# Anti-epileptic drug utilization and treatment outcome among epileptic patients on follow-up in a resource poor setting

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## ABSTRACT

**Introduction:** Anti-epileptic drugs (AEDs) are the primary therapeutic modes for epileptic patients and have been demonstrated to control seizure, which decreases morbidity and mortality associated with epilepsy. There is a paucity of data on treatment outcome among epileptic patients in resource poor settings. The aim of this study was to assess AED utilization pattern and treatment outcome among epileptic patients on follow-up. **Materials and Methods:** A retrospective cross-sectional study was conducted among epileptic patients on follow-up at Epilepsy clinic of Jimma University specialized hospital. A total of 290 patient record cards which had 3 years of follow-up information was used to evaluate AED utilization pattern and treatment outcome through medical records review. **Results:** From a total 290 cards of epileptic patients on follow-up, 170 (58.6%) were males. The common type of seizure diagnosed was generalized tonic clonic seizure, 232 (80%). Monotherapy was commonly used in the management of seizure, 54.5%, among which phenobarbitone was the most commonly utilized single anticonvulsant drug. One hundred and sixty-five (56.7%) patients were seizure free during follow-up periods and 125 (43.3%) patients were not, of which 121 (73.3%) of patients had 1 up to 5 seizure attacks per 3 months during the 3 years follow-up period. **Conclusion:** All studied epileptic patients were put on traditional AEDs; phenobarbitone being the most frequently prescribed single drug. About one in every two epileptic patients evaluated were seizure free during the 3 years follow-up period.

**Key words:** Anti-epileptic drugs utilization, epilepsy, ethiopia, seizure outcome

## INTRODUCTION

Epilepsy is a major health concern worldwide. It is a chronic disorder characterized by recurrent seizures and second most common chronic neurologic disorder seen by neurologists. It is diagnosed clinically based on signs and symptoms, and its management is based on identification of goals, assessment, development of care plan and follow-up evaluation. Thus, it is critical to establish an accurate diagnosis of the seizure type and classification prior to therapeutic management to individualize drug therapy with the ultimate goal of improving quality of patients' life by seizure free periods, and minimizing side effects.[1-9] Uncontrolled seizures may be associated with adverse effects, psychiatric co-morbidities, and cognitive impairment resulting in employment restriction, physical injuries and finally to death.[10]

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Treatment with anti-epileptic drug (AED) is selected based on the type of seizure and is to be continued till the patient is seizure free often for 1-5 years. However, about 90% of epileptic patients in developing countries are not receiving appropriate treatment due to the cultural attitude, lack of prioritization, poor health care system, economic problems and inadequate supply of AEDs.[11-14]

Treatment outcome depends on several factors such as drug related factors, disease-related factors and patient-related factors. Drug-related factors include pharmacokinetics of the drugs, drug-drug interactions and toxicity among others. Similarly, irrational prescribing will result in poor treatment outcome. Thus, in only 70% of children and 60% of adults the seizure was completely controlled with AEDs. To withdraw AED patient has to be seizure free for 3-4 years since sudden withdraw increases seizure frequency and severity.[11,15-20]

Though different studies have been conducted in different parts of the world including Africa, to our knowledge analysis of treatment outcome among epileptic patients in the general hospitals of Ethiopia was not well studied except in particular wards and disease conditions. This is particularly true in the study. Thus, the aim of this study was to assess AED utilization pattern and treatment outcomes among epileptic patients visiting the epileptic clinic of Jimma University Specialized Hospital (JUSH).

