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"DRUG UTILIZATION STUDY OF ANTISEIZURE PROPHYLAXIS IN PAEDIATRIC SUBJECTS – A PROSPECTIVE, OBSERVATIONAL, SINGLE CENTRE STUDY"

General Medicine

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ABSTRACT

There has been few research on the drug utilisation pattern and adverse drug reactions of anti-epileptic medications (AEDs) in children. So, this study was designed to investigate the drug utilisation pattern of anti-epileptic drugs in paediatric population. Total 120 paediatric patients visiting the OPD, aged 1 to 14 years of either sex, diagnosed with epilepsy, and prescribed at least one anti-epileptic medicine were analysed. The most commonly prescribed anti-epileptic medicine was sodium valproate, followed by levetiracetam, phenytoin, and carbamazepine. 85% of patients were given monotherapy, whereas 15% were given polytherapy. The most common adverse drug reactions (ADR) recorded was nausea, followed by headache, stomach discomfort, sleepiness etc. AED prescribing is a multifaceted practise driven by a variety of circumstances. Thus, auditing prescriptions at regular intervals will assist physicians in modifying their prescribing pattern in accordance with current recommended standards for managing paediatric epilepsy.

KEYWORDS

Epilepsy, Valproate, Anti-epileptic drugs, Drug utilization study.

INTRODUCTION:

Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages. around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. [1] The risk of premature death in people with epilepsy is up to three times higher than for the general population. Three quarters of people with epilepsy living in low-income countries do not get the treatment they need. In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination. [1]

Childhood epilepsy remains a challenge to treat. It is the second most common frequently encountered neurological condition that imposes heavy burden on growing children, families, and also on healthcare systems. [1] An epileptic seizure is a transient paroxysm of uncontrolled discharges in neurons and a medical condition with recurrent, unprovoked seizures.[2] In a community study of epilepsy in children from North India, the prevalence rates are 6.99 for rural area, 5.48 for urban areas, and 4.07 for active epilepsy per 1000 population.[3] Worldwide age-specific lifetime prevalence of epilepsy among children and adolescents (< 18 years of age) is 9.7/1000. [4] In world the incidence of epilepsy in children ranges from 41 to 187/100,000. [5] In India paediatric epilepsy with an incidence of about 8 per 1000 children under the age of seven years despite the increase in the number of Antiepileptic Drugs (AEDs), more than 25% of children with childhood epilepsy continue to have seizures. About 5% of children are at risk of experiencing a seizure, half of them encounter their first seizure in infancy.[2]

Seizures in children have many causes. Common causes of childhood seizures or epilepsy include genetic causes, head injury, infections of the brain and its coverings, lack of oxygen to the brain, hydrocephalus (excess water in the brain cavities), disorders of brain development, fever (these are called febrile seizures) Most seizures in childhood are not associated with a definite cause, however.[6] In worldwide, 60-90% of people with epilepsy receive no treatment or is inadequately treated.[7] The majority of people with epilepsy have a good prognosis if they receive appropriate treatment.[8]

Despite advances in the treatment of epilepsy, 30- 40% of patients remain uncontrolled on a single AED. Combination therapy is recommended when two successive AEDs given as monotherapy have failed. [9] Agents with a low risk of pharmacokinetic interactions are preferred for combination therapy, and the success of combination therapy can be improved by paying attention to mechanisms of action and using lower dosages. [9] With correct, early, and uninterrupted therapy, up to 75% of patients with epilepsy eventually become seizure-free, many of them within 5 years after diagnosis. [9] About 25% of patients may not respond to any kind of therapy. AEDs are highly successful in suppressing seizures in most patients.[10]

The growing number of newly approved drugs have contributed to the increased adverse drug reactions (ADRs).[11] Adverse effects are highly prevalent in the drug treatment of epilepsy. Polytherapy is a common practice for the management of epilepsy despite of significant increase in side effects. Lack of systematic pharmacoepidemiologic studies investigating drug use pattern and ADRs related to AEDs has made it difficult to assess accurately the exact incidence of AED related ADRs.[12]

The present study offers a unique opportunity to analyse prescribing pattern of AEDs in terms of their efficacy with respect to different types of seizures, age groups, and gender. This, in turn, will result in enhancement of public health and safety with respect to the usage of AEDs, which will be a pertinent and imperative issue for prescribers, health authorities, and policymaker.

