

Anti-Convulsant Drugs Prescribing Pattern and Efficacy Comparison in Paediatric Epilepsy Population in a Tertiary Care Teaching Hospital

Mounika Antham¹, Mounika Mulukuntla², Goverdhan Puchchakayala¹, Vijay Kumar Guduru^{2,*}

¹Department of Clinical Pharmacy, Vaagdevi College of Pharmacy, Kakatiya University, Mahatma Gandhi Memorial Hospital, Warangal, Telangana, INDIA.

²Professor of Pediatrics, Mahatma Gandhi Memorial Hospital, Kakatiya Medical College, Warangal, Telangana, INDIA.

ABSTRACT

Objectives: To conduct the study of the drug usage pattern and its efficacy and tolerability comparison of most commonly used anti-epileptic drugs. **Methods:** The data included patient's age, sex, types of seizure, aetiology, past and present treatments, dose and duration of therapy and associated adverse effects. A total of 150 subjects (children) who received Sodium valproate ($n=88$), Carbamazepine ($n=21$), Phenytoin ($n=7$), Clobazam ($n=11$), Levetiracetam ($n=4$) and remaining in combinations ($n=19$) as long-term management, were enrolled in the study. Assessed for a period of 12 months for the management of seizures and also the adverse effects incidents. **Results:** Total, 91 (60.7) subjects endured from seizure episodes throughout the study interval of 12months. 131 (87.3%) patients were treated with Monotherapy, the rate of seizure remission was 81 (61.8%) and 19 (12.6%) patients were with multidrug therapy, the rate of seizure remission was 11 (57.8%). The rate of seizure remission was found statistically significant. 60 patients treated with Sodium Valproate, 19 patients treated with Carbamazepine, 1 patient treated with Phenytoin, 9 patients with Clobazam, 2 patients treated with Levetiracetam were observed to be seizure free. The most commonly occurred type of seizures was GTCS and Focal/Partial type. Overall, 67 (44.6%) patients had adverse effects; of the highest incidence was cognitive impairment, mood alterations and dizziness which developed more often with Sodium Valproate and Carbamazepine. **Conclusion:** In our collected and observed study in tertiary care teaching hospital the majority of patients were prescribed with Sodium Valproate and Carbamazepine. It appears that Sodium Valproate and Carbamazepine has highest efficacy rate and Levetiracetam had better tolerability. Sodium valproate and Carbamazepine had balanced effectiveness and tolerability.

Key words: Anti-epileptic drugs, Efficacy, Tolerability, Monotherapy, Polytherapy, reoccurrence.

INTRODUCTION

A chronic neurological disorder specified with repeated unprovoked seizures is called as epilepsy.¹⁻⁴ Recurrent, episodic, involuntary, clinical events associated with abnormal electrical activity from the neurons are the characteristic features. Abnormal excessive hypersynchronous electrical impulses produces single or paroxysmal events from the brain that is central nervous system resulting in abnormal involuntary, motor, sensory, autonomic or sensorial activity.⁵

Epileptic seizures commonly cause transitory loss of consciousness parting the single at risk of bodily harm and usually interferes

with education and employment.⁶

Epilepsy affects about 70million people worldwide. Nearly 90% of those suffering from epilepsy are in developing regions.⁷ In India the prevalence level of epilepsy sorts between 4.15 and 7.03 per 1000 population.⁸ In 2017, universally assessed that each year near and around 2.4 million people are identified with epilepsy. About 14 people per 1000 populations are disposed to suffer from epilepsy in India with upper evaluations in children, young adults and in rural areas.⁹ In 2018 the occurrence of epilepsy was found 0.3-0.5 percent among varied populations all over the world. In India the frequency is 5-10 persons per 1000 at a predictable rate.

DOI: 10.5530/ijopp.13.3.43

Address for correspondence:

Dr. Vijay Kumar Guduru
Professor of Pediatrics, Mahatma Gandhi Memorial Hospital, Kakatiya Medical College, Warangal-506007, Telangana, INDIA.

Phone no: +91 9849883029

Email Id: gudurukumar00@gmail.com



www.ijopp.org

Nearly 80% people suffer from epilepsy were in low and middle income countries.¹⁰

Compliance with medications has become a foremost problems because of the prolonged treatment associated with undesirable effects of many drugs.¹¹ Prevention of seizures and avoidance of adverse events with the regimen that is suitable and easy to follow is the primary goal of antiepileptic therapy. Antiepileptic drug of choice depends on type of seizures and patients age.¹²

The study focus is to analyse the antiepileptic medication safety, effectiveness and tolerability in paediatric department at MGM Hospital located in Warangal, Telangana, India.