## MATERIALS AND METHODS

### Study area and period

Retrospective cross-sectional study was conducted in JUSH from January 28 to February 8, 2013. JUSH is located in Jimma town, 346 km from Addis Ababa in Southwest Ethiopia. JUSH, established in 1930, is one of the oldest public hospitals in the country. Currently, it is the only teaching and referral Hospital in South-western Ethiopia comprising more than 750 staffs. It provides specialized service for approximately 9000 inpatients and 800000 attendants in a year.[21]

### Study participants

Two hundred and ninety adult epileptic patients' record cards were selected from total records and those selected cards from 2010 to 2012 were included in the study. Adult record cards which had no follow-up data and pediatric record cards were excluded from the study. Systematic

random sampling technique was used to select the study population. The sample size to be taken for the study was determined by using the following formula.[22]

$$n = \frac{Z^2 1 - \alpha/2 P(1-p)}{d^2}$$

Where, $n$ = sample size

$Z$ = confidence interval (1.95)

$p$ = estimated prevalence (0.5)

$d$ = Margin of error to be tolerated (0.05).

Based on the above formula and using 95% confidence

$$n = \frac{Z^2 1 - \alpha/2 P(1-p)}{d^2}$$

$$n = \frac{(1.96)^2 \ (0.5)(0.5)}{(0.05)^2} = 384$$

since the total population is <10,000 the sample was recalculated based on the following formula:

$1 + n/N$

n = sample size, Nf = actual sample size

N = total number of adult epileptic patients who attend epilepsy clinic of JUSH, ($N$ = 1200).

Therefore, the sample size was: Nf = 1 + 384/1200 = 290.

### Data collection process and statistical analysis

Pre-tested well-structured data collection format was designed to collect data from the patient cards including patient demographics, type of drug and treatment outcomes. Data were collected by the principal investigator. The collected data were cleared, categorized and analyzed using Statistical Package for the Social Sciences version 19 (Chicago, IL, USA) for Microsoft window, and the results were presented in tables and figures as necessary. Descriptive analysis was used to describe the percentages and number distributions of variables.

### Ethical considerations

The management of the hospital was requested for permission by a formal letter from the University. Names of physicians involved in the health care provision and those of patients were replaced by initials. All data obtained in the course of the study were kept confidential, and used solely for the purpose of the study.

# RESULTS

## Socio-demographic characteristics

A total of 290 patient medical records were included in the retrospective study. The demographic data revealed that the number of male and female patients were 170 (58.6%) and 120 (41.4%) respectively, among these 16-30 and 31-45 years of age groups, are more prevalent that accounted 114 (39.2%) and 85 (29.2%), respectively (Table 1).

## Classification of epileptic seizures

Generalized tonic-clonic seizure (GTCS) accounted about 232 (80%), followed by unknown type of epilepsy, 44 (15.17%) (Table 2).

## AED utilization pattern

Monotherapy was commonly used in the management of seizure which accounted 54.5%, followed by dual therapy, 35.9%. The least commonly used was treatment that included 4 drugs (phenobarbitone, phenytoin, carbamazepine and valproic acid) which accounted about 2% from the total patients. The most common drug that is used in monotherapy was phenobarbitone (Table 3).

Regarding the number of AEDs prescribed, from a total of 456 prescribed AED drugs, corresponding to an average of 1.57 AEDs per patient, phenobarbitone accounted about 284 (62.3%) with a dose range of 50-600 mg/day, followed by phenytoin with a dose range of 40-500 mg/day, 141 (30.9%). The utilization profile of anti-epileptics for the treatment of different types of epileptic seizures is summarized in Table 4.

## Adverse effects of AEDs

Hundred (33.4%) patients reported that they had experienced adverse effects related to his/her AED therapy. Headache was the commonest adverse effect recorded, 21 (21.6%), followed by epigastric pain, 18 (18.5%) and

**Table 1:** Socio-demographic characteristics of epileptic patients on follow-up at epilepsy clinic of JUSH from January 2010 to December 2012

| Socio-demographic variables | Frequency, *N* (%) |
|---|---|
| Sex | |
| Male | 170 (58.6) |
| Female | 120 (41.4) |
| Total | 290 (100) |
| Age at the time of diagnosis | |
| 1-15 | |
| Male | 9 (3.1) |
| Female | 12 (4.2) |
| 16-30 | |
| Male | 60 (20.6) |
| Female | 54 (18.6) |
| 31-45 | |
| Male | 51 (17.5) |
| Female | 34 (11.7) |
| 46-60 | |
| Male | 44 (15.1) |
| Female | 18 (6.2) |
| >60 | |
| Male | 6 (2) |
| Female | 2 (0.2) |
| Total | 290 (100) |

