

# Prescription Pattern of Antiepileptic Drugs in Patients with Refractory Epilepsy: A Cross-Sectional, Observational Study from a Tertiary Care Centre in North India

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## ABSTRACT

**Background:** Refractory epilepsy poses significant therapeutic challenges due to poor seizure control and adverse drug effects despite multiple antiepileptic drug (AED) therapies.

**Objective:** To assess the proportion of patients with refractory epilepsy achieving good seizure freedom on polytherapy, along with their seizure control, clinical profile, radiological profile, EEG patterns and adverse events.

**Materials and Methods:** This cross-sectional, observational study was conducted over 18 months and involved 130 patients diagnosed with refractory epilepsy who had been receiving polytherapy for more than 6 months. Demographic, clinical, EEG, MRI data and adverse effects of AEDs were analysed. Statistical analyses were conducted using t-tests and Chi-square test, with significance of  $p \leq 0.05$ .

**Results:** Among 130 patients, 64.62% achieved a good outcome (seizure-free for 6 months). 70.24% males belong to good

outcomes in comparison to females (29.76%). Mean age of patients with good outcomes ( $29.40 \pm 11.14$  years) and ( $26.76 \pm 10.53$  years) in poor outcomes. Mean BMI in the good outcome group is ( $22.70 \pm 2.57$ ), while ( $21.15 \pm 3.28$ ) in the poor outcome group (p-value of 0.003, demonstrating a statistically significant association). Vegetarians (40.48%) had better outcomes in contrast to non-vegetarians (p-value = 0.026, statistically significant association). Idiopathic epilepsy was the most common etiology followed by granuloma. Levetiracetam, Oxcarbazepine, and Valproic acid are used in similar proportions among patients with both good and poor seizure outcomes. Generalised seizures were more common than focal seizures. Most common adverse effects reported were constipation, anxiety, sedation, dizziness, fall, sedation and weight gain.

**Conclusion:** Although polytherapy remains essential in refractory epilepsy management, rational prescription is crucial. Increased use of newer AEDs may improve outcomes while minimizing adverse effects.

**Keywords:** Refractory epilepsy, Antiepileptic drugs, Polytherapy, Prescription patterns

## INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures caused by excessive and synchronous neuronal discharges in the brain. An estimated 50 million people worldwide suffer from it, making it a common neurological disorder.[1] The global prevalence is 0.5% to 1%, with treatment gaps of over 75% in resource-limited settings.[2] Patients with epilepsy suffer physical damage, cognitive impairment, psychological comorbidities and a threefold increased risk of early mortality. These characteristics emphasize the need for treatment strategies.

Approximately 30–40% of patients do not achieve seizure control with single antiepileptic drug (AED).[3] According to Kwan et al. (2010), refractory epilepsy is present when two or more effective AEDs do not result in sustained seizure freedom.[4] Focal seizures, which are more difficult to treat, complicate the treatment of this patients group.[5] Due to the frequent seizures, the pharmaceutical side effects and the emotional burden of the chronic disease, refractory epilepsy impairs quality of life. In addition, it places a significant economic burden on healthcare systems, particularly in underdeveloped countries with limited access to modern treatments.[6] In India for epilepsy care older AEDs are generally used due to price and availability. Tertiary care centres have shown that Sodium Valproate, Carbamazepine and Phenytoin dominate in monotherapy and polytherapy.[7]

Personalized AED treatment is possible using pharmacogenomics. Genetic differences affect drug metabolism, efficacy and tolerability and enable patient-specific therapy. For example, Genetic indicators associated with Phenytoin toxicity can help to make prescribing safer.[8] It also claims that 70% of epilepsy patients worldwide could be cured with low-cost AEDs.[9] In

developed countries, Phenobarbital is discouraged as an AED due to its neurotoxicity, causing sedation, mood changes, behavioural and cognitive changes, and other symptoms.[10,11] A 1984 study by Kovalenko in drug-resistant epilepsy patients showed a significant benefit of antioxidant therapy, including alpha-tocopherol (vitamin E isoform with the highest biological activity).[12] The positive results, including reduced seizure frequency and improved abnormal electroencephalogram (EEG) findings, have been replicated by other authors.[13]

## MATERIALS & METHODS

The study was conducted jointly by the Departments of Pharmacology and Neurology at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India. It was a cross-sectional, observational study on patients with refractory epilepsy, carried out over 18 months in the Neurology Outpatient Department and refractory epilepsy clinics of this tertiary care hospital. Ethical approval was obtained from the Institutional Ethics Committee (IEC No.-04/23).

