ASSESSMENT OF PATIENT REPORTED ADVERSE DRUG REACTIONS AND QUALITY OF LIFE IN EPILEPTIC PATIENTS RECEIVING POLYTHERAPY: A HOSPITAL BASED STUDY

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Abstract:

Objectives: Aims to collect and assess the patient reported adverse drug reactions and quality of life in patients receiving anti-epileptic polytherapy.

Methods:A cross-sectional study was carried out in the Psychiatric Out Patients Department (OPD) of Krishna Rajendra Hospital, Mysuru. Patients who were above 18 years of age and willing to participate in the study, met with the specified inclusion criteria were included. The causality of reported ADRs and quality of life were assessed using Naranjo algorithm and QOLIE-10 respectively and analysed.

Results: In a study of 108 subjects, anti-epileptic ADRs were reported by males (50.52%) and females (49.48%). Naranjo scale classified 49% ADRs as probable, 51% as possible. Central nervous system was most affected. Mean quality of life score was 27.17±4.51; 57.4% had good quality of life. No association found in chi-square analysis for age, gender, or number of antiepileptics($p>0.05$).

Conclusion: Anti-epileptic polytherapy's adverse reactions impact mental health and patient quality of life. Rising prevalence underscores the need for vigilant monitoring and prompt reporting to healthcare providers, with clinical pharmacists playing a key role in fostering collaboration for successful epilepsy care.

Keywords: antiepileptics; polytherapy; adverse drug reactions; causality; central nervous system; quality of life; clinical pharmacist

INTRODUCTION

Epilepsy as defined by international league against epilepsy (ILAE), is a characteristic cluster of clinical and electroencephalographic feature, often supported by specific etiological factors. It is a chronic neurological disorder associated with recurrent unprovoked seizures that may involve sensory, motor or autonomic phenomena with or without loss of consciousness.

Globally around 50 million people are affected with epilepsy and in India it is estimated that more than 10 million patients are diagnosed with epilepsy and more than 2 million patients with drug resistant epilepsy.

Disruption of normal homeostasis of the neuron and disturbances in its stability may trigger abnormal neuronal discharge. There are many underlying causes which leads to epilepsy, but in about 50% of the cases the etiology is unknown. According to the ILAE Task Force has developed a criterion which categories the epilepsy causes into six types; genetic, structural, metabolic, infectious, immune and unknown.

Antiepileptic drug (AED) therapy, in epileptic patients are given with four main goals; to eliminate seizure or reduce their frequency to maximum degree, to minimize the occurrence of adverse effects associated with long-term use of AEDs, in either to maintain or

restoring their usual psychological and vocational activities and to maintain normal lifestyle.

Paroxysmal discharges occurring synchronously in a large population of cortical neurons are the characteristic feature of seizure activity. It can be visualized as a sharp wave or a spike on EEG.

Successful therapy is based on evaluating the type of seizure, family history, and extent of associated neurological abnormalities. Initiating AED treatment should be based on the probability of seizure recurrences, the consequences of continuing seizures, and the beneficial and adverse effects of the agent in preventing recurrence. Currently available AEDs occasionally not only fail to control seizure in some patients but also frequently produce adverse effects that ranges from minimal impairment of CNS to death from aplastic anaemia or hepatic failure.

There are numerous bio-psycho-social factors affecting the quality of life in patients with epilepsy especially on polytherapy, patients receiving anti-epileptic polytherapy had are addressed to have higher prevalence of psychiatric comorbidities. It is required to evaluate the development of psychiatric comorbidities in patients receiving anti-epileptic treatment especially on polytherapy. The adverse effects of the ant-epileptic medication and incidence of cognitive impairment is established to have negative impact on quality of life. So, it is important to address the factors such as adverse drug reactions, adverse events and psychiatric comorbidities in epilepsy patients, thus will promote adherence, seizure control, emotional well-being and socio-occupational well-being

MATERIAL AND METHODS

Study design: It is a cross sectional observational study

Study site: Krishna Rajendra Hospital, MMCRI, Mysore.

Study population: An aggregate of 108 study participants with a diagnosis of epilepsy and complying our inclusion criterion from Psychiatry OPD were analysed..

Study period: This study was conducted over a period of six months from March 2023 to August 2023.

Ethical approval for the study: Institutional ethics committee of Mysore Medical College And Research Institute approved this research.