MATERIALS AND METHODOLOGY:

The study was an observational, prospective, non-interventional, single centre study. The study was conducted in a Tertiary Care Hospital's paediatrics Outpatient Department (OPD) in collaboration with department of pharmacology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh. The study was performed after receiving the necessary ethical clearance from the Institutional Ethics Committee. The study was carried out for a duration of 18 months, from February 2021 to July 2022 followed by data compilation and statistical analysis.

Inclusion Criteria:

Patients aged 1 to 14 years, of either sex, diagnosed with epilepsy, and who were prescribed at least one anti-epileptic drug were included in the study.

Exclusion Criteria:

Children>14 years of age, patients/guardians not willing to participate in the study, trauma (head injury), were excluded from our study. Patients fulfilling the inclusion and exclusion criteria were included in the study. Patients / Legally Authorized Representatives (LAR) were informed about the nature of study. Written informed consent from the patient's parent/guardian if child < 7 years and child assent statement if age > 7 years was taken.

Data were collected from OPD case papers and entered in specially designed patient data entry forms. Demographic details of the patient, types of seizures, diagnosis, Number of drugs and type of antiepileptic prescribed, dose and route of administration and dose frequency of AED, concomitant medications, and adverse drug reactions (ADR),

relevant investigation were noted in a restructured case record form. The causality assessment of ADR was assessed by using WHO Causality Scale.

Statistical Analysis:
The data was stored, segregated, processed with the help of computer software MS Excel. Statistical analysis was conducted using Data analysis tool pack, add on feature with MS Excel.

RESULT:
Out of total 120 patients 74 (61.7%) were male and 46 (38.3%) were females with male/ female ratio of 0.6. maximum number of patients belonged to the age group of 6-14 year 76 patients (63.3%), followed by the age group of 1-3 year and 3-6 years both contain equally 20 patients (16.7%) each. Whereas 0–1-year age of patients were only 4 (3.3%). (Table 1) Various duration of epilepsy patients were described in table no. 1. In this study period most frequently encountered type of epilepsy was GTCS in 95 patients (79.16%), followed by Partial type in 15 patients (12.5%) as shown in table no. 1. 91 (75.8%) patients were having epilepsy only and 27(22.5%) were having epilepsy with underlaying brain conditions and 2(1.6%) were having comorbidities. (table 1)

Table 1. Demographics details and disease characteristics of study participants

Parameters		Frequency n (%)
Gender	Male	74 (61.7 %)
	Female	46 (38.3 %)
Age Group	0 – 1 Year	4 (3.3 %)
	1 – 3 Years	20 (16.7 %)
	3 – 6 Years	20 (16.7 %)
	6 – 14 Years	76 (63.3 %)
Duration of Epilepsy	06 Months	26 (21.67%)
	1 Year	18 (15 %)
	2 Years	23 (19.17%)
	3 Years	22 (18.33 %)
	4 Years	15 (12.5 %)
	≥ 5 Years	16 (13.33 %)
Type of Epilepsy	GTCS	95 (79.17 %)
	Partial	15 (12.5 %)
	Febrile	6 (5 %)
	Unclassified	4 (3.33 %)
Diagnosis of Epilepsy primary / secondary	Primary Epilepsy	91 (75.8 %)
	Secondary Epilepsy	27 (22.5 %)
	Epilepsy with co-morbidities	2 (1.7 %)

GTCS: Generalized Tonic Clonic Seizure

Table 2. Routes of administrations of AED.

Formulation	Frequency	Percentage
Oral	95	79.2%
Syrup	21	17.5%
Both	4	3.3%
Total	120	100%

Above table showed oral formulation was used in 95(79.2%) and syrup was prescribed in 21(17.5%) patients.

