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Insights into Anti-Epileptic Drug Therapy: A Cross-Sectional Comparison of Adverse Drug Reactions In Monotherapy Vs. Polytherapy at a Tertiary Care Hospital

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ABSTRACT

Epilepsy, a widespread neurological disorder, poses significant challenges to effective treatment, often resulting in a diminished quality of life for affected individuals. Despite its prevalence, managing epilepsy remains a complex task, as many patients experience treatment non-compliance due to adverse effects or perceived lack of efficacy. The conventional approach to treatment involves monotherapy, wherein a single anti-epileptic drug (AED) is prescribed. However, this method often leads to adverse effects necessitating dose escalation, which can ultimately prompt treatment cessation.

In recent years, polytherapy has emerged as an alternative strategy for managing epilepsy. Polytherapy involves combining multiple AEDs at reduced doses to mitigate adverse effects and enhance therapeutic efficacy. While monotherapy is favored for its simplicity and historical effectiveness, there is growing interest in exploring the comparative effectiveness and safety between monotherapy and polytherapy.[1] Understanding the nuances of these treatment approaches is essential for clinicians and patients alike to make informed decisions regarding epilepsy management, considering factors such as seizure control, adverse effects, and overall quality of life.

This review aims to provide a comprehensive analysis of the efficacy and safety profiles of monotherapy and polytherapy in epilepsy treatment. By evaluating existing evidence and clinical outcomes, this study offers valuable insights that can guide clinicians in tailoring treatment regimens to individual patient needs, ultimately improving outcomes and enhancing the overall quality of care for individuals living with epilepsy.

Results from our study have established that out of the 563 patients included in our study, about 50% have developed some sort of adverse drug reaction (ADR). Of these 282 patients that have developed an ADR, about 62% of patients were on monotherapy and the remaining 38% were on polytherapy. Establishing

the fact that monotherapy is more effective than polytherapy in reducing the incidence of adverse drug reactions.

Keywords: Epilepsy, Seizure, Polytherapy, Monotherapy, Adverse Drug Reactions

INTRODUCTION

Epilepsy, a condition of the central nervous system, manifests as abnormal brain activity, leading to seizures and episodes of unusual behavior or feelings. It affects approximately 50 million individuals worldwide, presenting a significant public health challenge. The hallmark of epilepsy is recurring seizures, characterized by brief periods of involuntary movement that may affect specific body parts (partial) or the entire body (generalized), sometimes accompanied by loss of awareness. While not communicable, epilepsy poses substantial morbidity and mortality risks if not managed effectively.[2]

Timely detection and prevention of adverse drug reactions (ADR) in epilepsy patients undergoing anti-epileptic drug (AED) therapy are crucial. Regular monitoring of patients on AEDs not only enhances adherence to drug therapy but also enables healthcare practitioners to provide better treatment options, reducing associated morbidity and mortality. Pharmacovigilance plays a pivotal role in safeguarding public health by preventing, identifying, and assessing ADRs associated with pharmaceutical drugs intended for human consumption.[3]

Understanding seizures and epilepsy requires familiarity with the terminology and nomenclature established by the International League Against Epilepsy (ILAE). A seizure is defined as an abnormal electrical perturbation resulting from a network of neurons, while epilepsy is characterized by recurrent seizures. The ILAE's 2014 revision of epilepsy's definition emphasizes criteria such as unprovoked or reflex seizures occurring at specific intervals, diagnosis of an epilepsy syndrome, or a calculated probability of further seizures. This revised definition underscores epilepsy as a disease, aligning it with other serious health conditions like cancer and heart disease.[4]

Not all individuals suffering from epilepsy attain the desired therapeutic outcome with the initial treatment plan. Treatment failure may arise from inappropriate drug selection and dosages, as well as poor compliance with the therapeutic regimen. Failure to comply with antiepileptic drugs (AEDs) has been linked to increased mortality rates, more frequent emergency hospital visits, economic burden, reduced job efficiency, and a decline in the quality of life. Furthermore, non-adherence to the AED regimen results in a higher cost of epilepsy care. Patients receiving first-generation AEDs were observed to have a higher rate of discontinuation. The cost-effectiveness of treatment was assessed by determining the mean therapy cost, which is greatly influenced by treatment compliance, AED medication, and the age of the patient.[5]