MATERIALS AND METHODS

Methods

The study is a prospective, observational and comparative. It is performed in Paediatrics department at Mahatma Gandhi Memorial Hospital Warangal, Telangana, India. MGM hospital is a 1000-bedded tertiary care hospital facilitated with advanced diagnostics and therapy. Patients from various regions includes Telangana and Andhra Pradesh visited the hospital belonged to diverse socioeconomic divisions. The study was done for a period of 12 months.

Consent

The study protocol was submitted to Institutional Human Ethics committee and got approved. The IHEC number was MGMH/VCOP/PHARM D/V/015/2017. All the patients were explained about the process of work in their language and procured informed consent from them.

Inclusion criteria

1. The study included subjects of paediatric population who were diagnosed with epilepsy.
2. Patients of both genders (male and female).
3. Patients who are interested to participate are considered and given informed written consent.

Exclusion criteria

1. Patients with other genetic or medical disorder.
2. Adults are excluded.
3. Patients of age above 14 years are not considered in study.

4. Newly diagnosed patients are excluded.

Statistical Analysis

Baseline data of demography, aetiology, types, severity and frequency of seizures, efficacy and anti-epileptics were calculated using Statistical package for social sciences software, version 20. The obtained data was statistically evaluated using one-way analysis of variance (ANOVA). Significance was identified between two dependent variables using spearman rank correlation and found statistically significant result that is a two-tailed *P*-value less than 0.05.

RESULTS

Socio-demographic details of patients

Table 1 shows the study included a paediatric population of 150 subjects for the study period of 12 months in which incidence of female were 62 (41%) and males were 88 (59%). The AED's were prescribed highly to the age group of 7-12 years (50%) then 1-6 years (40%).

Seizure aetiology, types and frequency of seizures

Table 2 reveals the seizure aetiology in the present study was found to be the most with febrile condition 43(28.7%), idiopathic seizures 35(23.3%), family history 29(19.3%), head injury 23(15.3%). We found scanning reports (EEG, CT-Scan, MRI Scan) for 102 patients in that 63 patients were found with normal condition and 15 patients from abnormal to normal condition after long-term treatment with anti-epileptics. The reoccurrence of seizures was high in age group of 1-6 years there was a statistically significant correlation. GTCS type 64 (42.7%) and focal/partial type 21 (14%) of seizures were the most commonly occurred type of seizures in the collected and observed study.

Tolerability

Table 3 shows the tolerability, was assessed by incidence of adverse effects of drugs while on long term treatment. The most frequently occurred adverse effects were mood alterations and cognitive impairment, which developed more often with sodium valproate and Carbamazepine. Dizziness was frequently occurred with sodium valproate and Clobazam. Anger that is behavioural problems was most occurred with sodium valproate.

Anti-epileptic drugs prescribed among different types of seizure patients in the collected subjects

Figure 1 and 2 shows Sodium valproate 88(58.7%) then Carbamazepine 21 (14%) were the commonly prescribed

drugs. Overall antiepileptic drugs usage as monotherapy and polytherapy.

Efficacy in Monotherapy

Figure 3 reveals the reoccurrence rate was as follows: sodium valproate 25.90%, Carbamazepine 10%, Levetiracetam 50%, phenytoin 71.40%, Clobazam 85%. The data was represented in Figure 3. The lowest reoccurrence rate was with carbamazepine and then sodium valproate. So, these were observed to be most efficacious.

Efficacy in combinational therapy

Figure 4 shows the Sodium valproate and Carbamazepine combination was found to be better efficacious with lowest reoccurrence rate of 12.5%.

DISCUSSION

Many factors persuade treatment collection include age, sex, types of seizures, aetiology, simultaneous anti-epileptics. Successful therapy ought to obtain balance in procuring remission or control of seizure episodes and side effects.^{13,14} Only paediatric subjects were included

in this study.