JUSH: Jimma University Specialized Hospital

**Table 2:** Distribution of the types of epileptic seizures at epilepsy clinic of JUSH from January 2010 to December 2012

| Type of seizure | Frequency, *N* (%) |
|---|---|
| GTCS (grandmal) | 232 (80) |
| US* | 44 (15.17) |
| CPS | 5 (1.72) |
| AS | 4 (1.37) |
| TCS | 3 (1.03) |
| As | 1 (0.35) |
| GTS | 1 (0.35) |
| Total | 290 (100) |

*The assessment written just as epilepsy without categorization of the seizure type. JUSH: Jimma University Specialized Hospital, GTCS: Generalized tonic clonic seizure, CPS: Complex partial seizures, GTS: Generalized tonic seizures, As: Atonic seizures, AS: Absence seizure, TCS: Tonic-clonic seizures, US: Unclassified seizures

**Table 3:** Distribution of mode of AEDs therapy based on the type of seizure atepilepsy clinic of JUSH from January 2010 to December 2012

| AED therapy | Number of patients | | US | Total (%) |
|---|---|---|---|---|
| | Partial seizures | Generalized seizures | | |
| Monotherapy | 2 | 135 | 21 | 158 (54.5) |
| Dual therapy | 3 | 87 | 14 | 104 (35.9) |
| Triple therapy | 0 | 12 | 10 | 22 (7.6) |
| Quadruple therapy | 0 | 6 | 0 | 6 (2) |
| Total | 5 | 240 | 45 | 290 (100) |

JUSH: Jimma University Specialized Hospital, US: Unclassified seizures, AED: Anti-epileptic drug

**Table 4:** Number of AEDs prescribed as per the type of seizure in epilepsy clinic of JUSH from January 2010 to December 2012

| AEDs | Number of drugs per the type of seizure | | | | | | | Dose (mg/d) |
|---|---|---|---|---|---|---|---|---|
| | GTCS | CPS | US | AS | TCS | As | GTS | Dose range |
| Phenobarbital | 232 | 2 | 40 | 5 | 3 | 1 | 1 | 15-600 |
| Phenytoin | 106 | 3 | 25 | 3 | 3 | 0 | 0 | 50-400 |
| Carbamazepine | 18 | 1 | 4 | 1 | 0 | 0 | 0 | 100-1000 |
| Vapoiric acid | 6 | 0 | 0 | 1 | 1 | 0 | 0 | 200-1000 |
| Total | 361 | 6 | 70 | 10 | 7 | 1 | 1 | |

TCS: Tonic-clonic seizures, JUSH: Jimma University Specialized Hospital, US: Unclassified seizures, AEDs: Anti-epileptic drugs, GTCS: Generalized tonic clonic seizure, CPS: Complex partial seizures, GTS: Generalized tonic seizures, As: Atonic seizures, AS: Absence seizure

confusion, 17 (17.5%). The least frequently reported adverse effects, as documented in the record card; include forgetfulness, skin rash, depression and gingival hypertrophy, 2 (2.1%) patients (Table 5).

## Seizure frequency and treatment outcome

From 290 epileptic patients, 165 (56.7%) patients were seizure free and 125 (43.3%) were not free during the 3 follow-up years. Among those not free, most patients experienced 1-5 seizure attacks, which accounted about 121 patients (73.3%) followed by 6-10 attacks per 3 months in which 30 (18.2%) patients are experienced during 3 years follow-up (Table 6).