Inclusion criteria:

- Patients with epilepsy aged 18 yrs. Or older,
- Patients who are willing to participate and patients receiving anti-epileptic multi-drug regimen for at least one year were included

Exclusion criteria:

- Patients with significant disability, major psychiatry disorders, substance abuse, severe medical comorbidity confounding the QOL assessment.
- Patients who are pregnant and breast feeding are excluded.
- **Study tools:**

1. .The Informed Consent Form and the Information to participants were initially given to the patient and our objective was explained to the patient prior to each interview with a patient. After approval and signature from the patient, the study was proceeded to collect the demographic details of the patient (Name, Age, Sex, occupation, etc.) and data regarding past and present medical history are collected other data according to the questionnaire and data collection form.
2. Detection of ADRs was performed by face-to-face interview with patients and (or) caretakers at follow up visits and by review of their medical charts containing physical examinations and laboratory findings.
3. MedDRA system organ classification was used to categorize the reported ADRs. The causality relationship between reported ADRs and suspected medication was assessed by Naranjo algorithm. The suspected reactions were informed to concerned physicians and actions take after reaction was also noted.
4. Naranjo scale scoring: Naranjo scale comprises of 10 questions concerning the implicated medication and reaction phenotype. Each answered question has an individual score, which is then totalled to provide a final score that is associated with one of four categories of likelihood that the drug was associated with the reaction (unlikely, possibly, probably, or definitely).Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.
5. QOLIE10 questionnaire scoring: The QOLIE-10 screening questionnaire includes 10 questions. Three questions have opposite response sets, requiring reverse-scoring. The scoring should be calculated so that all positive responses are lower numbers and all negative responses are higher numbers. The total score is the sum of scores for all

questions divided by the number of items answered. Thus, if a patient skipped an item, it is not reflected in the total score. Patients with lowest scores have the least problems.

6. All data obtained from 108 patients were entered and analysed using MS excel software. Data were presented in frequency and percentage. Chi-square test was used in analysis and P ≤ 0.05 considered as significant.

RESULTS: An aggregate of 108 study participants with a diagnosis of epilepsy and complying our inclusion criterion from Psychiatry OPD were analysed.

DEMOGRAPHICS	NUMBER OF PATIENTS(n)	PERCENTAGE
Gender		
Male	57	52.77%
Female	51	47.23%
Age (in years)		
18-25	11	10.2%
26-44	56	51.9%
45-70	41	37.9%
Marital status		
Married	76	70.37%
Unmarried	32	29.62%
Education		
Educated	20	18.51%
Uneducated	88	81.48%
Occupation		
Employed	58	53.70%
Unemployed	50	46.29%

Table 1: Demographics of the study population

Comorbidities: In the included study population, the patients were presented with psychiatric related comorbid conditions and were reported as following, depression being the common condition 11.11% (n=12), followed by anxiety 7.61% (n=8) and psychosis 6.48% (n=7). Majority of patients, 75% (n=81) had no reports of psychiatric illness.

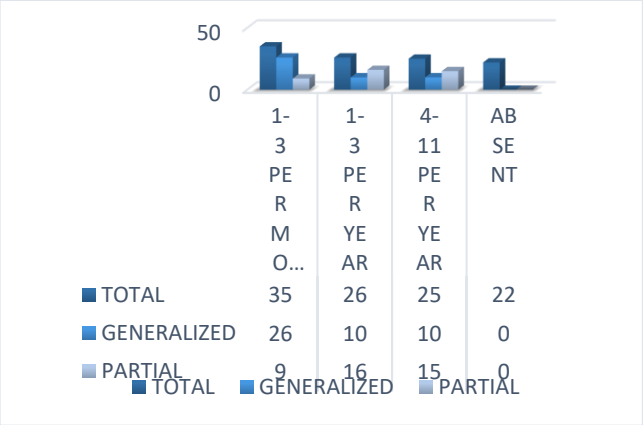

Fig 1: Distribution of Psychiatric illness as comorbidities in study population taking anti-epileptic polytherapy

Types and Frequency of seizures in the study population:

The study conducted among n=108 patients having epilepsy showed that 79.62% (n=86) were presented with epilepsy with ongoing medications, and only 20.37%(n=22) were free from epilepsy and were continuing the medications. The study focused on to the type of seizures and were broadly classified, and showed result, as patients with generalized seizure were about 53.48% (n=46) and partial seizures were 46.51% (n=40). The frequency of epileptic attacks were obtained and were found to be as follow, number of patients having seizure incidence of 1-3 per month were n=35 and within that n=26 (69.44%) were generalized and n=9 (25%) were partial type of seizures, and seizure incidence of 1-3 per year were n=26 and within that n=10 (38.46%) were identified as generalised and n=16(61.53%) as partial seizures, followed by n=25 were having seizure frequency of 4-11 per year were n=10 (40%) identified as generalized and n=15 (60%) as partial seizures