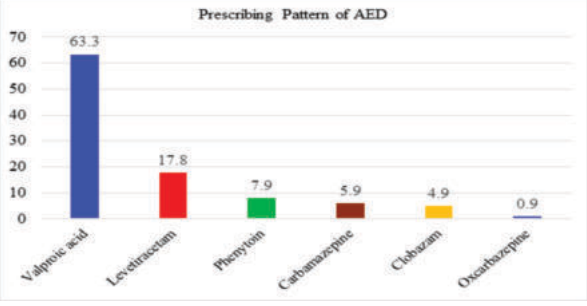

Figure 1. Prescribing Pattern of various AED.

Most commonly prescribed antiepileptic agents in paediatric department during study period was Sodium valproate in 64 patients (63.3%), levetiracetam in 18 patients (17.8%), phenytoin in 8 patients (7.9%), carbamazepine in 6 patients (5.9%), clobazam in 5 patients (4.9%), oxcarbazepine in 1 patient (0.9%).

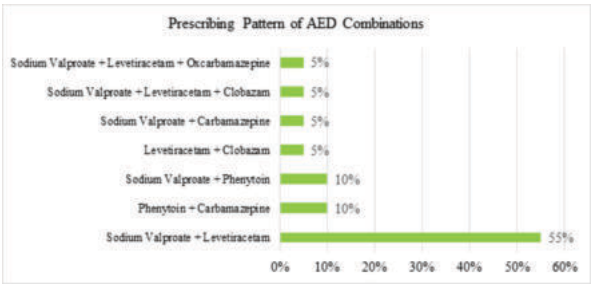

Figure 2. Prescribing Pattern of AED Combinations

This figure showed sodium valproate+ levetiracetam was most frequently used dual drug therapy in 11 patients (50%), followed by phenytoin + carbamazepine and sodium valproate + phenytoin (10%) each, followed by levetiracetam + clobazam and sodium valproate + carbamazepine (5%) each and for triple drug therapy sodium valproate + levetiracetam + clobazam and sodium valproate + levetiracetam + oxcarbazepine (5%) each was used.

Table 3. Types and Generations of prescribing Antiepileptic drugs

Parameters		Frequency n (%)
Therapy type	Monotherapy	102 (85 %)
	Polytherapy	18 (15 %)
Generation of Antiepileptic Drugs	Newer Generation	33 (23.4 %)
	Older Generation	108 (76.5 %)

This table shows that the most commonly used therapy was monotherapy prescribed to 102 patients (85%) and the other therapy was polytherapy in 18 patients (15%). Above table showed newer generation antiepileptic agent which accounts for 33(23.4%) remaining 109 i.e., 76.5% were older generation antiepileptic agents.

Table 4. other drugs prescribed to patients

DRUGS	Frequency	Percentage (%)
Multivitamin	11	9.1
Multivitamin + Calcium/Vit-d3	78	65
Multivitamin + Calcium/Vit-d3 + folic acid	11	9.1
Calcium/Vit-d3	3	2.5
Folic acid	2	1.6
Paracetamol	3	2.5
Calcium/Vit-d3 + Folic acid	2	1.6
Multivitamin + Calcium/Vit-d3 + Folic acid + Insulin	1	0.8
Multivitamin + Calcium/Vit-d3 + Albendazole	1	0.8
Multivitamin + Calcium/Vit-d3 +Paracetamol	2	1.6
Multivitamin + Folic acid	1	0.8
Multivitamin + Paracetamol	1	0.8
No concurrent drug prescribed	4	3.3
TOTAL	120	100

Above table illustrates most commonly co-prescribed drug was Multivitamin + calcium in 78 (65%) patients followed by multivitamin & multivitamin + calcium + folic acid in 11(9.1%) patients. (Table 4) Out of 120 patients 87 were advised for EEG, 80 (66.6%) showed abnormal EEG, 7 (5.8%) patient showed normal EEG.