Patients aged 18–75 years, of both genders, diagnosed with refractory epilepsy and on polytherapy for at least six months were included. Exclusion criteria were pregnancy, lactation, hypersensitivity to study drugs, renal/hepatic/cardiac failure, HIV, Hepatitis B and C, chronic alcoholism, or being a drug defaulter. Written informed consent was taken from all participants.

Data collected included demographic details [age, gender, place of living, occupation, body mass index (BMI), dietary and smoking habits], comorbidities (e.g., diabetes, hypertension etc.), magnetic resonance imaging (MRI), EEG patterns, AED regimens, adverse effects in the past six months and clinical details of epilepsy including etiology and seizure outcomes.

Refractory epilepsy is a rare disease, out of the 147 patients initially considered, only 130 patients attended the Neurology OPD/refractory epilepsy clinic during the

recruitment period of the study. Therefore, the final analysis was conducted on these 130 patients.

### Study Flow Chart

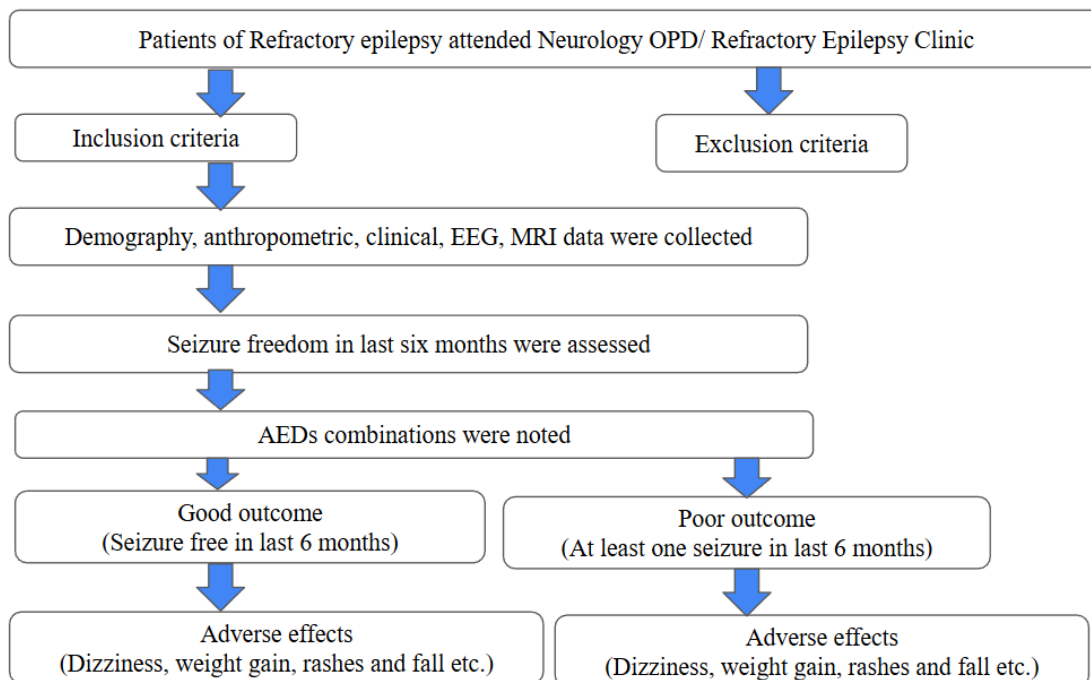


Figure 1: Study flow chart.

### Statistical Analysis

Statistical analysis was done using SPSS v21.0, with data expressed as mean ± SD and percentages. Chi-square test/Fisher’s exact test compared categorical variables,

independent t-test was used to assess discrete variables and  $p < 0.05$  was considered statistically significant.