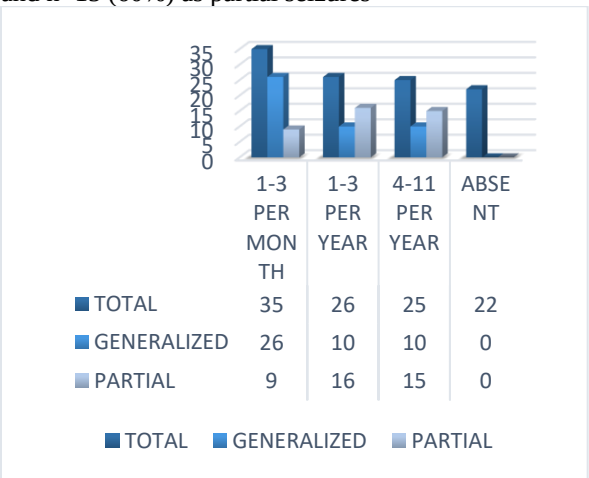

Figure2: Distribution of seizure frequency and type of seizure among the patients

Adverse Drug Reactions

The study conducted among n=108 participants, who were best fit for the inclusion criterion resulted in estimation of 249 ADRs in total during the Psychiatry OPD visit. It was found that among the n=108 participants 89.81% (n=97) were reporting that they were experiencing ADRs and only 10.18% (n=11) were reported to have no ADRs.Among the reported ADRs about 127 ADRs were classified as possible and 122 ADRs as probable according to the use of Naranjo Scale of causality assessment.

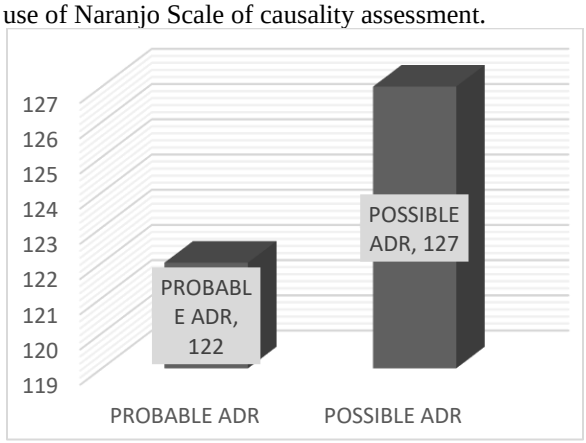

Figure3 :Distribution reported ADRs according to Naranjo scale

It is understood that male 53.41% (n=133) experienced a greater number of ADRs compared to female 46.58% (n=116). From the table, gastric irritation (8.03%) is more prevalent ADR among the patient taking anti-epileptic drugs.

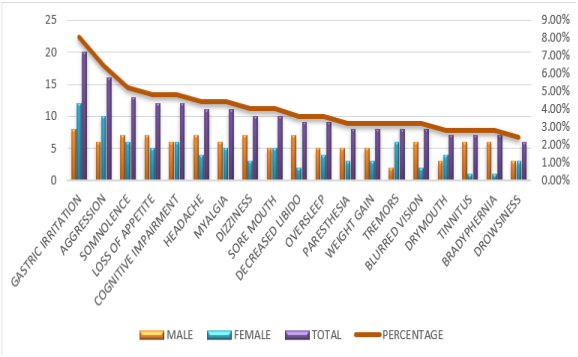

Figure 4:Distribution of ADRs on gender basis and percentage of each ADRs against total reported ADRs (1)

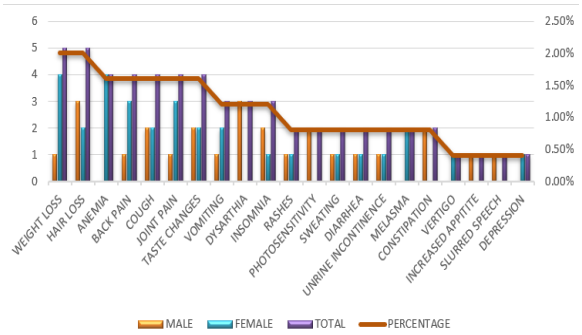

Figure 5: Distribution of ADRs on gender basis and percentage of each ADRs against total reported ADRs (2)

Adverse drug reactions classified under MedDRA System Organ Classification

The number of total ADRs were reported n=249, and the same was classified according to the MedRA system organ classification, to understand the reported ADRs affects which part of organ system by the intake of anti-epileptic polytherapy. It was found that ADRs reported were more in number under the CNS related disorders 30.92% (n=77), followed by GI disorders 19.27% (n=48) .

