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Medication adherence in epilepsy and potential risk factors associated with non adherence in tertiary care teaching hospital in southwest Ethiopia

Epilepside tedavi uyumu ve güneybatı Etiyopya'daki üçüncü basamak eğitim hastanesinde tedaviye uyulmamasına bağlı potansiyel risk faktörleri

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Abstract
Medication non-adherence to antiepileptic medications is detrimental to the perceived outcome of treatment. Non-adherence to medication regimen accounts for substantial worsening of disease, death and increased health care costs. In this study, we aimed to determine adherence rate to antiepileptic medications and identify the potential risk factors associated with non-adherence in Jimma University Specialized Hospital/JUSH. A hospital based cross-sectional study was conducted on 265 patients using patients self report and pharmacy refill record. The self report involved the structured patient interview after verbal informed consent was obtained. Data were analyzed using SPSS for windows version 16.0. Chi-square test was used to observe the association of variables with adherence. The adherence rate of patients (n=265) to antiepileptic drugs/AED was found to be 63.2% based on their refill records, compliant fill rate. On the basis of patient's self report for their pattern of drug use, 155 (58.5%) patients reported that they had never missed (neither daily dose nor time of taking), 78 (29.4%) missed daily dose some times, 12 (4.5%) missed only time of taking, and 7.5% (n=20) missed both time of taking and daily dose sometimes. The most common reasons for missing dose were forgetfulness (31.8%) followed by being busy (20.9%). Sedation (39.4%) was the commonest side effect faced by the patient. The rate of adherence absorbed in this study was low. Pill burden, co-morbid conditions and appointment missing were found to affect adherence. The high rate of non-adherence, in this study calls for further research and due consideration in planning appropriate strategies to improve the existing conditions.
Keywords: Adherence; antiepileptic drugs; Jimma

Özet
Antiepileptik tedavilere uyulmaması tedaviden beklenen sonuca zarar verir. Tedavi rejimine uyulmaması hastalığın daha da kötüleşmesine, ölüme ve sağlık sigorta harcamalarına mal olmaktadır. Bu çalışmada antiepileptik tedavilere uyum oranını ve Jimma Üniversitesi Özelleşmiş Hastanesi/JUSH'ta tedaviye uyulmamasına bağlı potansiyel risk faktörlerini belirlemeyi amaçladık. Hastane temelli kesitsel bir çalışma 265 hastanın hasta bilgileri ve eczane ilaç kayıtları kullanılarak gerçekleştirildi. Hasta bilgileri kademeli hasta ile mülakat bilgilerini ve bilgilendirildikten sonra alınan sözlü onayı içermektedir. Veriler SPSS for Windows v.16 kullanılarak analiz edildi. Ki-kare testi uyuma bağlı değişkenlerin gözlenmesinde kullanıldı. Eczane ilaç kayıtlarına bağlı olarak ve kullanım oranları ile uyumlu olarak hastaların (n=265) antiepileptik ilaçlara tedavi uyum oranları %63.2 olarak tespit edildi. Hastaların ilaç kullanım şekli ile ilgili kendi ifadelerine göre 155 hasta (%58.5) asla doz aksatmadığını (ne günlük dozu ne de doz zamanını), 78 hasta (%29.4) günlük dozu bazen aksattığını, 12 hasta (%4.5) sadece doz alım zamanını aksattığını ve 20 hasta (%7.5) hem doz zamanını ve günlük dozu bazen aksattığını belirtmişlerdir. En sık görülen doz aksatma nedenleri unutkanlık (%31.8) ve onu takip eden işinin çok olması (%20.9) idi. Hastaların karşılaştığı en sık görülen yan etki ise sedasyon (%39.4) idi. Bu çalışmada tespit edilen uyum oranı düşüktü. Günlük doz yükü, eşlik eden koşullar ve muayene randevusu kaçırmanın uyumu etkilediği bulundu. Bu çalışmada görülen yüksek oranda tedaviye uyulmaması daha ileri çalışmaların ve mevcut şartların iyileştirilmesi için uygun stratejilerin planlanmasının ve değerlendirilmesinin gerekli olduğunu göstermektedir.
Anahtar kelimeler: Uyum; antiepileptik ilaçlar; Jimma

Introduction

Epilepsy is a chronic disorder of the brain that affects people in every country of the world. It is characterized by recurrent seizures and is one of the world's oldest recognized conditions (1).

About 10% of the whole world population living a normal life span can have at least one epileptic seizure. At least 50 million will have recurrent

seizures, of which 40 million receive no treatment when, for only a small amount of money, 70% of these could lead seizure-free lives (2).

The effectiveness of antiepileptic drugs (AED) is limited if patients do not adhere to their regimens. The general estimates of epilepsy patients' adherence to medication regimens vary but tend to but less than optimal (3).