### RESULT

Table 1: Demographic and anthropometric characteristics of patients

Parameters		Good outcome (n=84, 64.62%)	Poor outcome (n=46, 35.38%)	p-value
Gender	Male (83)	59 (70.24%)	24 (52.17%)	0.063
	Female (47)	25 (29.76%)	22 (47.83%)	
Age (years)	(Mean± SD)	(29.40±11.14)	(26.76±10.53)	0.190
Place of living	Urban (34)	27 (32.14%)	7 (15.22%)	0.059
	Rural (96)	57 (67.86%)	39 (84.78%)	
BMI (Kg/m <sup>2</sup> )	(Mean± SD)	22.70±2.57	21.15±3.28	0.003*
Dietary habits	Vegetarian (43)	34 (40.48%)	9 (19.57%)	0.026*
	Non-vegetarian (87)	50 (59.52%)	37 (80.43%)	
Smoking habits	Smokers (6)	4 (4.76%)	2 (4.35%)	1.00
	Non-smokers (124)	80 (95.24%)	44 (95.65%)	

\*p-value<0.05= statistically significant n= number of patients

Among 130 patients, 84 (64.62%) remained seizure-free in the past six months, while 46 (35.38%) continued experiencing seizures. This shows most patients achieved good

control, though a smaller group still faced poor outcomes.

Good outcomes and poor outcomes were seen in 70.24% of males versus 29.76% of females and 52.17% of males versus

47.83% of females respectively. Although males showed better control, the p-value (0.063) indicates no significant association. The mean age of patients with good outcomes ( $29.40 \pm 11.14$  years) was not significantly different from those with poor outcomes ( $26.76 \pm 10.53$  years), p-value = 0.190).

Among urban patients, 32.14% were seizure-free and 15.22% had continued seizures, while in rural patients, 67.86% were seizure-free and 84.78% had continued seizures. Despite higher poor outcomes in rural residents, the p-value shows no significant association.

Mean BMI for the good outcome group is ( $22.70 \pm 2.57$ ), while for the poor outcome group, it is ( $21.15 \pm 3.28$ ). The p-value of 0.003, demonstrating a statistically significant association between BMI and seizure outcomes.

Among vegetarians, 40.48% were seizure-free versus 19.57% with continued seizures, while among non-vegetarians, 59.52% were

seizure-free and 80.43% had poor outcomes. The statistically significant p-value (0.026) indicates better seizure control in vegetarians.

In the good outcome group, 4.76% were smokers and 95.24% non-smokers, while in the poor outcome group, 4.35% were smokers and 95.65% non-smokers. A p-value of 1.00 shows no significant association between smoking and seizure outcomes. [Table 1]

Among students, 35.71% were seizure-free while 54.35% continued seizures; workers showed 4.76% good and 8.70% poor outcome. Skilled workers had mostly good outcomes, whereas all service employees and shopkeepers achieved seizure freedom. Among farmers (n=26, 20%), 19 (22.62%) achieved seizure freedom, while 17.86% housewives had good outcomes. The association between occupation and seizure outcome was not statistically significant (p=0.089). [Fig. 2]

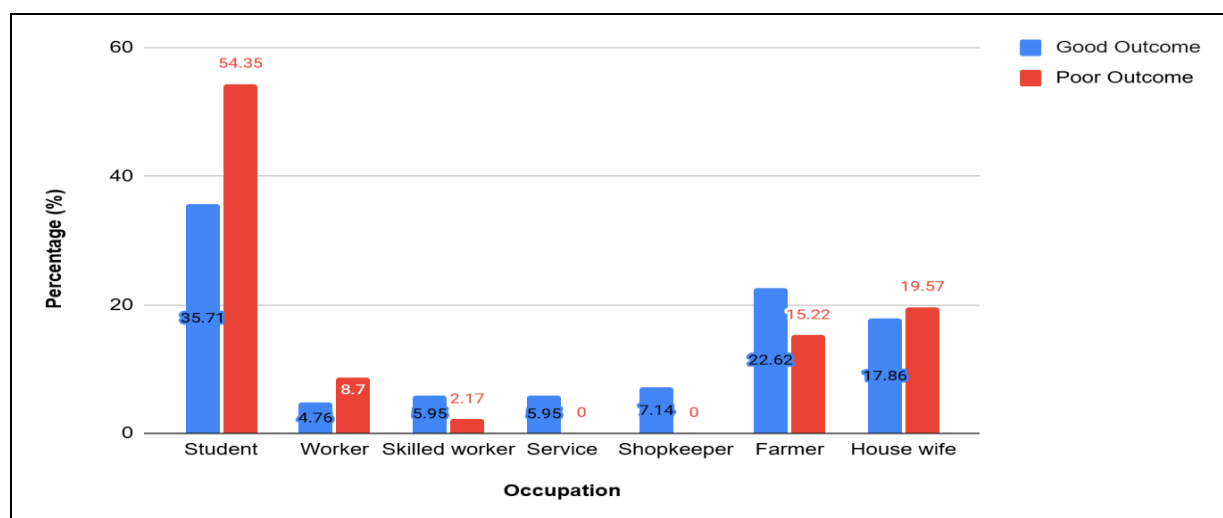


Figure 2: Association of frequency of Occupation with good outcome and poor outcome