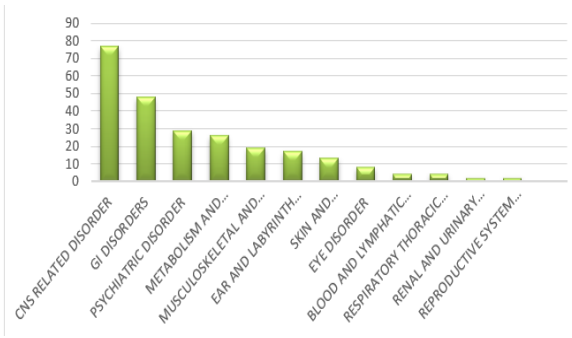

Figure 6:Distribution of ADRs according to MEdDRA System Organ Classification

Risk Factor Analysis of Adverse Drug Reaction

The probable risk factor for developing ADRs such as Gender, Age, Regimen were considered for the risk factor analysis and the result are shown in following table.

Factors	Number (n)	Chi-square value	P-value
Gender Male Female	 57 51	1.955739451	0.16197
Age ≤45 >45	 71 37	0.6815576	0.4090509
Regimen ≤3 Drugs >3 Drugs	 74 34	0.100575	0.751141

table 2: Details of factors influencing adverse drug reaction Statistically significance level p≤0.05
(*) indicates results are significant

Quality of life of patients having epilepsy involved in the study

The factors affecting the quality of life of the study participants having epilepsy is listed in table 5 and their respective QoL scores are being listed. The quality of life of the participants were assessed by QOLIE-10 questionnaire and the result obtained showed that mean score of QoL was found to be 27.17 ± 4.51. For patients having less than or equal to the mean value then, they are said to have good quality of life and those who are having greater than the mean value, poor quality of life. Broadly, among n=108 study participants, 57.4% (n=62) were having good quality of life and the remaining 42.6% (n=46) were having poor quality of life. Quality of life score each variable were carried out and are listed on table6.

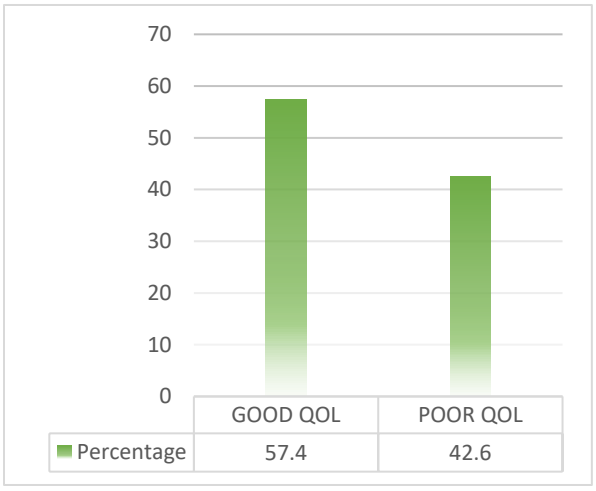

Figure7: Graph depicting percentage of quality of life in study population

VARIABLES	CHARACTERISTICS	NUMBER OF PATIENTS (n)	TOTAL QOL SCORE MEAN (SD)
GENDER	MALE	57	26.75 ± (4.63)
	FEMALE	51	27.64 ± (4.37)
AGE	18-36	42	27.23 ± (4.50)
	37-54	51	27.31 ± (4.55)
	55-72	15	26.53 ± (4.65)
EDUCATION	EDUCATED	20	26.88 ± (5.33)
	UNEDUCATED	88	28.02 ± (4.35)
OCCUPATION	EMPLOYED	58	26.10 ± (4.31)
	UNEMPLOYED	50	28.42 ± (4.46)
PSYCHIATRIC ILLNESS	ANXIETY	8	31.70 ± (4.24)
	DEPRESSION	12	32.00 ± (2.95)
	PSYCHOSIS	7	29.80 ± (2.28)
	NO PSYCHIATRIC ILLNESS	81	25.74 ± (3.90)
FREQUENCY OF ILLNESS	1-3 PER MONTH	35	29.71 ± (3.61)
	1-3 PER YEAR	26	27.98 ± (4.46)
	4-11 PER YEAR	25	26.89 ± (3.29)
	ABSENT	22	22.68 ± (3.90)
ONSET OF ILLNESS	≤3YRS	6	28.33 ± (4.17)
	≤5YRS	34	27.52 ± (4.22)
	≤10YRS	68	26.89 ± (4.71)
ADVERSE DRUG REACTION	ADR PRESENT	97	27.73 ± (4.27)
	ADR ABSENT	11	22.27 ± (3.60)

Table 3: Factors affecting the quality of life according to demographics and current clinical characteristics and their respective QoL score

DISCUSSION

Characteristic of study population

Data regarding socio demographic details of patients in our study showed that 52.8 % were male and 47.2% were female. The male predominance in our study was also found by similar study conducted by Mohammed BisetAyalew et alreporting 61 % male and 39% female and KeerthiJayelakshmi et al reporting 60% male and 40% female.

