large population. Majority of ADRs had probable causality according to WHO-UMC scale.

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