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Research Article

Prevalence of Anti-Epileptic Drugs Polypharmacy and Associated Factors among Epileptic Patients in Hiwot Fana Specialized University Hospital, Harar, Ethiopia

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ABSTRACT

Every newly diagnosed patient with epilepsy should be initiated on appropriate monotherapy, based on the seizure type and the epilepsy syndrome. Anti-Epileptic Drugs (AED) poly pharmacy did not necessarily improve seizure outcome and could increase the propensity for side effects. This study evaluates the prevalence and factors associated with Antiepileptic Drugs (AEDs) polypharmacy among patients with epilepsy at Hiwot Fana Specialized University Hospital, Harar, Ethiopia. Hospital based cross sectional study was conducted on selected 252 patients from April–March, 2018. The collected data were analyzed by using Stata corp version 14, and the result was presented in the form of tables and figures. The overall prevalence of antiepileptic polypharmacy was found to be 24.2%. Variables such as, place of residence (AOR=3; 95% CI: 1.1-8.3), long duration of illness (AOR=5.8; 95% CI: 1.1- 30.3), drug non adherence (AOR=0.02; 95% CI: 0.01- 0.06), and complain of side effect (AOR=3.4; 95% CI: 1.1-10.8), were found to be significantly associated with antiepileptic polypharmacy. Variables such as age, sex, duration of treatment, substance use characteristics and repeated hospitalization were not found to be significantly associated with AEP. Prevalence of AED polypharmacy was found to be high among the current study participants. It is important for physicians, to choose AED appropriate for seizure type and epilepsy syndrome so that patients are maintained on mono therapy.

Keywords: Antiepileptic drugs; Polypharmacy; Epilepsy; Seizures

Abbreviations: AEDs-Antiepileptic drugs; AS-Absence Seizure; CBZ-Carbamazepine; CNS-Central nervous system; CPS-Complex Partial Seizures; GTCS-Generalized Tonic-Clonic Seizure; GTS-Generalized Tonic Seizures; HFSUH-Hiwot Fana Specialized University Hospital; PHB-Phenobarbitone; PHT-Phenytoin; TCS-Tonic-Clonic Seizures; VPA-Valproic Acid

INTRODUCTION

Epilepsy refers to a group of chronic brain conditions characterized by recurrent epileptic seizures. Epileptic seizures are the clinical manifestations of excessive and/or hyper-synchronous, usually self-limited, abnormal activity of neurons in the brain [1,2]. It affects more than fifty million people in the world, and about one hundred million people will have at least one epileptic seizure at some time in their life [3]. If not treated, epileptic seizures lead to physical injury, and frequent seizures have detrimental effects on education, employment, and marital life whereby it may result in separation of the spouses; divorce, and so forth [4].

Antiepileptic drugs are effective in the treatment of epilepsy, but poor medication adherence is a major problem to sustained remission and functional restoration resulted in treatment failure and recurrence. Due to their complex pharmacokinetic properties, Anti-Epileptic Drugs (AEDs) are among the drug classes most susceptible to be involved in Drug-Drug Interactions (DDIs) [5,6].

In current day practice, every newly diagnosed patient with epilepsy should be initiated with appropriate monotherapy, based on the seizure type and the epilepsy syndrome. This approach is reasonable because, in 60% of newly diagnosed epilepsy patients, seizures are controlled on the first monotherapy. If the first monotherapy cannot be used in full doses because of idiosyncratic side effects, alternative monotherapy should be tried [7]. Concerns were raised about polytherapy including unfavorable interactions, and difficulty in evaluating individual

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pharmacological effects. This study evaluates the prevalence of polypharmacy and associated factors among patients with epilepsy in HFSUH, Harar, Ethiopia.

METHODOLOGY

Study design and setting

A facility-based cross-sectional was conducted in HFSUH located in Harar town which is found 525 kilometers from Addis Ababa, the capital city of Ethiopia. The hospital serves as a referral hospital for the entire Eastern part of the country. The study was conducted at a chronic follow up clinic of the hospital from April to march 2018.

Study population

All epileptic patients on AED in chronic follow-up clinic of Hiwot Fana Specialized University Hospital (HFSUH), and who had been on treatment for at least 6 months in the hospital during the data collection period were included in the study. Patients with missing or incomplete data were excluded.

