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

Background

Every newly diagnosed patient with epilepsy should take appropriate monotherapy based on the seizure type and the epilepsy syndrome. Anti-epileptic drugs (AED) polypharmacy did not necessarily improve seizure outcomes and could increase the propensity for side effects. This study evaluates the prevalence of AED polypharmacy and its associated factors in Hiwot Fana Specialized University Hospital, Harar, Ethiopia.

Methodology

A hospital-based cross-sectional study was conducted from April to March 2018. Patient chart review and an interview were made with selected epileptic patients and analyzed by using Stata corp version 14 software. A logistic regression model was fitted to identify the contribution of selected independent variables to AED polypharmacy. The results were presented using an adjusted odds ratio (AOR) with a 95% confidence interval (95% CI) and, a p-value of <0.05 was considered as a cut-off point for declaring significance.

Results

A total of 252 epileptic patients were included in the analysis with a mean age of 30.4 ($\pm$ SD7.8). More than half of the respondents were male (54.0%) and rural residents (52.8%). About 49% had 15 to 25 years duration of illness, and more than half had 3 to 5 years duration of treatment (50.8%). The most common type of seizure diagnosed was Generalized Tonic-Clonic Seizure (GTCS) (49.2%), while the most common type of AED prescribed was Phenobarbitone (PHB) (69.8%). The prevalence of antiepileptic polypharmacy was 24.2%. The most frequently prescribed combination therapy was phenobarbitone with carbamazepine (15.5%) 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 complaint of side effect (AOR=3.4; 95% CI: 1.1-10.8), had a significant association with antiepileptic polypharmacy.

Conclusion

The prevalence of AED polypharmacy was high among the study participants. The physicians should choose the drugs based on the seizure type and epilepsy syndrome to maintain patients on the appropriate mono-therapy.

Introduction

Epilepsy refers to a group of chronic brain conditions characterized by recurrent epileptic seizures [1, 2]. Epilepsy affects more than fifty million people in the world, and about one hundred million people have at least one epileptic seizure at some time in their life (Neligan et al., 2011). If not treated, epileptic seizures

lead to physical injury. And the frequent seizures have detrimental effects on education, employment, and marital life [3].

Antiepileptic drugs are effective in the treatment of epilepsy, but poor compliance results in treatment failure and recurrences [2]. Due to their complex pharmacokinetic properties, AEDs are among the drug classes most susceptible to be involved in drug-drug interactions (DDIs) [5, 6]

Every newly diagnosed patient with epilepsy should take appropriate monotherapy based on the seizure type and the epilepsy syndrome. In 60% of epileptic patients, seizures are controlled with monotherapy. If the first monotherapy cannot be used in full doses because of idiosyncratic side effects, alternative monotherapy is tried [7].

Concerns were raised about polytherapy including unfavorable interactions and difficulty in evaluating individual pharmacological effects. This study evaluates the prevalence of polypharmacy and associated factors among patients with epilepsy in HFSUH, Harar, Ethiopia. We believe that conducting this kind of study will serve to offer insight into current practice and improve upon it in the future.

Result

Socio-demographic characteristics

We included a total of 252 epileptic patients were in the analysis with a mean age of 30.4 ($\pm$ SD7.8). More than half of the respondents were male (54.0%) and rural residents (52.8%). The majority of participants were Muslim religion followers 184(73.0%) and married 117(46.4%). (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
Sex	Male	136	54.0
	Female	116	46.0
Religion	Muslim	184	73.0
	Orthodox	54	21.4
	Protestant	12	4.8
	Other	2	8.0
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

About 49% of the patients had 15 to 25 years duration of illness. More than half had 3 to 5 years duration of treatment and a history of one admission. Around 24% had been nonadherent to their treatment. The most common type of seizure was Generalized Tonic-Clonic Seizure (GTCS) (49.2%). The most frequently prescribed monotherapy was phenobarbitone (PHB) (69.8%), and the most commonly prescribed combination therapy was phenobarbitone with carbamazepine(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) (Table 2)

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 &cigarette	5	2.0
	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	69.0
	PHB+PHT+CBZ	3	1.2
	PHT	7	2.8

CBZ	10	4.0
PHB+PHT	9	3.6
PHB+CBZ	39	15.5
PHB+VPA	8	3.2
PHT+CBZ	2	0.8

Note: AS= Absence Seizure ; TCS= Tonic-Clonic Seizures; CPS= Complex Partial Seizures; GTCS= Generalized Tonic-Clonic Seizure; GTS=Generalized Tonic Seizures; SE= Status epilepticus; CBZ=Carbamazepine; PHB= Phenobarbitone; PHT=Phenytoin; VPA=Valproic Acid