## Patient hospitalization during follow-up periods

From 290 patients studied, 11 (3.8%) patients were hospitalized during the 3 years follow-up period, among which seven were hospitalized due to status epileptics and four were hospitalized due to other reasons. From those patients hospitalized due to status epileptics, 1 patient had absence seizure, 4 patients had GTCS and 2 patients had

**Table 5:** Adverse effects faced by the patient at epilepsy clinic of JUSH from January 2010 to December 2012

| Adverse effect experienced | Frequency, N (%) |
|---|---|
| Headache | 21 (21.6) |
| Epigastric pain | 18 (18.5) |
| Confusion | 17 (17.5) |
| Weakness | 12 (12.3) |
| Blurring of Vision | 11 (11.8) |
| Irritability | 6 (11.3) |
| Nightmare | 4 (4.1) |
| Forgetfulness | 2 (2.1) |
| Skin rash | 2 (2.1) |
| Depressed mood | 2 (2.1) |
| Gingival hypertrophy | 2 (2.1) |
| Total | 97 (100) |

JUSH: Jimma University Specialized Hospital

**Table 6:** Number of seizure attacks experienced for those who are not seizure free per each 3 follows-up month period among epileptic patients at JUSH from January 2010 to December 2012

| Type of seizure | Number of patients | Number of seizure attacks per 3 months, *N* (%)** | | |
|---|---|---|---|---|
| | | 1-5 attacks | 6-10 attacks | >10 attacks |
| AS | 3 | 3 (2.5) | 0 | 0 |
| GTC | 139 | 108 (89.2) | 20 (66.6) | 11 (78.6) |
| CPS | 2 | 1 (0.8) | 1 (3.3) | 0 |
| TCS | 1 | 1 (0.8) | 0 | 0 |
| Unknown | 20 | 8 (6.6) | 9 (30) | 3 (21.4) |
| Total | 165 | 121 | 30 | 14 |

**The number of seizure attacks per 3 months in the whole 3 years follow-up, GTC: Generalized tonic seizures, CPS: Complex partial seizures, AS: Absence seizure, JUSH: Jimma University Specialized Hospital, TCS: Tonic-clonic seizures

an unknown seizure. The main reasons for hospitalizations among these seven patients were due to medication non-adherence, i.e., missing of doses.

## DISCUSSION

According to this study result, GTCS was the most common type of epileptic seizure encountered which accounted about 232 (80%). This result is different from a study done on drug use evaluation (DUE) of AEDs at a multispecialty tertiary care teaching hospital in India in which GTCS is about (55.22%).[6] The difference may be associated with the presence of neuroimaging methods that can facilitate proper classification and diagnosis. Second, in our study uncategorized epilepsy which accounted about 44 (15.17%) of the sample population might have contributed to the specific types if the facility has the capacity to categorize the specific type of seizure. The choice of the most appropriate AEDs depends on the proper classification of seizures and the type of epilepsy or epileptic syndromes. Lack of proper classification of seizure type affects treatment outcome and selection of drugs. In our study, a significant proportion of epileptic patients' specific category of the type of seizure is not recorded that might affect the selection of appropriate AEDs selection. This requires due attention to help clinicians to identify the specific seizure type.

Most patients with epilepsy respond to one of the first-line AEDS; second-line agents may be useful in patients who do not respond to one or a combination of the first-line agents. In this study, phenobarbitone was the first-line drug prescribed, as mentioned in national treatment guideline, followed by phenytoin in generalized seizure. The best AED therapy is dependent on optimal seizure control and absence of unacceptable side-effects.[23] This is in contrary to the recent evidenced based treatment recommendation for newly diagnosed epilepsy in developed countries, as phenobarbitone is considered a second/third line option.