Idiopathic epilepsy was the most common etiology, seen in 52 patients (61.90%) with good outcomes and 28 (60.87%) with poor outcomes, suggesting prognosis depends on other factors. Granuloma [Calcification + Neurocysticercosis (NCC)] was found in 18 (21.43%) good and 14 (30.43%) poor outcome cases, with no significant

association (p=0.614). TBM occurred in 2 (2.38%) good outcome patients only. Mental Retardation was present in 1 (1.19%) good and 1 (2.17%) poor outcome case. MTS appeared in 5 (5.95%) good and 1 (2.17%) poor outcome patients, while Old Gliosis was reported in 6 (7.14%) good and 2 (4.35%) poor outcome patients. [Fig. 3]

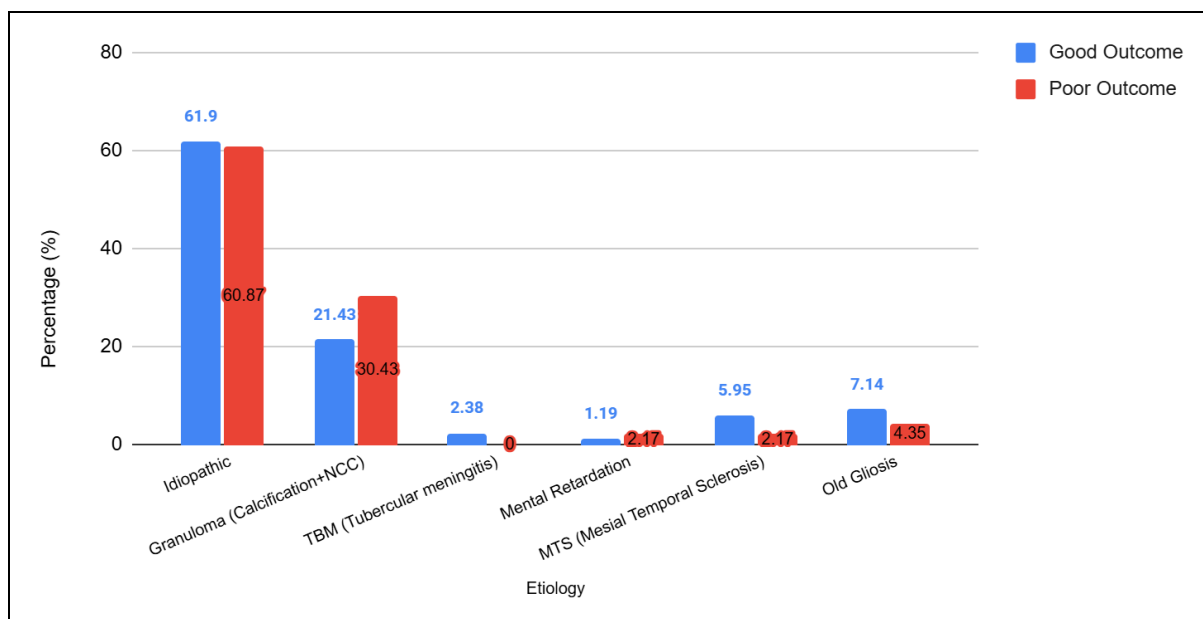


Figure 3: Association of frequency of Aetiology with good and poor outcome

Among good outcomes (n=84), 70.24% had generalized and 29.76% focal seizures, while in poor outcomes (n=46), 60.87% had

generalized and 39.13% focal seizures. The difference was not significant (p=0.373). [Fig. 4]