To ensure timely detection and prevention of adverse drug reactions (ADR), it is essential to regularly monitor patients taking anti-epileptic drugs (AEDs). This not only enhances patients' adherence to drug therapy but also enables healthcare practitioners to provide better treatment options and reduce associated morbidity and mortality. Pharmacovigilance plays a crucial role in safeguarding public health by preventing, identifying, and assessing ADR associated with pharmaceutical drugs intended for human consumption. While AEDs are prescribed for various neurological disorders, they may lead to different types of ADR such as tremors, loss of appetite, skin rashes, gum hypertrophy, and other symptoms.[6]

Monotherapy, heralded for its potential to minimize adverse effects, avoid drug interactions, enhance patient compliance, and reduce costs, stands as an appealing approach in epilepsy management. With the advent of several new AEDs, the concept of monotherapy has gained further traction, as these drugs have

demonstrated efficacy not only as adjunctive treatments but also as standalone agents. The availability of these newer AEDs, including clobazam, lamotrigine, vigabatrin, gabapentin, and topiramate, has prompted considerations of employing them as first-line therapies.

However, while monotherapy presents a promising avenue, a significant proportion of patients with refractory epilepsy find themselves on polytherapy regimens. This scenario, although beneficial for select individuals, underscores the need for a critical evaluation of the polytherapy approach. Rationalizing polytherapy becomes imperative in light of the plethora of available AEDs, each with distinct mechanisms of action. The concept of "rational polytherapy," aimed at exploiting potential synergies between different agents or leveraging pharmacokinetic interactions, emerges as a tantalizing prospect, albeit one lacking robust empirical support.

Moreover, the evolving landscape of epilepsy treatment demands comprehensive studies comparing the efficacy and tolerability of newer AEDs both in monotherapy and polytherapy settings. As our understanding of epilepsy pathophysiology deepens and as more data on specific drug combinations becomes available, the judicious use of polytherapy, particularly with newer agents, holds promise for optimizing patient care.[7]

In this context, this review aims to explore the benefits and considerations surrounding monotherapy in epilepsy treatment, with a focus on the advantages it offers over polytherapy and the potential implications of integrating newer AEDs into clinical practice. Through an examination of existing evidence and emerging perspectives, we seek to elucidate the role of monotherapy as a cornerstone in epilepsy management while acknowledging the evolving nature of therapeutic paradigms in this complex neurological disorder.

OBJECTIVE

The objective of this study was to compare the proportion of adverse drug reactions in Monotherapy versus Polytherapy in a Tertiary care Hospital in Kerala, India.

MATERIALS & METHODOLOGY

A Retrospective Descriptive Cross-Sectional Study was conducted in the Neurology Department of a tertiary care hospital in Kerala, India for six months starting from November 2022 to April 2023. A total of 563 patients, diagnosed with epilepsy, and taking anti-epileptic drugs for at least one year were enrolled in the study. The patients below 18 years, the Pregnant population, and Lactating women were excluded from the study. The Data were collected from medical records and patient drug charts. It was also obtained by follow-up through Telephonic communication. The medical records and patient drug chart were analyzed and telephone interviews were conducted for follow-up data on further events. The medical records with incomplete information on drugs were excluded from data collection.