Present study demonstrates that Carbamazepine and Sodium valproate were most frequently prescribed monotherapy drugs. Childhood epilepsy had a generally favourable outcome, with 90% no reoccurrence rate with Carbamazepine and 74.1% with Sodium valproate which shows better efficacy in seizure control. The AED's Sodium valproate, Carbamazepine, Clobazam, Levetiracetam and Phenytoin were compared with monotherapy and their combinations. It was observed that 131 (87.3%) patients were treated with monotherapy, the rate of seizure remission rate was 81 (61.8%) and 19 (12.6%) patients were with multidrug therapy, the rate of seizure remission was 11 (57.8%).

Efficacy

In previous study, Unsal *et al.* 2014 had shown that 83.7% where the rate was significantly higher for seizure-free with Valproate Monotherapy in children. They observed total remission rate of 84.8% for twelve months which shows similar or slightly higher than several other studies where the control rate of seizures was between 50% and 84% for first line anti-seizure drug treatment in children.¹⁵ Our study in paediatrics, 131 (87.3%) were on

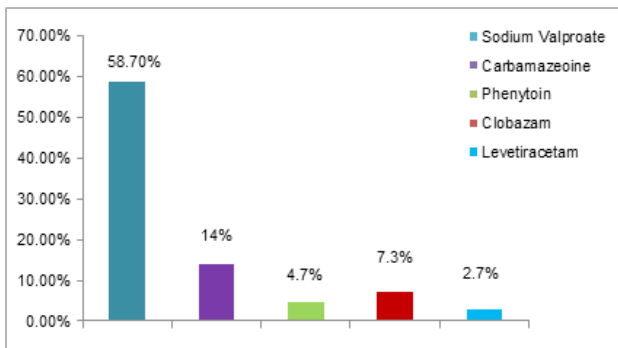


Figure 1: Frequencies of Monotherapy of anti-epileptics prescribed to patients to control seizure episodes

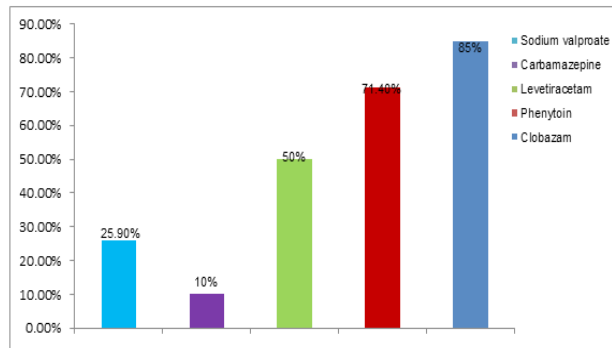


Figure 3: Reoccurrence of seizure episodes during long term Monotherapy.

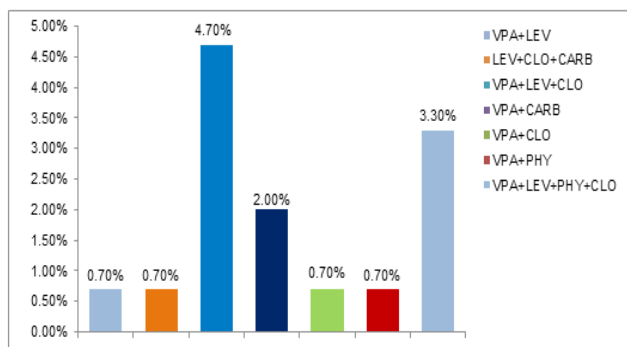


Figure 2: Frequencies of antiepileptic drug combinations (Polytherapy) prescribed to patients to control seizure episodes.

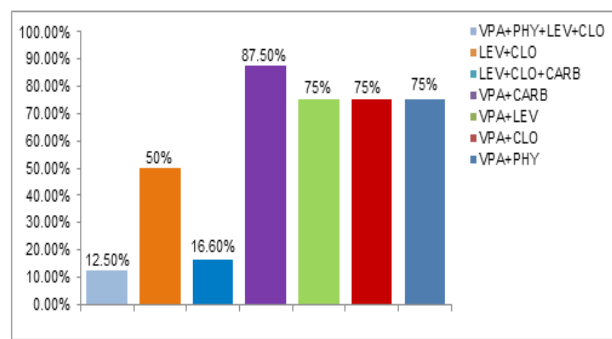


Figure 4: No reoccurrence of seizure episodes during the usage of anti-epileptic drug combinations (Polytherapy).

monotherapy in that 81 (61.8%) seizure control rate was observed, which was significant.