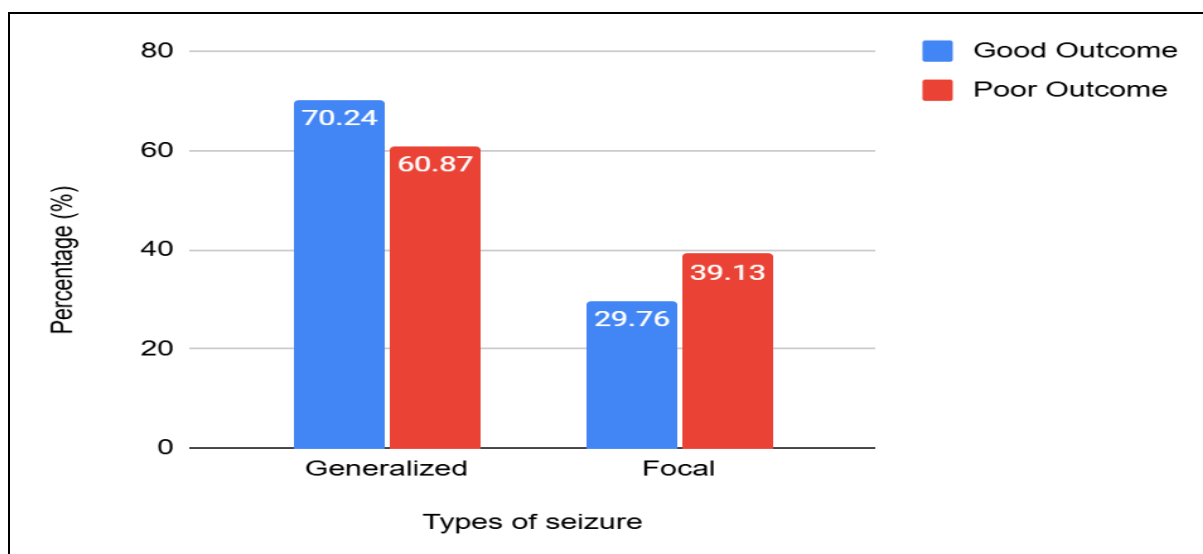


Figure 4: Association of frequency of Type of seizure with good outcome and poor outcome

Levetiracetam (LEV), Oxcarbazepine (OXC), and Valproic acid (VPA) were used in similar proportions across groups: LEV in 60 (71.43%) good vs. 33 (71.74%) poor, OXC in 54 (64.29%) vs. 32 (69.57%), and VPA in 62 (73.81%) vs. 33 (71.74%). Phenobarbital use was higher in poor outcomes (15, 32.61%) than good (17, 20.24%), while Lacosamide (LCM) was

given to 23 (27.38%) good vs. 17 (36.96%) poor. Lamotrigine (LTG), Carbamazepine (CBZ), Clonazepam (CLZ), Topiramate, and Lorazepam were used infrequently, Zonisamide (ZNS) appeared only in poor outcomes (2, 4.35%), and Brivaracetam (BRV) was prescribed to 5 (5.95%) good vs. 7 (15.22%) poor outcome patients. [Fig. 5]

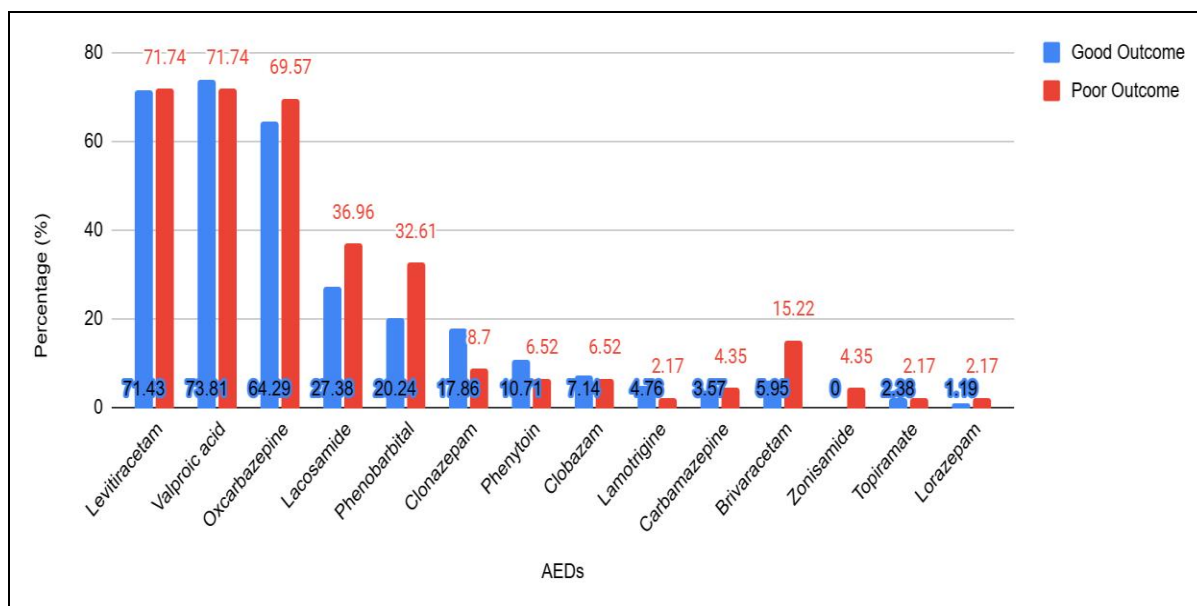


Figure 5: Association between combination of various antiepileptic drugs (AEDs) and seizure outcomes