Sample size determination and sampling technique

The sample size was calculated using the single population proportion formula, with 50% prevalence, 5% marginal error, 95% confidence interval, and since the exact number of source population was less than 10,000, a correction formula was used and a sample of 229 was reached. After adding a 10% non-response rate, a final sample of 252 was found. The total number of epileptic patients who attend the epilepsy clinic of HFSUH was 568. A systematic random sampling technique was used, hence the data was collected every two-interval where the first patient was selected by lottery method.

Data collection instrument

Both chart review and interview aided questionnaires were used to collect information from the study participants. Data regarding type of AEDs, duration of treatment, admission frequency, and duration of illness were found from the patient record. Drug adherence was assessed using the four-item version of the self-reporting questionnaire of Morisky Medication Adherence Rating Scale (MMARS).

Data processing and analysis

The collected data were analyzed using stata corp version 14. Description of the collected data was done using frequency and percentages. Multiple logistic regressions were performed to assess the association between binary outcomes and different explanatory variables. The strength of association was interpreted using Odds Ratio (OR) and 95% Confidence Interval (CI) and, p value <0.05 was considered statistically significant.

Data processing and analysis

AED polypharmacy: The practice of prescribing or using two or more AEDs.

RESULTS AND DISCUSSION

Data processing and analysis

A total of 252 epileptic patients and their medical records were included in the study. The demographic data revealed that the number of male and female patients were 136 (54.0%) and 116 (46.4%) respectively. Among these, the 20-45 years of age group were most prevalent accounting for 182(72.2%). The majority 184 (73.0%) of the participants were Muslim religion followers, married 117 (46.4%), and from rural area 133(52.8%) (Table 1).

Table 1: Distribution of socio-demographic characteristics of epileptic patients attending chronic follow up clinic of HFSUH, March 2018 (n=252).

Variables		Frequency	Percent
Age	<20 years	30	11.9
	20-45	182	72.2
	>46	40	15.9
	Male	136	54
Sex	Female	116	46
	Muslim	184	73
Religion	Orthodox	` 54	21.4
	Protestant	12	4.8
	Other	2	8
Residence	Urban	119	47.2
	Rural	133	52.8
Marital status	Single	107	42.5
	Married	117	46.4
	Divorced	21	8.3
	Widowed	7	2.8

Clinical and patient-related factors

The duration of illness between 15-25 years was (48.8%) and the duration of treatment between 3-5 years was (50.8%). On the other hand, (50.4%) had a history of one admission followed by two or more admissions (34.5%). Around 24% had been nonadherent to their antiepileptic treatment. The most common type of seizure was Generalized Tonic-Clonic Seizure (GTCS) (49.2%) followed by Generalized Tonic Seizure (GTS) (21.4%). On the other hand, the most common type of AED prescribed was Phenobarbitone (PHB) (69.8) followed by PHB with Carbamazepine (CBZ) (15.5%) (Table 2).

Table 2: Distribution of clinical and patient-related factors among epileptic patients at chronic follow up clinic of HFSUH, Harar, Ethiopia, March 2018 (n=252).

Variables		Frequency	Percent
Duration of illness	<15	99	39.3
	15-25	123	48.8
	>26	30	11.9
Duration of treatment	>2 years	98	38.1
	3-5 years	128	50.8
	>6 years	28	11.1
Number of admissions	None	38	15.1
	One	127	50.4
	Two and more	87	34.5
Have complaint of side effect	Yes	41	16.3
Substance use characteristics	Yes	123	48.8
	Chat	106	42.1

	Cigarette and alcohol	8	3.2
	Chat, alcohol and cigarette	5	2
	Other	4	1.6
Mode of therapy	Monotherapy	191	75.8
	Polypharmacy	61	24.2
Drug adherence	Adherent	192	76.2
	Non-adherent	60	23.8
Type of seizure	GTCS	124	49.2
	SE	2	0.8
	CPS	11	4.4
	AS	14	5.6
	TCS	47	18.7
	GTS	54	21.4
Type of AED prescribed	PHB	174	69
	PHB+PHT+CBZ	3	1.2
	PHT	7	2.8
	CBZ	10	4
	PHB+PHT	9	3.6
	PHB+CBZ	39	15.5
	PHB+VPA	8	3.2
	PHT+CBZ	2	0.8