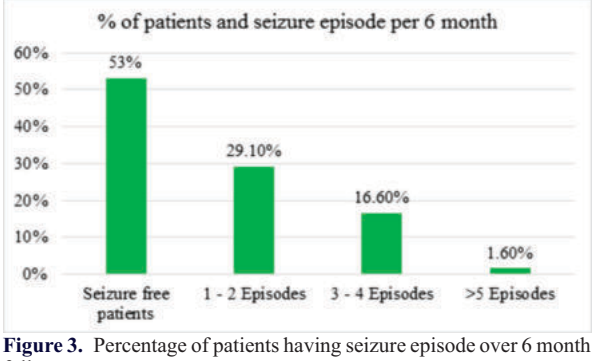

Figure 3. Percentage of patients having seizure episode over 6 month follow up

Table 5. Adverse Drug Reaction with Anti-epileptic Drugs

Adverse Drug Reaction	Sodium valproate	Levetiracetam	Carbamazepine	Phenytoin
Nausea	5	2	1	1
Headache	4	2	1	1
Abdominal pain	1	-	-	-
Stevens-Johnson syndrome	1	-	-	-
Drowsiness	-	-	1	-
Total (20)	11	4	3	2

Table 6. Causality Assessment of Reported ADR

DRUGS	Certain	Probable	Possible	Unlikely
Sod Valproate	0	2	9	0
Levetiracetam	0	0	4	0
Carbamazepine	0	1	2	0
Phenytoin	0	0	2	0
Total	0	3	17	0

Nausea was noted in 9 patients and headache was noted in 8 patients because of Sodium valproate, Levetiracetam, carbamazepine and phenytoin. Abdominal Pain and Stevens-Johnson syndrome (SJS) were noted in 1, 1 patient because of Sodium valproate. Drowsiness was noted in 1 patient because of carbamazepine. (Table. 6)

DISCUSSION:

The present study was carried out in the Department of Pharmacology in collaboration with department of Paediatric OPD of Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, Madhya Pradesh. Data of total of 132 study subjects were collected during a period of one year (February 2021- July 2022) which was followed by compilation and statistical analysis of data. Out of 132 patients, 12 were excluded from the study because they were not fulfilling the inclusion criteria. Total 120 patients fulfilling the inclusion criteria were included for further analysis.

In the present study number of Male (61.7%) patients were predominant over females (38.3%) which is similar to previous study. [13-15] a study by Ajay Kumar Halwai et *al*., contrary to ours showed female predominance over male.[16]

Maximum patients in this study were age group of 6-14 year 76 patients (63.3%) like in previous study done by Mounika Antham et. *al*. (2020) [17] Most of the patients were having epilepsy since 6 months, followed by epilepsy since 2 years.

In this study we analysed that a higher percentage of patients were found to have GTCS (79.16%) type of seizure, 12.5% were having partial seizures and 5% were diagnosed with febrile seizures however in 4 patients type of epilepsy could not identified, same as in other studies done by Pathan Muzammil Khan et. al. (2015), Ajay Kumar Halwai et al. [18,16]

In this study most of the patients prescribed monotherapy (85%) whereas polytherapy were given to only 15% of patients like earlier studies Juny Sebastian et. al. (2019) [14, 19]

Standard textbooks and literature mentioned that the monotherapy is the goal pharmacological management of epilepsy and we also observed that most of our patients were treated with monotherapy. Despite availability of Various newer AED with equal effectiveness and better tolerability, conventional AEDs were mostly prescribed. Mostly all the AEDs were prescribed with generic name.

In the present study an average drug per prescription was 1.17%. A total of 120 prescription was encountered. Among conventional AED's Sodium Valproate (63.3%) was most commonly preferred drug as monotherapy followed by Phenytoin (7.9%) and carbamazepine in (5.9%) patient which are same as in previous studies Zahra Khoshdel et. al.(2021) [13,20,21] Sodium valproate was most commonly prescribed AED. This was in contradiction with earlier study Nethmie Chandrarathna et. al. (2019),[22] by where Phenytoin was found to be most commonly AED as monotherapy. In another study done by Hirenkumar H. Dave et. al.(2018) [19] carbamazepine (41%) was most commonly used AED followed by sodium valproate (38%). Among newer AED's Levetiracetam (17.8%) was most commonly used AED as monotherapy followed by Oxcarbazepine (0.9%). Similar as shown in previous study Krishnamoorthy Gayathri et. al.[23] conducted in (2020) and on the contrary another study Ngangom Gunindro et. al. (2018) showed Oxcarbazepine was first choice. [24]