It was observed from our study that majority of the patients around 51.9% were between the age category 26-44 years which was analogous with study conducted by Esileman et al that reported 42.4 % of patients falling in category of 26-44 years.

Demographic of patients experiencing adverse drug reactions

In this study, 249 adverse drug reactions related to antiepileptics were reported from 97 patients out of 108 patients. The overall ADR rate was 89.8% which coincides with the similar study conducted by Yanru Duet al reported more than 50% of total ADR. An average of 2.56 ADRs occurred per patient with an ADR which is comparable to study conducted by

Yanru Du et al and Sachin Kumar et al reporting 2.79 ADRs per PWE 1.96 ADRs per PWE respectively.
The data also shows that male reported 50.52% of ADRs and female shows 49.48% of ADRs which is comparable to study conducted by MudasilMaqbool et al reported male showing 60.9% of ADRs and female showing 39.1% of ADR and Sachin Kumar et al reported male showing 61.5% of ADR and female showing 38.5% of ADR.
The result of chi square implicated that that there was no statistically significant relationship between the gender and presence and absence of ADRs (p=0.86). This coincides with study conducted by Keerthi Jayelakshmi et al.
Causality assessment of reported ADRs
Causality assessment by the Naranjo algorithm revealed that 49%ADRs were probable and 51%ADRs were possible. Similar finding was observed from study conducted by SohaNamazi et al reporting 42.75 % probable ADRs and 57.25% possible ADRs.
Categorization of ADR
According to the system-organ classification of AED-related adverse reactions the most common involved system is central nervous system (30.92%) followed by gastro intestinal disorder (19.28%) which show similar result from earlier study conducted by B M Gajjar et al reporting 60.71% of ADRs related to CNS followed by 60.71%ADRrelated to CNS, KeerthiJayelakshmi et alreporting42.85% of ADRs related to CNS and SohaNamazi et alreporting 44.08% CNS related ADRs.
Psychiatric comorbidity among study subjects
The occurrence of depression (11.11%) was more followed by anxiety(7.40%) and psychosis (6.48%)among 108 study subjects. These finding are consistent with findings of study conducted by JagritiYadav et al reporting most patients receiving antiepileptic polytherapy with major depressive disorder(32%) followed by anxiety spectrum disorders(n=28%) and suicidality (18%). The higher risk of depressive symptoms in patients with antiepileptic polytherapy can be associated with mechanism of antiseizure medications. The study conducted by Carlos Artega Rodriguez et al also reported that most frequent disorder found were depression disorder (22.8%), anxiety disorder (17.8%), psychosis (10%), bipolar affective disorder (8.5%) and psychogenic non epileptic seizure (5%).
Assessment of quality of life
The mean overall quality of life score of patients in this study is 27.17 ± 4.51. This result is in line with the study conducted by EsilemanAbdelaMuche et al which reported a mean quality of life of 19.86 and study conducted by JagritiYadav et al reported mean quality of life of 37.58±18.45.

CONCLUSION

Adverse reactions have significant safety concerns and they cause treatment failure due to impaired adherence to medication and thus effects the quality of life of patients. The prevalence of adverse drug reactions tends to increase when individuals with epilepsy are on antiepileptic polytherapy highlighting the need for careful monitoring and management. Indeed, in the context of managing epilepsy, altering medications or adjusting dosages can be challenging due to seizure recurrence. Therefore, it becomes essential to promptly report any adverse drug reactions to healthcare providers. Early reporting allows for effective management of ADRs through symptomatic treatment and adjustments that minimize the impact on overall quality of life of patient.

In tertiary hospital clinics, where time with doctors is limited, clinical pharmacists' step in as valuable allies in educating and ensuring compliance among epilepsy patients by conveying vital information about epilepsy, treatment option and potential adverse drug reactions in a concise manner.

ADR management in antiepileptic polytherapy is a delicate task where collaboration between patients, clinical pharmacists and healthcare professionals is pivotal for successful epilepsy care.

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