Prevalence and factors associated with anti-epileptic polypharmacy

The overall prevalence of anti-epileptic drugs polypharmacy was 61 (24.2%) with 95% CI (19.0- 29.9); of these 58(23%) were on two anti-epileptics. Multiple logistic regression analyses were undertaken for variables that were significant on binary logistic regression to see the relationship of variables with antiepileptic poly-pharmacy. From sociodemographic variables, place of residence was found to be significantly associated with AED Polypharmacy. Accordingly, AED polypharmacy was 3 times higher among rural residents compared to urban residents (AOR=3; 95% CI: 1.1-8.3). Among clinical factors, duration of illness was found to be significantly associated with AED polypharmacy where the odds of AED Polypharmacy was 5.8 times higher among patients whose duration of illness was more than 25 years compared to those whose duration of illness was less than 15 years (AOR=5.8; 95% CI: 1.1- 30.3). AED polypharmacy was 3.4 times higher among patients who had complain of side effects compared to those who had no complain (AOR=3.4; 95% CI: 1.1-10.8). On the other hand, patients who had poor adherence to their treatment were found more prevalent among patients with AED polypharmacy compared to those who were on single drug treatment (AOR=0.02; 95% CI: 0.01-0.06). Variables such as age, sex, duration of treatment, substance use characteristics, and repeated hospitalization were not found to be significantly associated with AED polypharmacy (Table 3).

Table 3: Multiple logistic regression analysis of factors associated with antiepileptic polypharmacy among epileptic patients under follow-up at chronic follow-up clinic of HFSUH, Harar, Ethiopia, March 2018(n=252).

	Polypharmacy			
Variables	**Yes**	**No**	**P. Value**	**AOR (95% CI)**
Age				
<20	4	26		1
20-45	42	140	0.513	1.8 (0.3-9.8)
>=45	15	25	0.846	1.2 (0.14-10.9)
Sex				
Male	27	109		1
Female	34	82	0.865	1.08 (0.4-2.7)
Residence				
Urban	24	95		1
Rural	37	96	0.033*	3 (1.1- 8.3)
Duration of illness				
<15 year	17	82		1
15-25 year	29	94	0.321	1.7 (0.6 -5.1)
>25 year	15	15	0.039*	5.8 (1.1- 30.3)
Duration of treatment				
<2 year	18	78		1
3-5 year	30	98	0.546	0.7 (0.2- 2.1)
>6 year	13	15	0.189	2.8(0.6- 12.5)
No of hospitalization				
None	6	32		1
One	23	104	0.865	0.8(0.2-3.4)
Two or more	32	55	0.72	1.3(0.3- 5.3)
Complains of side effects from the medication				
No	36	175		1
Yes	25	16	0.039*	3.4 (1.1- 10.8)
Substance use characteristics				
No	20	109		1
Yes	41	82	0.299	1.6(0.6- 4.2)
Drug adherence				
Poor	41	7		1
Good	20	184	0.000*	0.02(0.01- 0 .06)

Note: *Significant association.

The study has attempted to identify the prevalence of anti-epileptic drugs polypharmacy and associated factors among epilepsy patients attending the chronic follow-up clinic of HFSUH.

According to the present study's finding, the most common type of epileptic seizure encountered was GTCS (49.2%) followed by GTS (21.4%) and TCS (18.7%). Similarly, a study conducted among 270 epileptic patients in Jimma University specialized hospital, Ethiopia revealed the common type of seizure was GTCS (80%) followed by unclassified seizures (15.2%) [8]. Another study in a tertiary hospital in Norway also found out GTCS the most common seizure type accounting for 55.2%, followed by simple partial seizure (16.42%) [9]. The differences in the seizure type among the studies could be due to the lack of availability of neuroimaging methods that can facilitate proper classification and diagnosis. However, the choice of appropriate AEDs depends on the proper classification of seizures and/or epileptic syndromes. Therefore, due attention should be given especially in resource-limited settings to help clinicians identify the specific seizure type and treat patients accordingly.