In the good outcome group, common adverse effects included constipation (6, 7.14%), anxiety (4, 4.76%), sedation (3, 3.57%), dizziness (3, 3.57%), and decreased appetite (2, 2.38%), with weight gain, visual symptoms, and hypersalivation each in 1 (1.19%). In the poor outcome group, reported adverse effects included fall (4,

8.70%), skin lesions, piloerection, increased seizure frequency and sedation (each 2, 4.35%), and weight gain (1, 2.17%). Falls, seizure worsening, and skin lesions were exclusive to poor outcomes, while dizziness, headache, visual symptoms and hypersalivation occurred only in good outcomes. [Fig. 6]

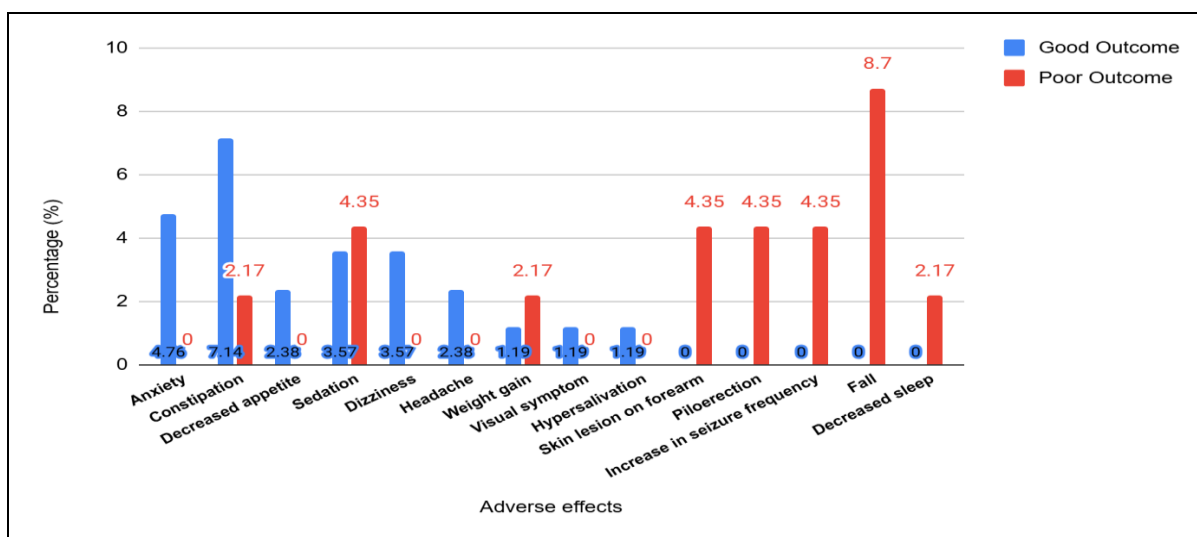


Figure 6: Association between various adverse effects with seizure outcomes

In the good outcome group, 79 (94.05%) had normal EEG and 5 (5.95%) abnormal, while in the poor outcome group, 41 (89.13%) had normal and 5 (10.87%) abnormal EEG, with no significant association ( $p=0.508$ ). MRI findings were

also not significant ( $p=0.942$ ): 51 (60.71%) normal vs. 33 (39.29%) abnormal in good outcomes, and 29 (63.04%) normal vs. 17 (36.96%) abnormal in poor outcomes. [Fig. 7]