The statistical formula used for calculating sample size was:

$[Z^2 * p * (1-p)/e2] / [1 + (Z2 * p * (1-p)/e2 * N]$

Where,

P = Standard Deviation

N = Population Size

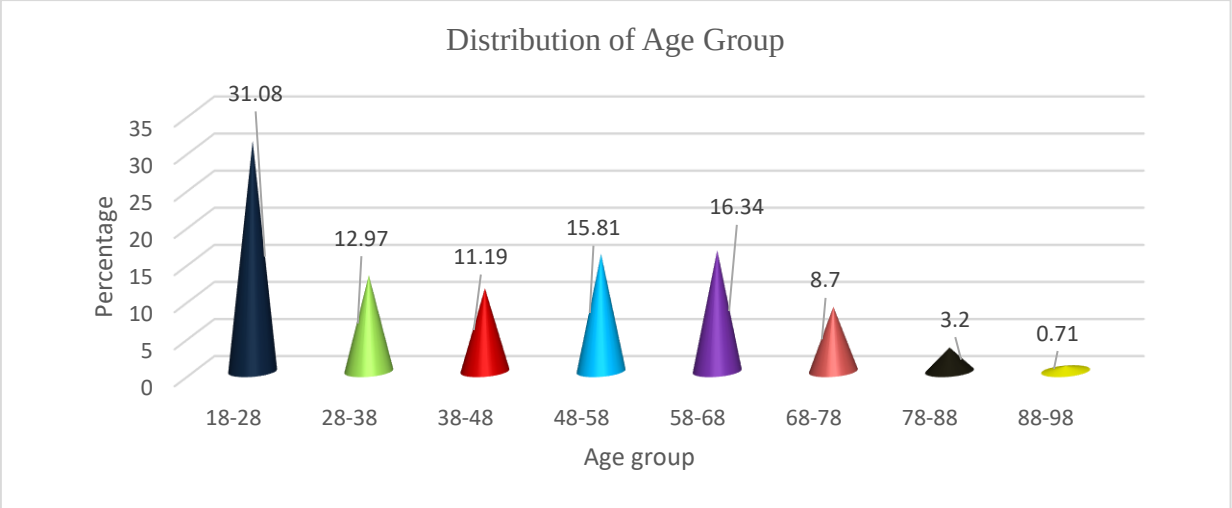
e = Margin of error

Z = 95% Confidence interval of Z

The data was entered in Microsoft Excel – 2021. The results were analyzed in tabular form and percentages. A Descriptive Analysis was performed. The study was approved by the Institutional Review Board of the Tertiary Care Hospital in Kerala, India.