Antiepileptic drug efficacy comparison in our study

In our analysis, the majority given antiepileptic drugs were Sodium valproate and Carbamazepine. The potency was not similar in all drugs which were taken in our study. Unsal *et al.* 2014 had shown related beneficial rates with all AEDs which includes Carbamazepine, Valproate, Oxcarbazepine, Phenobarbital and Levetiracetam. Based on their comparative study under conventional care with phenytoin, carbamazepine, valproate and phenobarbital had shown analogous result of benefits and adverse events.¹⁵ In our study, Sodium valproate, Carbamazepine, Clobazam, Levetiracetam, Phenytoin were compared with monotherapy and their combinations for efficacy and safety. The results were found to be, Carbamazepine and Sodium valproate had shown better efficacy with statistically significant.

In previous study Lage *et al.* 2005 reported that, among 90% of patients taking Levetiracetam mono therapy shown greater than 50% subjects with seizure depletion.¹⁶ The data availability on efficacy of carbamazepine and phenytoin in our study were limited. In the present study, Levetiracetam and Phenytoin doesn't have better efficacy in monotherapy.

Table 1: Socio-demographic details.

| Gender | No. of patients (n=150) | Percentage |
|-------------|-------------------------|------------|
| Male | 88 | 59% |
| Female | 62 | 41% |
| Age | No. of patients (n=150) | Percentage |
| 0-12 months | 3 | 2% |
| 1-6 years | 60 | 40% |
| 7-12 years | 75 | 50% |
| 13-14 years | 12 | |

Tolerability

Adverse effects: In our study, the drugs carbamazepine, clobazam, levetiracetam, sodium valproate and phenytoin tolerability was assessed by using the highest incidence of adverse drug effects. The highest incidence of three major adverse effects was cognitive impairment, mood alterations and dizziness with sodium valproate and Carbamazepine. Even though there is highest incidence of adverse effects with sodium valproate and Carbamazepine the study was observed that these drugs had better tolerability. We found no significant difference in the efficacy and tolerability with these drugs. Monotherapy of Levetiracetam had shown no adverse effects in the present study.

Dudley *et al.* 2009, evaluated that therapy failed in terms of adverse effects and ineffectiveness put up parallel to anti-epileptic first line agents in children.¹⁷ Our study suggest, that adverse effects which occur with the most frequently prescribed drugs and better efficacious drugs are to be monitored cautiously and/or to avoid the risks of cognitive problems setting of low doses is to be followed.

Table 2: Types of seizures and their frequencies.

| Types of seizures | Frequency (150) | Percentage |
|--------------------------|-----------------|------------|
| GTCS | 67 | 44.6% |
| Focal seizures | 23 | 15.3% |
| Complex partial seizures | 10 | 6.6% |
| Simple partial seizures | 6 | 4.0% |
| Complex febrile seizures | 5 | 3.3% |
| Simple febrile seizures | 5 | 3.3% |
| Absence seizures | 5 | 3.3% |
| Atonic seizures | 2 | 1.3% |
| Status epilepticus | 14 | 9.3% |
| Tonic seizures | 8 | 5.3% |
| Unprovoked seizures | 3 | 2% |
| Provoked seizures | 2 | 1.3% |

Table 3: Tolerability of drugs.

| Adverse effects | Sodium valproate | Clobazam | Carbamazepine | Phenytoin |
|----------------------|------------------|----------|---------------|-----------|
| Cognitive impairment | 28.55 | 7.1 | 35 | 0 |
| Mood alterations | 22 | 7.1 | 30 | 14.2 |
| Dizziness | 10.3 | 14.2 | 5 | 0 |
| Anger | 7.7 | 0 | 3 | 0 |
| Dullness | 3.8 | 7.1 | 0 | 0 |
| Weight gain | 1.2 | 0 | 5 | 0 |
| Rashes | 2.5 | 0 | 0 | 0 |
| Hypotension | 1.2 | 0 | 0 | 0 |

CONCLUSION

In conclusion, our study observed that the majority of patients were prescribed with sodium valproate and Carbamazepine. Based on seizure free and seizure control rate sodium valproate and Carbamazepine were considered as better efficacious drugs. Levetiracetam had better tolerability. Even though there was highest incidence of adverse effects, i.e., cognitive impairment, mood alterations and dizziness with sodium valproate and Carbamazepine the study were observed that these drugs had better tolerability. Our study suggests that drugs which had highest efficacy also had highest incidence of adverse effects hence monitor cautiously.