Prevalence and factors associated with anti-epileptic polypharmacy

The overall prevalence of AEDs polypharmacy was 24.2% [95% CI (19.0- 29.9)]. AED polypharmacy was significantly higher among rural residents (AOR=3; 95% CI: 1.1-8.3), in patients with more than 25 years duration of illness (AOR=5.8; 95% CI: 1.1- 30.3) and, with a complaint of side effects from the drug (AOR=3.4; 95% CI: 1.1-10.8) (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		1.00
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		1.00
Female	34	82	0.865	1.08 (0.4-2.7)
Residence				
Urban	24	95		1.00
Rural	37	96	0.033*	3 (1.1- 8.3)
Duration of illness				
<15 year	17	82		1.00
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		1.00
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		1.00
One	23	104	0.865	0.8(0.2-3.4)
Two or more	32	55	0.720	1.3(0.3- 5.3)
Complains of side effects from the medication				
No	36	175		1.00
Yes	25	16	0.039*	3.4 (1.1- 10.8)
Substance use characteristics				

No	20	109		1.00
Yes	41	82	0.299	1.6(0.6- 4.2)
Drug adherence				
Poor	41	7		1.00
Good	20	184	0.000*	0.02(0.01- 0 .06)
Note: *Significant association.				

Discussion

The study assessed the prevalence of anti-epileptic drugs polypharmacy and associated factors among epileptic patients attending the chronic follow-up clinic of HFSUH.

Based on the present study's finding, the most common types of epileptic seizure encountered were GTCS (49.2%) followed by Generalized Tonic Seizures (21.4%) and Tonic-Clonic Seizures (18.7%). A similar study conducted among 270 epileptic patients in Jimma University specialized hospital, Ethiopia revealed the common type of seizure was GTCS (80%) and unclassified seizures (15.2%) [8].

Another study in a tertiary hospital in Norway found GTCS the most common seizure type (55.2%) [9]. The different results 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 should depend on the proper classification of seizures or epileptic syndromes. Therefore, it is essential to give due attention, 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) [9]. 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 [10].

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%) [8]. 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%)[11]. 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%) [10]. 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%)[11]. 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 [10].

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 [10].

Conclusions

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 more likely to take antiepileptic polypharmacy. 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.

Limitation Of The Study

This study is a cross-sectional study design type; hence, it did not examine the cause and effect relationship. Hence, further studies, which consider this, will be needed.

Methodology

Study design and setting

This study was conducted in Harar city, which is located about 525 km away from the capital, Addis Ababa, in the eastern direction. The hospital serves as a referral hospital for the entire Eastern part of the country. The present study was conducted at the chronic follow-up clinic from April to March 2018. A descriptive cross-sectional study was employed to assess the prevalence of polypharmacy and associated factors among patients with epilepsy.

Study population

We included all epileptic patients on treatment for at least 6 months in the chronic follow-up clinic of HFSUH hospital. We excluded patients with missing or incomplete data.

Sample size determination and sampling technique

We calculated the sample size using single population proportion formula, with 50% prevalence, 5% marginal error and 95% confidence interval. After using a correction formula and a 10% non-response rate, we found a final sample of 252. The total number of epileptic patients attending the epilepsy clinic of HFSUH was 568. We used a systematic random sampling technique to select respondents, hence we collected the data every two-interval where we selected the first patient by using a lottery method.

Data collection instrument

We used chart review and interview aided questionnaires to collect information from the study participants. We found data regarding types of AEDs, duration of treatment, admission frequency, and

duration of illness from a patient record. We used the four-item version of the self-reporting questionnaire of Morisky medication adherence rating scale to assess drug adherence.

Data processing and analysis

We analyzed the collected data by using Stata corp version 14. The association between binary outcomes and different explanatory variables was performed using multiple logistic regression analyses. We interpreted the strength of the association using odds ratio (OR) and 95% confidence interval (CI) and, p value <0.05 was considered statistically significant.

Ethics approval and consent to participate

This study was approved by Haramaya University, College of Health and Medical and Science, School of Pharmacy and carried out in line with the Declaration of Helsinki. Prior informed consent was obtained from all individual participants included in the study. All data obtained in the course of the study were kept confidential and used solely for the study.

Operational definition

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

Declarations

Data availability

The datasets used in the current study are available from the corresponding author on reasonable request.

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Author contributions

KE designed the study, collected data, and analyzed data. NL reviewed the study plan, questionnaires, and the article, analyzed data, and reviewed the manuscript. YT and AT reviewed the article, analyzed data, and reviewed the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

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