Among Dual drug therapy, Sodium valproate with Levetiracetam (61.1%) was most commonly used it was contradicted with study done in 2015 by Ajay Kumar Halwai et al.[16] which showed sodium valproate & phenytoin was most commonly used. And for Triple drug therapy, Sodium valproate with levetiracetam with clobazam was given to (5.5%) patient. Another study Meenakshi B et. al. (2016) showed a combination of sodium valproate + carbamazepine + phenobarbitone was most commonly preferred.[25]

In this present study 108 (76.5%) were older generation AED like Sod valproate, phenytoin, carbamazepine and clobazam prescribed whereas 33 (23.4%) were newer generation AED prescribed. Same as study conducted in 2009 by Bijoy Kumar Panda et. al. [26] Oral route was preferred in all the patients for drug administration. Because oral administration is easy and painless. Same route was preferred in another study Ajay Kumar Halwai et. al. 2015.[16]

In this study, out of 120 patients 87 were advised for EEG, 80 (66.6%) which showed abnormal EEG, 7(5.8%) patient showed normal EEG, which was lesser as compared to previous study conducted by Hirenkumar H. Dave et. al. (2018).[19] As per American academy of neurology guideline for epilepsy, EEG plays only a part of routine neurodiagnostic evaluation for diagnosis of epilepsy and on the basics of normal and abnormal EEG alone, we can't confirm the diagnosis of epilepsy.

In present study Multivitamin + calcium/vit-D3 in 78 (65%) patients followed by multivitamin & multivitamin + calcium/vit-D3 + folic acid in 11 (9.1%) A study of Teagarden DL et. al. (2014) showed Antiepileptic drugs (AEDs), especially enzyme inducing AEDs (EIAEDs), have been associated with reduced bone mineral density and fracture risk vitamin D therapy in children with epilepsy have shown positive effects on bone mineral density or bone biomarkers.[27]

In present study out of 120 patients 63 (53%) patients were seizure free while 35 (29.1%) patients had 1-2 episode per month after starting AED therapy. 23 (16.6%) patients were having 3-4 episodes per month and 2 (1.6%) patients had >5 episode per month after starting AED therapy. A study Hirenkumar H. Dave et. al. [19] showed similar data about seizure control after starting AED therapy.

In our study, a total of 20 adverse drug reactions were reported out of which 9 were nausea and 8 were headache due to sod valproate, carbamazepine, phenytoin, levetiracetam and 1 was abdominal pain due to sod valproate and drowsiness due to carbamazepine and SJS was seen in 1 patient who were taking Sodium valproate. Another study Sundeep Kaushik et. al. (2019) showed behavioural problems and somnolence were more commonly seen.[15]

The causality assessments of ADRs were also done according to WHO Scale which categories ADRs as “certain”, “probable”, “possible” and “unlikely”. It is seen in our study that out of 20 ADRs reported, 3 were classified as probable and 17 ADRs as possible, whereas none could be categorized as certain or unlikely. Most of the antiepileptic drugs were not stopped after reporting ADR because of the more Risk: Benefit ratio.

CONCLUSION:

The findings of the study revealed that a significant proportion of paediatric subjects received antiseizure prophylaxis, with a notable variation in the choice of medications. While the majority of prescriptions aligned with the recommended guidelines, a proportion of cases deviated from the standard practices, emphasizing the importance of ongoing monitoring and education of healthcare professionals regarding best practices in this field.

The study highlighted the need for continued efforts to improve the rational utilization of antiseizure prophylaxis in paediatric patients. This includes raising awareness among healthcare providers about the evidence-based guidelines for prescribing antiseizure medications in this population and promoting adherence to these guidelines to ensure optimal therapeutic outcomes and minimize potential risks.

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