Despite the availability, of phenobarbitone, a cheap and effective treatment, more than 90% of patients living in rural areas remain untreated. Potential reasons for this include cultural factors, lack of awareness of medical treatment and inaccessibility of medical services (4). Adherence to long-term therapy for chronic illnesses in developed countries averages 50%. In developing countries, the rates are even lower. It is undeniable that many patients experience difficulty in following treatment recommendations. Poor adherence to long-term therapies severely compromises the quality of life and of health economics (5).

Poor adherence to medication regimen accounts for substantial worsening of disease, death and increased health care cost (6). Reasons for non-adherence are complex and multilayered. Patients can accidentally fail to adhere through forgetfulness, misunderstanding, or uncertainty about clinician's recommendations, or intentionally due to their own expectations of treatment, side-effects, and lifestyle choice (7). Adherence to medication is crucial in preventing or minimizing seizures and their cumulative impact on everyday life. Non-adherence to AED can result in breakthrough seizures many months or years after a previous episode and can have serious repercussions on an individual's perceived quality of life (7). Improved adherence can optimize the therapeutic benefits and results in better patient outcomes and substantial cost reductions (8). The current study aimed at to determine rate of medication adherence to AED and identify potential barriers for non-adherence.

Patients and Methods
Study setting
A hospital based prospective cross-sectional study was conducted using patients self report and pharmacy refill record, to evaluate adherence rate to antiepileptic medications and identify possible reasons for non- adherence in Jimma University Specialized Hospital, ambulatory clinic for adults. Jimma town is located 346 km south west of Addis Ababa. The study was conducted from January 31 to March 14, 2013.

Study design
Patients who were receiving chronic maintenance therapy, that is, all patients prescribed antiepileptic medications within a 3-month time period were identified and consecutive patients meeting selection criteria were included. The sample was restricted to patients with a diagnosis of epilepsy and thus the study populations were patients with diagnosis of epilepsy attending the ambulatory clinic during the study period. Excluded were patients who are taking antiepileptic medications for non-epileptic seizure disorders or other medical diseases, patients who have started medication recently (<3 months), and patients below the age of 18, severely ill patients and patients who were not willing to participate in the study. Since there is no previous study in the area, prevalence rate (p) of 50%, confidence interval of 95% and margin of error 5% was taken and thus, the sample size, was 384. Using the single population correction formula, the final sample size was corrected to 265.

Data collection
Demographic and relevant clinical information, including age, gender, ethnicity, epilepsy diagnosis, and antiepileptic medications, were obtained. Adherence to prescribed regimens was determined by both qualitative and quantitative methods. The quantitative methods involves using structured questionnaire by interviewing patients who are coming to refill and the qualitative method is by reviewing patient refill records from the pharmacy. Medication profiles were also examined to calculate the number of scheduled oral daily medications and the total number of prescribed medications consumed per day. If a patient was prescribed more than one agent for a disorder, the agent with the highest non adherence was recorded and used for data analysis. Selection and training of data collectors was done. Data collectors were selected from graduating class pharmacy students. As part of the training the collectors conduct a pretest of the questionnaire with the guidance of the principal investigation.

Statistical analysis
Data was then coded, checked for completeness and consistence, and analyzed using SPSS for window version 16.0. Descriptive statistics were used to determine patient demographics, medication information, and adherence rates for antiepileptic medications. The association between variables was calculated by Chi-square test of association where necessary.

Ethics
A formal letter written from school of pharmacy, Jimma University to Student Research Program (SRP) and permission was obtained from Ethical Approval Committee. Written informed consent was obtained from the respondents and brief explanation of aim of study was provided with the questionnaire. Only those who were volunteer were included in the study.

Results

A total of 265 patients were included in the study and all of them consented and completed the interview. The study subject was comprised of 157 (59.4%) male and 108 (40.6%) female. The majority [102 (38.5%)] of the patients were in the age group between 21-30 years of age. The majority of the study subjects (n=163) were Muslims (61.3%) and 61 (23.1%) were farmers. Majority [162 (61.1%)] of the patients participated in the study were unmarried and only 21 (7.9%) had tertiary education (Table 1).