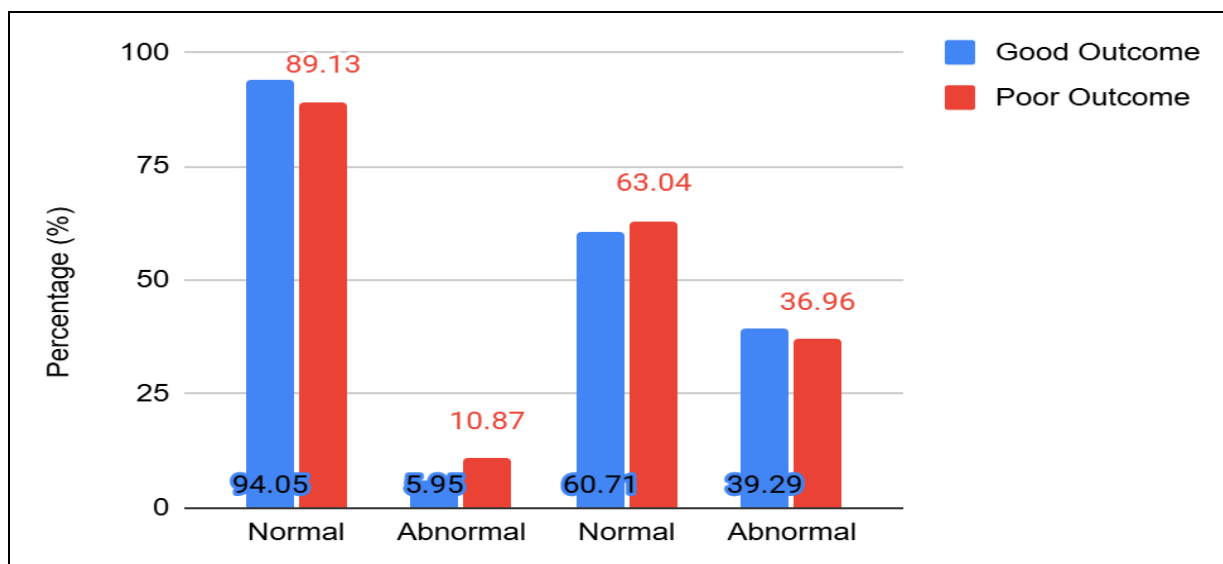


Figure 7: Association between EEG and MRI findings with seizure outcomes

Family history of seizures, chronic kidney disease (CKD) and chronic liver disease (CLD) were absent in both groups ( $p=1.00$ ). Diabetes mellitus (DM) was reported in 1 (1.19%) good and 1 (2.17%) poor outcome patients ( $p=1.00$ ), while hypertension (HTN) occurred in 3 (3.57%) good vs. 1 (2.17%) poor ( $p=1.00$ ). Cardiovascular disease (CVD) was seen in 2 (2.38%) good

outcome patients only ( $p=0.539$ ). Other neurological disorders were nearly equal 4 (4.76%) good vs. 2 (4.35%) poor ( $p=1.00$ ). Hospitalization due to seizure exacerbation was higher in poor outcomes (4, 8.70%) vs. good (3, 3.57%) ( $p=0.243$ ), and intubation was noted in 2 (4.35%) poor outcomes only ( $p=0.127$ ). [Fig. 8]

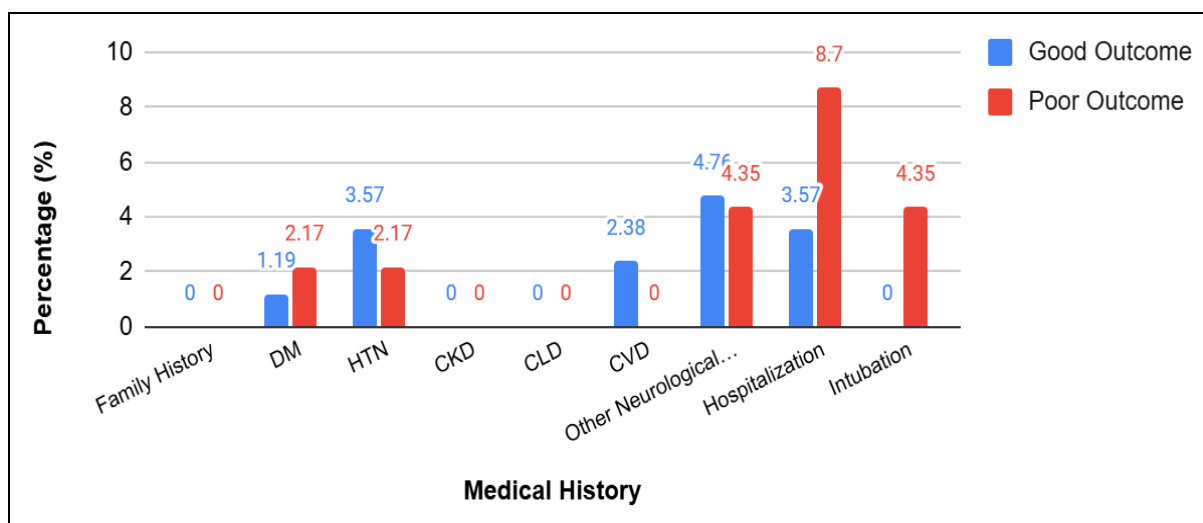


Figure 8: Association between various medical history with seizure outcomes

## DISCUSSION

Our study examined AEDs prescription patterns in refractory epilepsy, revealing that 84 of 130 patients (64.62%) achieved seizure freedom over six months, while 46 (35.38%) continued to experience seizures. These results underscore the effectiveness

of current therapies, though additional strategies are needed for non-responders.