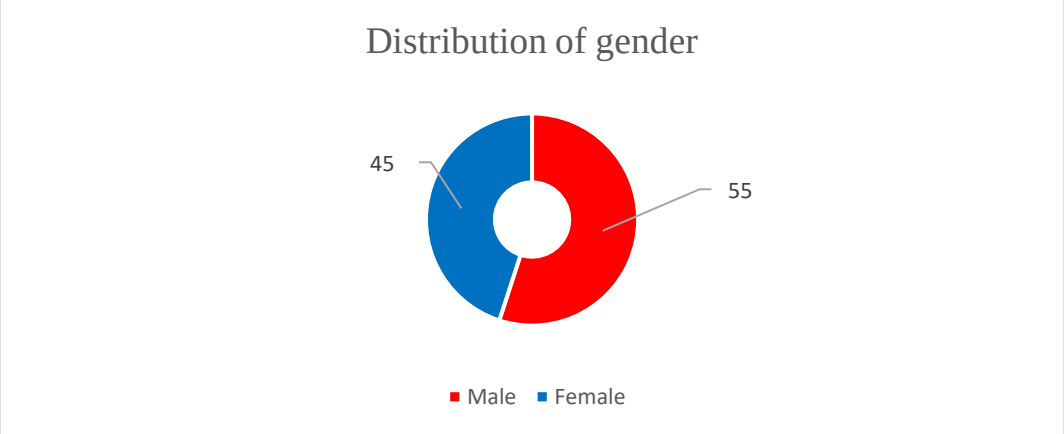
RESULTS

Figure 1: Distribution of age group



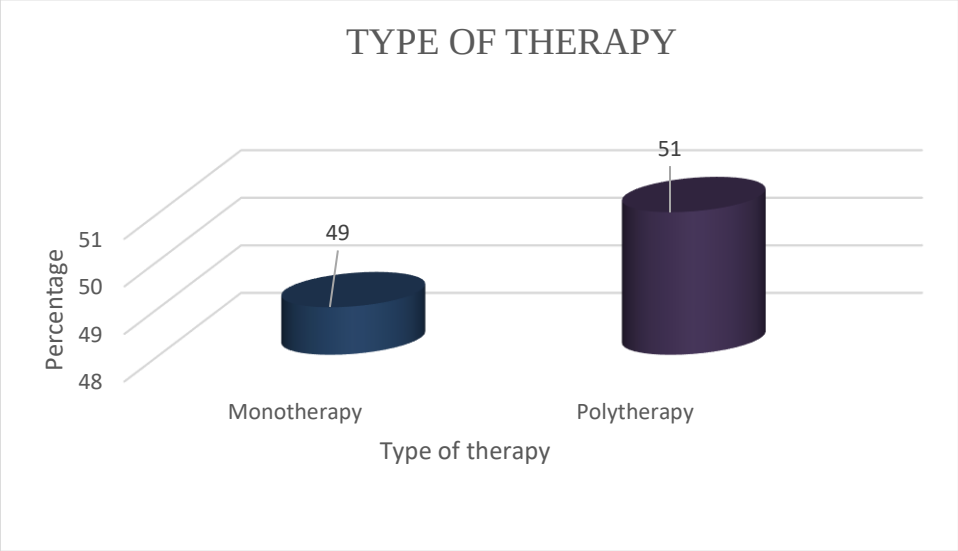
It was observed from our study conducted on 563 epilepsy patients that epilepsy was most frequently found to occur in the age group of 18-28 (about 175 people accounting for 31.08 %) followed by the respective age groups 58 - 68 (92 people accounting for 16.34%), age group of 48 - 58 (89 people accounting for 15.81%), age group of 28 - 38 (73 people accounting for 12.97%), age group of 38-48 (63 people accounting for 11.19%), age group of 68 - 78 (about 49 patients accounting for 8.70%), age group of 78 - 88 (about 18 patients accounting for 3.20%), age group of 88-98 (4 patients accounting for 0.71%).

Figure 2: Distribution of gender



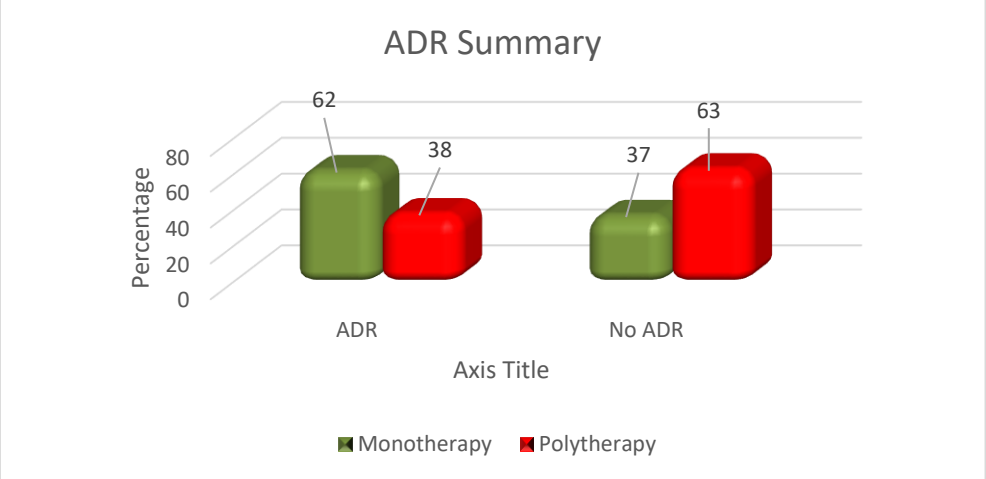
Out of the 563 patients included in our study about 55% (307 patients) were men and 45% (256 patients) were women.