Table 1. Socio-demographic and socio-economic variables of the study subjects in Jimma University Specialized Hospital, ambulatory Clinic, Jimma, January 31-March 14, 2013

Socio-demographic characteristic	Number	Percentage (%)
Age		
</=20	38	14.3
21-30	102	38.5
31-40	65	24.5
41-50	43	16.2
>/=51	17	6.4
Sex		
Male	157	59.4
Female	108	40.6
Ethnicity		
Oromo	151	56.9
Kulo	62	6.8
Silte	40	23.4
Amara	18	15.1
Others	5	1.9
Religion		
Muslim	163	61.3
Orthodox	71	26.7
Protestant	25	9.4
Others	6	2.3
Occupation		
Government employee	20	7.5
Farmer	61	23.1
Unemployed	42	15.8
Merchant	42	15.8
Student	51	19.3
Others	24	9.1
Educational status		
Illiterate	80	29.9
Grade 1-8	120	45.1
Grade 8-12	44	16.5
Tertiary	21	7.9
Marital status		
Unmarried	162	61.1
Married	55	20.8
Divorced	40	15.1
Widowed	8	3.01
Monthly income in birr		
>300	30	11.3
200-300	48	18.1
100-200	61	23.0
<100	85	32.1
Unknown	41	15.5

Patient's self report: On the basis of patient's self report for their pattern of drug use, 155 (58.5%) patients reported that they had never missed (neither daily dose nor time of taking), 78 (29.4%) missed daily dose some times, 12 (4.5%) missed only time of taking, and 7.5% (n=20) missed both time of taking and daily dose sometimes (Figure 1). Among those who had missed their medication, their most common reasons for missing were forgetfulness (31.8%) followed by being busy (20.9%) (Table 2).

On the basis of number and frequency within 24 hours duration, the majority of the patients, 123 (46.4%) were taking one medication, 99 (37.4%) were taking two medications and 43 (16.2%) were taking more than two medications. Regarding the frequency of medications, 96% of the patients were taking once daily. Among the study subjects those who know the name of their medications (48.4%) were slightly lower than those who do not know (51.6%). Of the reported side effects of medications 39.4% reported about the feeling of sedation, 13.1% had gingival hyperplasia, and 18.2 % had more than one side effect (Table 2).

Table 2. Pattern of medication adherence of epileptic patients in Jimma University Specialized Hospital, Ambulatory Clinic, Jimma, January 31-March 14, 2013

Characteristics	Number	Percent
Reasons for missing doses		
Forgetting	35	31.8
Lack of information	11	10.0
Being busy	23	20.9
Decision to avoid taking drug	11	10.0
Others	30	27.3
Number of medications		
One	123	46.4
Two	99	37.4
More than two	43	16.2
Measures taken to avoid the side effects		
No measures taken	137	51.7
Inform health professionals	19	7.2
Inform family members	16	6.0
Avoid taking drugs	31	11.7
Stop going to work	36	13.6
Other	26	9.8

Among those who experienced different side effects, the patients asked on measures they had taken to avoid the side effects, 51.7% responded that they did nothing, 11.7 % of them avoid taking their medications sometimes, 7.2% inform the health professionals, and 13.6% stop going to work (Table 2). Of the total 265 patients, 91 (34.3%) patients had additional co-morbid medical problems such as HIV/AIDs, hypertension, heart failure, diabetes and others.

Of the total patients, more than half [147 (55.3%)] of the patients had no idea of their illness and 50 (18.8%) patients perceive that their illness is spiritual and only 33 (12.4%) patients know it is neurological disease (Figure 2).

Majority [191 (71.8%)] of the patients were on AED for more than 2 years and 25 (9.4%) were started recently (6 month-1 year). One hundred eighty nine (71.7%) patients had improvement after starting

AED and 76 (28.6%) did not have improvement after starting their AED (Figure 3).

Compliant Fill Rate (CFR): By compliant fill rate over socio-demographic variables it was found that; of the subjects with 100% CFR (n=87) the number of males (71.3%) is greater than the number of females. The number of female patients is greater only at CFR of 50% (n=63). When the rate of adherence is defined by marital status, among the unmarried patients (n=162) large proportion of patients (n=56) had CFR of 50% and among the married patients (n=55), 40% of them had CFR of 50%. Statistical analysis did not support significant association between adherence rates and marital status of patients (P>0.05).

Distribution of rate of adherence by education status indicated that among patients with CFR=100% (n=56) the majority (53.6%) had a primary educational status of grade 1 to 8. The number of patients with tertiary educational status (n=4) having CFR=100% were found to be lower than patients without any formula schooling (n=12). Among patients with no any formula schooling (n=80), large proportion (n=36) had low adherence rate (CFE <25%). nevertheless, patients' educational status was not found to be significantly associated with adherence rate (Table 3).