In the present study, monotherapy accounted for 76.2% of the prescriptions, whereas poly- therapy with two and three AED combinations accounted for 23% and 1.2% respectively. The finding in the present study is in line with a study in a multispecialty tertiary care teaching hospital in India where 23.13% of epileptic patients were prescribed an AED in polytherapy (≥ 2 AEDS) [10]. On the other hand, the result was much lower than what has been reported in a study conducted on 372 adult epileptic patients at a tertiary hospital in Omani where polytherapy with two or three AED combinations accounted for 27% and 20% respectively [11], and study on 174 patients at the National Center for Epilepsy, Norway where 56% used AED polytherapy (2–5 AEDs). Putting patients on monotherapy, however, is important as epileptic patients on polytherapy are more likely to be depressed and non-adherent to their treatment. According to a study conducted on 405 patients in Northwest Ethiopia, depression among patients on AED polypharmacy was 7.63 times higher compared to those on monotherapy [12]. A study on Health-Related Quality Of Life (HRQOL) among patients with epilepsy at Ambo General Hospital, Ethiopia also found out that, absence of poly-pharmacy was found to be a strong predictor of the HRQOL score of social health [13]. Besides, polytherapy increases the potential for drug-drug interactions, results in failure to evaluate the individual drugs, can increase the risk of chronic toxicity, and is associated with a higher cost of medication.

Phenobarbitone was the most frequently prescribed monotherapy (69.8%), followed by carbamazepine (4%). This was in line with a study conducted among 270 epileptic patients in Jimma University specialized hospital, Ethiopia where phenobarbitone was the most commonly utilized single anticonvulsant drug (62.3%), followed by phenytoin (30.9%). This is contrary to the recent evidenced-based treatment recommendation for newly diagnosed epilepsy in developed countries, where phenobarbitone is considered a second or third-line option. Conversely, our result was contrary to what has been found in Omani where Sodium valproate (27%) was the commonest AED used followed by carbamazepine (23%), levetiracetam (16%), and phenytoin (16%). A study on 882 patients in Norway revealed that carbamazepine (21.4%), pregabalin (16.4%), lamotrigine(15.2%), and gabapentin (15.1%) were the most commonly used AEDs [14]. Similarly, a study at a multispecialty tertiary care teaching hospital in India identified sodium valproate (23.27%) as the most frequently prescribed AEDs, followed by carbamazepine (22.77%) and phenytoin (16.83%). Even though the most commonly diagnosed seizure type was GTCS in most of the studies conducted, there was a discrepancy in the most commonly prescribed AEDs indicating that medications were not selected appropriate to the seizure types. On the other hand, differences in the availability of AEDs in different settings could be the reason for the discrepancies among the medications selected. The most frequently prescribed combination therapy according to the present study's finding was phenobarbitone with carbamazepine (15.5%) followed by phenobarbitone with phenytoin (3.6%). The finding is different from a study in Omani in which the commonly prescribed AED combination was sodium valproate with clonazepam (12%) followed by sodium valproate with lamotrigine (12%).Even though the combination of phenobarbitone with phenytoin or carbamazepine is important in maximum control of seizure occurrence, the risk of combined toxicity is high.

In the current study, patients whose duration of illness was more than 25 years were found to be about six times more likely to be on antiepileptic polypharmacy compared to those whose duration of illness was less than 15 years. This could be due to patients with a long history of epilepsy treatment would more likely develop resistance to the medications. According to a study on 135 epileptic patients in Norway, a long duration of illness increases the risk of drug resistance and polypharmacy by 7% and 5% respectively [15].

In the present study's finding, patients who were nonadherent to their treatment were more likely to be on anti-epileptic polypharmacy compared to those who were adherent. Since epilepsy is a chronic disease condition requiring a longer duration of treatment, adherence to the medication is essentially required. However, according to a systematic review of articles, the prevalence of anti-epileptic medication non-adherence was 39.77% [16]. On the other hand, polypharmacy will also lead patients to be nonadherent to their medications indicating that putting patients on monotherapy has a substantial advantage.

CONCLUSION

The prevalence of AED polypharmacy was found to be high among the current study participants. Patients who lived in a rural area, had a longer duration of illness, had side effects from the medication, and those who were non-adherent to their medication were found to be more on antiepileptic poly-pharmacy. As polytherapy offers no advantage over monotherapy, it is important to maintain patients on monotherapy as compliance is better and side effects are less. It is important for physicians, to choose AED appropriate for seizure type and epilepsy syndrome so that patients are maintained on monotherapy.

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