Figure 3: Distribution of type of therapy



In our study on epilepsy and anti-epileptic medication-induced adverse drug reactions, it was found that the most commonly used treatment modality is polytherapy with a slight margin over monotherapy with polytherapy comprising about 51% vs monotherapy about 49%.

Figure 4: Summary of ADR



This table shows the number of patients who experienced an adverse drug reaction (ADR) and the number who did not, broken down by whether they received monotherapy or polytherapy. Out of a total of 563 patients, 280 (50%) experienced an ADR while 283 (50%) did not. Of the 280 patients who experienced an ADR, 173 (62%) received monotherapy while 107 (38%) received polytherapy. On the other hand, of the 283 patients who did not experience an ADR, 104 (37%) received monotherapy while 179 (63%) received polytherapy.

Table 1: ADR distribution according to monotherapy

Sl.No	Drugs	ADR	Frequency	Percentage(%)
1.	Levetiracetam (n=74)	Aggression	8	11

		Blurred vision	1	1.35
		Depression	7	9.3
		Eruptions in the oral cavity	1	1.35
		Headache	38	51.2
		Hypersomnia	1	1.35
		Mood swings	11	15
		Rashes on body	1	1.35
		Sleep deprivation	1	1.35
		Syncope	3	4.05
		Vomiting	1	1.35
		Tachycardia	1	1.35
2.	Phenytoin (n=23)	Allergy	4	17.3
		Constipation	3	13
		Dyspnea	1	4.3
		Eruptions in the oral cavity	7	30.2
		Hypersomnia	1	4.3
		Nausea	2	9
		Rashes on body	1	4.3
		Restlessness	1	4.3
		Vomiting	2	9
		Tachycardia	1	4.3
3.	Divalproex sodium (n=17)	Anorexia	1	6
		Dry mouth	8	47
		Weight gain	2	12
		Tremor	5	29
		Tachycardia	1	6
4.	Carbamazepine (n=41)	Ataxia	1	2.44
		Headache	1	2.44
		Mood swings	1	2.44
		Reduced development	1	2.44
		Restlessness	1	2.44
		Sleep deprivation	1	2.44
		Stomach upset	1	2.44
		Syncope	16	39.02
		Tachycardia	18	43.9
5.	Chlordiazepoxide (n=1)	Bradycardia	1	100
6.	Oxcarbazepine (n=1)	Weight gain	1	100
7.	Clobazam (n=3)	Constipation	1	33.3
		Flashes of light	1	33.3

		Sleep deprivation	1	33.3
8.	Pregabalin (n=1)	Double vision	1	100
9.	Clonazepam (n=5)	Flashes of light	1	20
		Muscle weakness	1	20
		Slurred speech	3	60
10.	Sodium Valporate (n=5)	Osteoporosis	1	20
		Sleep deprivation	1	20
		Stomach upset	3	60
11.	Lamotrigine (n=1)	Sleep deprivation	1	100
12.	Topiramate (n=1)	Weight loss	1	100

Table 2: ADR distribution according to polytherapy

SL. No	Drugs	ADR	Frequency	Percentage(%)
1.	Carbamazepine and Levetiracetam (n=44)	Aggression	2	4.5
		Blurred Vision	1	2.2
		Depression	1	2.2
		Mood swings	5	11.3
		Worsening of tremor	1	2.2
		Tachycardia	13	30
		Sleep deprivation	4	9
		Syncope	17	38.6
2.	Carbamazepine,levetiracetam and clonazepam (n=1)	Aggression	1	100
3.	Phenytoin and levetiracetam (n=26)	Allergy	5	19.2
		Ataxia	1	4
		Eruptions in the oral cavity	5	19.2
		Headache	15	57.6
4.	Clobazam,carbamazepine and topiramate (n=1)	Anorexia	1	100
5.	Lamotrigine and clonazepam (n=1)	Arrythmia	1	100
6.	Oxcarbazepine and Brivaracetam (n=1)	Allergy	1	100
7.	Levetiracetam and lacosamide (n=1)	Blurred vision	1	100
8.	Phenobarbitone and lacosamide (n=1)	Blurred vision	1	100
9.	Phenytoin and Phenobarbitone (n=2)	Bradycardia	2	100
10.	Phenytoin and divalproex sodium (n=13)	Constipation	1	7.69
		Dry mouth	4	30.77