A higher proportion of males had better seizure control compared to females, supporting observation by Joshi et al. (2020).[14]

The mean age of patients with good outcomes ( $29.40 \pm 11.14$  years) was not significantly different from those with poor outcomes ( $26.76 \pm 10.53$  years).

In this study we found that a higher proportion of rural residents experienced continued seizures (67.86%), the p-value showed no statistically significant association.

In our study weight, height and BMI had a significant impact on seizure outcomes. Higher BMI was associated with better seizure control, supporting the observation by Chen et al. (2018) that healthier patient profiles improve outcomes.[15]

We found that vegetarian patients had a higher proportion of seizure freedom compared to non-vegetarians. The p-value showed statistically significant association between dietary habit and seizure outcome.

Our study found no significant associations between smoking and seizure control, comparable to Joshi et al. (2020).[14]

In our study we found that among students, 35.71% experienced seizure-free outcomes, while 25 (54.35%) experienced poor outcomes. Workers, skilled workers, service employees, and shopkeepers had good outcomes, while farmers and housewives had similar outcomes. Service employees and shopkeepers had 100% seizure-free outcomes, while farmers had 22.62% good outcome and 15.22% poor outcome respectively. Housewives had an almost equal distribution, with 17.86% showing good outcomes and 19.57% having poor outcomes.

In our study, we examined the association between different etiologies and patient outcomes to determine their impact on prognosis. Idiopathic epilepsy was the most common etiology, present in both good (61.90%) and poor outcome (60.87%) groups, indicating that factors beyond etiology, such as treatment response and patient characteristics, may influence prognosis followed by granuloma. Similarly, other etiologies, including TBM, Mental Retardation, MTS, and Old Gliosis

were found in smaller proportions without significant outcome differences.

In this study we found that generalized seizures were more common than focal seizures. According to Shilpa et al. (2018), generalized tonic-clonic seizures (GTCS) were the predominant type of epilepsy, accounting for 79% of cases, with males (62%) and people aged 20 to 40 years (52%) being the most affected.[16]

Our study reveals that common AEDs like Levetiracetam, Oxcarbazepine, and Valproic acid are used in similar proportions among patients with both good and poor seizure outcomes. However, other AEDs show differing patterns.

In our study, constipation, anxiety, sedation, dizziness and decreased appetite were the most prevalent adverse effects among the good outcome group. Most common adverse effects among the poor outcome group were fall, forearm skin lesions, piloerection and increase in seizure frequency followed by sedation and weight gain. To reduce adverse effects and maximize seizure control, vigilant monitoring, customized therapy modifications, and supportive management are essential. Chen et al (2018) found that newer AEDs were administered less frequently but had fewer adverse effects than older AEDs, which affected treatment response.[15]

In our study, we found no significant association between EEG or MRI findings and seizure outcomes.

In our study comorbidities such as hypertension, diabetes, CVD and other medical history may have an indirect impact on treatment adherence and AEDs metabolism and therefore require additional study.

This study cannot be generalized to all types of populations as socioeconomic status was not assessed in this study. Also, long term follow-up was not conducted to examine the long-term effects, durability of treatment or lifestyle changes. To overcome these limitations, long-term multicentre studies are required to confirm these results and

investigate treatment options for refractory epilepsy.

## CONCLUSION

This study explores AEDs use in refractory epilepsy and its impact on seizure control. Outcomes did not differ significantly between generalized and focal seizures, though idiopathic epilepsy responded best. While monotherapy is preferred, polytherapy is often necessary. Better nutrition and higher BMI were linked to improved results, while adverse effects hindered adherence in poorly controlled cases. Personalized AEDs selection based on seizure type, age and health status is crucial and larger long-term studies are needed to refine treatment strategies.

## Declaration by Authors

**Ethical Approval:** Approved

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**Conflict of Interest:** The authors declare no conflict of interest.

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