It is important to maintain patients on monotherapy as compliance is better, side effects are less and there is no problem of drug-drug interaction. In our study, monotherapy (54.5%) was followed by dual therapy (35.9%). A study done in UK and Singapore showed that the majority of the patients were on monotherapy (63%).[23] When our result was compared with the above study, there is a variation in drug utilization, and this might be associated with the presence of health care providers specialized in pharmacotherapy of epilepsy and the availability of first line AEDs recommended in recent guideline. However,

in our study, phenobarbitone was the most frequently prescribed monotherapy, followed by phenytoin. In contrast, carbamazepine was the commonest AED used in monotherapy or in combination therapy, followed by valproate and phenobarbitone in Singapore. Phenytoin with phenobarbitone was the most frequent 2-drug combination in our study. Even though combination of phenytoin and phenobarbitone is important in maximum control of seizure occurrence, the risk of combined toxicity is high.

Polytherapy offers no advantage over monotherapy. It increases the potential for drug-drug interactions, results in failure to evaluate the individual drugs, can increase the risk of chronic toxicity (including neurocognitive problems), may affect compliance and is associated with a higher cost of medication and necessity for therapeutic drug monitoring.[24]

As the adverse effects data retrieved from patient medical records showed, it is very likely that adverse effect reporting was under estimated. Most accurate data could have been obtained by questioning the patient directly. From 97 patients complaining side effect, headache was the most common adverse effect faced by 21 (21.6%) patients, which was followed by epigastric pain 18 (18.5%) patients and confusion 17 (17.5%) patients. Though most patients complain headache, severe adverse effects had been occurred in 2 (2.1%) patients and was gingival hypertrophy due to phenytoin. A study done on DUE on anti-epileptics at multispecialty tertiary teaching hospital in India, showed that 16 patients reported adverse drug reactions (ADR) related to his/her anti-epileptic therapy: phenytoin was involved in seven ADRs (rash, urticaria, ataxia, Steven Johnson syndrome, gingival hypertrophy), carbamazepine (crash, macolo, popular rash), and oxcarbazepine (hyponatremia, osteoporosis, rash), was reported in four patients. Sodium valproate was involved in one ADR (rash).[24]

Regarding seizure treatment outcome in terms of seizure-freedom, this study showed that almost 57% of patients were found to be seizure free for a consecutive 3 years follow-up periods. This study showed that conventional AEDs were still safe and effective for seizure control among a substantial segment of epileptic patients in resource-poor setting. For these groups of patients who achieved adequate seizure control, there must be a consideration of clinical assessment to either taper the dose of the AEDs or to withdraw AED treatment after investigations is done for intellect, neuro imaging and encephalography if possible. When compared to a study done on seizure frequency in medically treated adult epilepsy patients ($N = 934$) in

Cleveland clinic, USA, 63% of patients were completely seizure-free at 6 months, and 64% were completely seizure-free at 12 months, our data of seizure freedom was slightly lower though this study looked only for a period of 1 year.[25] For the remaining 43% patients who did not achieve seizure free in our study, still adequate support should be given either through reconsideration of AEDs being selected or dose optimization and/or reinforcing medication adherence, some patients' epilepsy might also be drug resistant type, which will have a significant extra cost and disease burden. They need to be assessed to look for any exacerbating factors to adequately control the seizure.

## CONCLUSIONS

In this study GTCS was the most prominent seizure encountered. Monotherapy was most frequently used mode of AED therapy in most of the epileptic seizures. The most common adverse effect patients faced while the follow-up period was headache. The most commonly prescribed AED was phenobarbitone, followed by phenytoin. Of epileptic patients in the study, around 57% of patients were seizure free during 3 follow-up years. This study showed that for a considerable number of epileptic patients, conventional AEDs were still safe and effective in achieving seizure control in resource-poor settings. Patients having a hospitalization during the follow-up period; most of them were due to status epileptics. Though using monotherapy is encouraged in terms of reducing side effects, reducing drug interactions and increasing compliance, its practice should be based on accurate diagnosis and classification of seizure types and adhering to the national guideline on prescribing protocols developed to reduce AEDs selection errors.

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