		Aggression	1	7.69
		Ataxia	1	7.69
		Weight gain	5	38.47
		Vomiting	1	7.69
11.	Phenytoin and lorazepam (n=2)	Constipation	2	100
12.	Phenytoin, levetiracetam, and clobazam (n=7)	Flashes of light	7	100
13.	Divalproex sodium,Levetiracetam and Lacosamide (n=1)	Hyponatremia	1	100
14.	Phenytoin and phenobarbital (n=3)	Hypothermia	3	100
15.	Topiramate and Clobazam (n=3)	Weight loss	3	100

DISCUSSION:

Epilepsy, a brain disorder marked by a persistent tendency to produce epileptic seizures and the accompanying neurobiological, cognitive, psychological, and social ramifications, typically begins its management with antiepileptic drug (AED) monotherapy, which is preferred for its efficacy; most patients respond well to the initial or subsequent monotherapy attempts. This article delves into the rationale and evidence supporting the prioritization of monotherapy and outlines guidelines for initiating and effectively implementing AED monotherapy. In cases where monotherapy fails, options include switching to a new AED monotherapy, introducing chronic maintenance AED polytherapy, or exploring non-pharmacological interventions such as epilepsy surgery or vagus nerve stimulation. Consolidating AED polytherapy into monotherapy often alleviates adverse effects and may enhance seizure management.

Monotherapy stands out as the preferred treatment approach for many individuals with epilepsy, with particular emphasis on special patient groups such as women, the elderly, and those with co-existing conditions. These populations are at heightened risk of adverse effects and drug interactions related to antiepileptic drugs (AEDs). Monotherapy offers advantages over polytherapy by mitigating the potential for drug interactions. Conditions like hepatic and renal dysfunction can substantially alter the metabolism and elimination of numerous AEDs, potentially compromising their tolerability and safety with prolonged use. Therefore, prioritizing monotherapy in these vulnerable patient subsets is essential to minimize risks and optimize treatment outcomes.

Adverse reactions that happened as a part of treatment with anti-epileptic drugs and epilepsy were found to occur more frequently in younger patients belonging to the age group of 18 – 28. However, published studies on similar topics have established that epilepsy was found to occur more commonly in the elderly. The results were in contrast to the study conducted by **J. Cloyd, W. Hauser, and A.**—Towne on the Epidemiological and medical aspects of epilepsy in the elderly.[8]

Epilepsy is more prone to occur and develop in males rather than females. This has been attributed to the increased risk factor of males to suffer from or be exposed to causes of lesional epilepsy. This has also been established in already published studies that have also shown that males are more likely to suffer from epilepsy rather than females. The results were similar to the study conducted by **John C. McHugh, and Norman Delanty** on Epidemiology and Classification of Epilepsy: Gender Comparisons.[9]

Polytherapy is more widely used in epileptic patients. However, published studies have established that newly diagnosed epileptic patients require monotherapy. Results of some experimental studies have found that drug combinations exert potent anticonvulsant activity with minimal or no adverse effects. The results of the study were similar to the study conducted by **Stanislaw J Czuczwar, and Kinga K Borowicz** on Polytherapy in epilepsy: the experimental evidence.[10]

ADVERSE DRUG REACTION (ADR) PROFILES IN MONOTHERAPY:

The distribution of adverse drug reactions (ADRs) among various antiepileptic drugs (AEDs) reveals a nuanced landscape, often diverging from previous findings and highlighting the importance of considering individual patient responses. For instance, while the adverse effect profile of levetiracetam, as observed by **Gashirai K. Mbizvo, Peye Dixon,** and **Jane L. Hutton**, emphasized somnolence and infection, our study identified headache as the most prevalent side effect. This disparity underscores the variability in patient experiences and the necessity of individualized monitoring.[11] Similarly**, A. Del Negro, C. D. Dantas,** and **V. Zanardi** reported on phenytoin's potential to cause cerebellar atrophy, contrasting with our findings of predominantly oral cavity eruptions and allergies.[12]Such differences underscore the multifactorial nature of ADRs and the need for a comprehensive assessment. The adverse events associated with divalproex sodium in our study align with previous reports, despite **A. Beydoun, J. C. Sackellares,** and **V. Shu** advocating for its monotherapy efficacy in partial epilepsy.[13] This discrepancy emphasizes the complexity of AED responses and the importance of individual patient factors in treatment outcomes. **Zahra Tolou-Ghamari, Mohammad Zare,** and **Jafar Mehvari Habibabadi's** findings on carbamazepine-induced motor coordination destruction and rare risks of aplastic anemia contrast with our study's observation of syncope and tachycardia.[14] Such variations underscore the necessity of vigilant monitoring and consideration of diverse patient responses. In summary, the discrepancies in ADR distributions underscore the heterogeneous nature of patient responses and emphasize the necessity of individualized assessment and monitoring in epilepsy management.

ADVERSE DRUG REACTION (ADR) PROFILES IN POLYTHERAPY:

In our comprehensive study involving 44 patients receiving either Carbamazepine or Levetiracetam, a plethora of adverse drug reactions (ADRs) surfaced, including but not limited to aggression, blurred vision, depression, mood swings, worsened tremor, tachycardia, sleep disturbances, and syncope. Intriguingly, syncope emerged as the most prevalent ADR, affecting 38.6% of patients, with tachycardia following closely at 30%. Of particular note, the introduction of levetiracetam in patients with severe refractory epilepsy induced marked symptoms of carbamazepine toxicity, compelling adjustments in medication regimens. This contrasted with the findings elucidated by **Sanjay M Sisodiya, Josemir W.A.S Sander,** and **Philip N Patsalos**.[15] Similarly, in a cohort of 26 individuals prescribed Phenytoin and Levetiracetam, headaches prevailed as the most frequently reported ADR at a striking 57.6%, diverging starkly from the observations documented by **R.C. Mundlamuri, S.Sinha,** and **D.K. Subbakrishna**.[16] Despite these disparities, emerged promising prospects for intravenous levetiracetam as a potential alternative for managing seizures, particularly in select patient cohorts. Meanwhile, in another subset of 13 patients administered Phenytoin and Divalproex Sodium, dry mouth (30.77%) and weight gain (38.47%) emerged as the predominant ADRs, diverging significantly from the findings documented by **D M Turnbull, D Howl,** and **M D Rawlins**.[17] Conversely, a smaller cohort of five patients subjected to Phenytoin and Phenobarbital combination therapy experienced adverse effects such as bradycardia and

hypothermia, aligning closely with the observations made by **Matti Livanainen** and **Heikki Savolainen**.[18] Notably, Phenobarbital's notorious side effects encompass hyperactivity, sedation, and dementia, while phenytoin is associated with a spectrum of adverse reactions, ranging from sedation to megaloblastic anemia. These findings underscore the imperative for tailored treatment strategies and meticulous monitoring to optimize therapeutic outcomes while mitigating the burden of adverse effects, thereby enhancing patient care and quality of life.

CONCLUSION

Among the 563 patients in our study, approximately 50% experienced adverse drug reactions (ADRs). Of these 282 patients with ADRs, 62% were on monotherapy, while the remaining 38% were on polytherapy. These findings establish a higher incidence of ADRs among polytherapy users, supporting the notion that monotherapy may be more effective in reducing the occurrence of adverse drug reactions compared to polytherapy. Our study underscores a notable difference in the incidence of adverse drug reactions (ADRs) between polytherapy and monotherapy users among patients receiving anti-epileptic drugs. The higher occurrence of ADRs among polytherapy users provides evidence supporting the effectiveness of monotherapy in reducing such adverse events. These findings highlight the importance of considering monotherapy as a preferred treatment approach to minimize ADRs and enhance patient safety and quality of life in epilepsy management.