ACKNOWLEDGEMENT

The authors wish to thank B. Avanthi for their support.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

ABBREVIATIONS

AEDs: Anti-Epileptic Drugs; **ANOVA:** Analysis of Variance; **MRI:** Magnetic Resonance, **EEG:** Electroencephalogram; **CT scan:** Computed tomography; **GCTs:** Generalized Tonic Clonic Seizures; **VPA:** Sodium Valproate; **PHY:** Phenytoin; **CLO:** Clobazam; **LEV:** Levetiracetam; **CARB:** Carbamazepine.

SUMMARY

The most commonly prescribed anti-epileptic medications were sodium valproate and carbamazepine and these two drugs shown highest efficacy rate in controlling episodes of seizure occurrence. Even though they show highest efficacy they had highest incidence of adverse effects hence monitor attentively.

REFERENCES

- Jincy G, *et al.* Evaluation of drug utilization and analysis of anti-epileptic drugs at tertiary care teaching hospital. *Indian J Pharmacy Prac.* 2016;9(3):189-94. Available from: <http://www.ijopp.org/article/473>.
- National Institute for Health and Care Excellence. The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care. CG137. London: The National Institute for Health and Care Excellence. 2012. Available from: <http://www.nice.org.uk/guidance/cg137>.
- Ebru A, *et al.* Drug treatment failures and affectively in children with newly diagnosed epilepsy. *Department of Paediatric Neurology.* 2010;19(9):553-7. Available from: <https://www.sciencedirect.com/science/article/pii/S1059131110001810>.
- Lowenstein DH, *et al.* Harrison's Principles of Internal Medicine, Seizures and epilepsy, 17th Edition. New York, McGraw-Hill. 2008;e363-1-52. Available from: <https://accessmedicine.mhmedical.com/Content.aspx?bookId=2129§ionId=192531797>.
- Ghai, *et al.* Ghai Essential Paediatrics, Seizures and epilepsy, 8th edition. 2013;552-60.
- Epilepsy A Manual for Physicians. World Health Organization. New Delhi: Regional Office for South-east Asia. 2004;1.
- Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A, *et al.* Lamotrigine versus Valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. *Epilepsia.* 2004;45(9):1049-53. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/15329068>.
- Anuradhasingh S, *et al.* The Epidemiology of Global Epilepsy New York, Department of neurology. NYU School of Medicine. 2016;34(4):837-47. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/27719996>.
- Gilberg C, *et al.* Febrile seizures and epilepsy. *Sweden Paediatric Neurol.* 2017;74:80-6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28754226>.
- Ravi MR, *et al.* Being seizure free is every epileptic's right. Publisher: Express News Service, India. 2018. Available from: <http://www.newindianexpress.com/cities/bengaluru/2018/mar/14/being-seizure-free-is-every-epileptics-right-1787211.html>.
- McNamara JO. Drugs effective in the therapy of the epilepsies. 10th edition. Goodman and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill Companies Inc. 2001;521-48.
- Kumaran AK, *et al.* A study on drug use evaluation of antiepileptics at a multi-speciality tertiary care teaching hospital. *International Journal of Pharm Tech Research.* 2009;1(4):1541-7.
- Guevara J, *et al.* Preliminary study on the efficacy and tolerability of newer anti-convulsants in a population of epileptic patients. *Medical Principles and Practice.* 2005;14(1):31-4. Available from: <https://www.karger.com/Article/Pdf/81920>.
- Marson AG, *et al.* The new antiepileptic drugs: A systematic review of their efficacy and tolerability. *Epilepsia.* 1997;38(8):859-80. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/9579887>.
- Unsal Y. Efficacy and tolerability of first anti-epileptic drugs in children with newly diagnosed idiopathic epilepsy. *Seizure.* 2014;23(4):252-59. Available from: <https://www.sciencedirect.com/science/article/pii/S1059131113003245>.
- Lagae L, *et al.* Clinical experience with levetiracetam in childhood epilepsy: An add-on and monotherapy trial. *Seizures.* 2005;14(1):66-71. Available from: [https://www.seizure-journal.com/article/S1059-1311\(04\)00188-8/fulltext](https://www.seizure-journal.com/article/S1059-1311(04)00188-8/fulltext).
- Dudley RW, *et al.* First drug treatment failures in children newly diagnosed with epilepsy. *Paediatric Neurol.* 2009;40(2):71-7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19135617>.