LIST OF ABBREVIATIONS

ADR – Adverse Drug Reaction
AED – Anti-Epileptic Drug
ILAE - International League Against Epilepsy

REFERENCES:

1. Eatock J, Baker GA. Managing patient adherence and quality of life in epilepsy. Neuropsychiatric disease and treatment. 2007 Feb 1;3(1):117-31.
2. Epilepsy https://www.who.int/news-room/fact-sheets/detail/epilepsy
3. Schachter SC. Evaluation and management of the first seizure in adults. UpToDate. http://www. uptodate. com/(Sist oppdatert:[2017-02-21]). 2022.
4. Fisher RS, Cross H, D'Souza C, French JA, Haut S, Higurashi N, Hirsch E, Jansen FE, Peltola J, Moshé SL, Perucca E. 2017 International League Against Epilepsy classifications of seizures and epilepsy are steps in the right direction. Epilepsia. 2019 Jun;60(6):1040-4.
5. Asghar MA, Rehman AA, Raza ML, Shafiq Y. Analysis of treatment adherence and cost among patients with epilepsy: a four-year retrospective cohort study in Pakistan. BMC Health Services Research. 2021 Dec;21:1-8.
6. Maqbool M, Dugassa D, Fekadu G. Adverse drug reactions of antiepileptic drugs in the neurology department of a tertiary care hospital, Srinagar, Jammu & Kashmir, India. Archives of Neuroscience. 2021;8(2).
7. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. Bmj. 2014 Feb 28;348.
8. Cloyd J, Hauser W, Towne A, Ramsay R, Mattson R, Gilliam F, Walczak T. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy research. 2006 Jan 1;68:39-48.

9. McHugh JC, Delanty N. Epidemiology and classification of epilepsy: gender comparisons. International review of neurobiology. 2008 Jan 1;83:11-26.
10. Czuczwar SJ, Borowicz KK. Polytherapy in epilepsy: the experimental evidence. Epilepsy research. 2002 Nov 1;52(1):15-23.
11. Mbizvo GK, Chandrasekar B, Nevitt SJ, Dixon P, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant focal epilepsy. Cochrane Database of Systematic Reviews. 2020(6).
12. Del Negro AN, Dantas CD, Zanardi VE, Montenegro MA, Cendes FE. Dose-dependent relationship of chronic use of phenytoin and cerebellar atrophy in patients with epilepsy. Arquivos de neuro-psiquiatria. 2000 Jun 1;58(2A):276-81.
13. Beydoun A, Sackellares JC, Shu V. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. Neurology. 1997 Jan;48(1):182-8.
14. Tolou-Ghamari Z, Zare M, Habibabadi JM, Najafi MR. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2013 Mar;18(Suppl 1):S81.
15. Sisodiya SM, Sander JW, Patsalos PN. Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. Epilepsy research. 2002 Feb 1;48(3):217-9.
16. Mundlamuri, R.C., Sinha, S., Subbakrishna, D.K., Prathyusha, P.V., Nagappa, M., Bindu, P.S., Taly, A.B., Rao, G.U. and Satishchandra, P., 2015. Management of generalized convulsive status epilepticus (SE): A prospective randomized controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate, or levetiracetam–Pilot study. *Epilepsy research*, *114*, pp.52-58.
17. Turnbull DM, Howel D, Rawlins MD, Chadwick DW. Which drug for the adult epileptic patient: phenytoin or valproate? Br Med J (Clin Res Ed). 1985 Mar 16;290(6471):815-9.
18. Livanainen M, Savolainen H. Side effects of phenobarbital and phenytoin during long-term treatment of epilepsy. Acta Neurologica Scandinavica. 1983 Dec;68:49-67.