Based on the association of different variables and rate of adherence, number of medications, missing an appointment, medication adverse effects, duration of treatment, age and presence of co-morbid disease were significantly correlated with adherence rate (P<0.05). Other socio-demographic and socio-economic characteristic such as marital status, occupational status, monthly income, ethnicity and type of seizure were not associated with adherence rate.
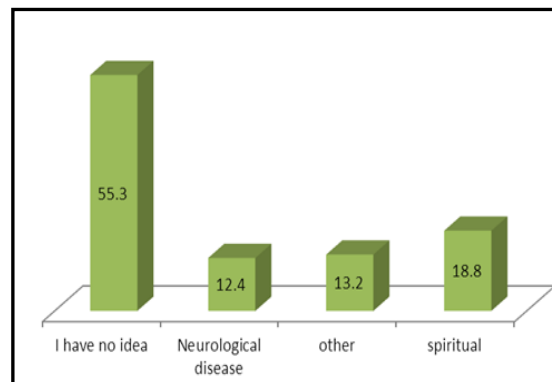
Figure 2. Percentage of patients' perception of their illness in Jimma University Specialized Hospital, Ambulatory Clinic, Jimma, January 31-March 14, 2013
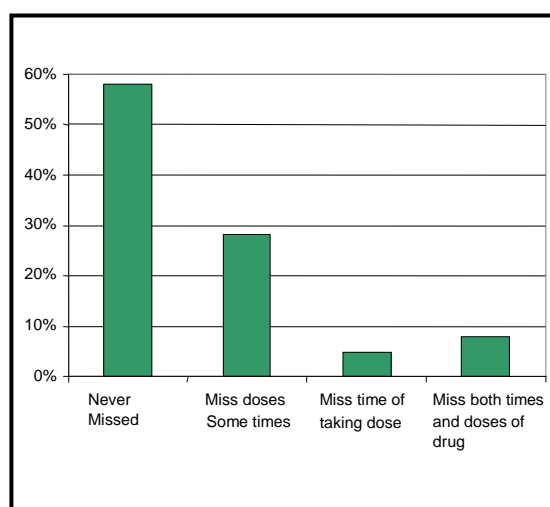
Figure 1. Distribution of patients by frequency of missing antiepileptic medications in Jimma University Specialized Hospital, Ambulatory Clinic, Jimma, January 31-March 14, 2013.
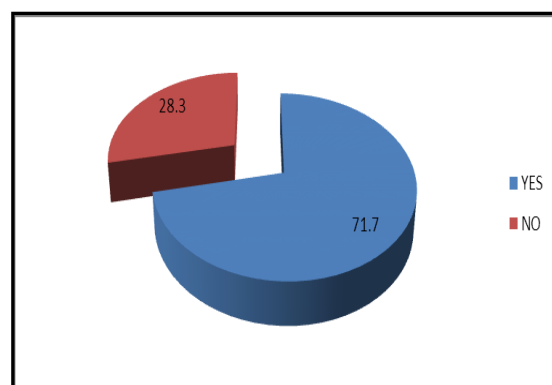
Figure 3. Patients disease improvement status after starting antiepileptic medications, Jimma University Specialized Hospital, Ambulatory Clinic, Jimma, January 31- March 14, 2013.

Discussion

Recently, there is no single measure accepted as the 'gold standard' because all commonly employed methods has draw backs and there is no consensus standard as to what constitute adequate adherence in epileptic patients who take their medications. Some trials consider rates greater than 80% to be acceptable. Others consider rates greater than 95% to be mandatory for adequate adherence, particularly among patients with human immune deficiency virus infection (HIV) (5).

The present study revealed that adherence to antiepileptic medications is low. Previously reported rates of adherence for antiepileptic medications

ranged from 31.8 % to 70% (10,11,15). The adherence rate in the present study is higher than the findings from Peru (31.8%), England (40%) and Brazil (40%) but lower than the study done in Ethiopia (70%) by Abula et al. (10). The inconsistency in the findings may be due to the difference in the data collection methods i.e. self-report may affect this result and there may be over or under reporting of certain variables due to patient personal variation in these settings. For instance, the study done in Brazil has used laboratory markers to calculate adherence rate whilst Abula et al. (10) used odds ratio to calculate adherence rate. Both are different from the method we have used to calculate adherence rate in this study such as interview and patient card review. However, if common methods of data collection such Medication Event Monitoring System (MEMS) cap, pill count in all studies were employed, this result might change. The high rates of poor adherence demonstrated in this and other studies are troubling, given the consequences of antiepileptic discontinuation and haphazard antiepileptic use. It might be assumed patients who discontinue medication will be more likely to relapse and poorly control the disease than those who continue medications.

In the present study, over half of patients reported that they had never missed taking their medications. However, those who were 100% adherent (CFR, 100%) on refilling their medications at appropriate time internal were found only to be 32 (12.1%) of the patients. This discrepancy proves the fundamental controversy on determining method for measuring medication adherence. It is recognized that patients' self report may still represent an under-reporting of the magnitude of the problem. Self-report questionnaires are less prone to suppression of undesirable responses. Therefore it may offer a better approximation to the true adherence status.

Table 3. Rate of adherence of patients defined by socio-demographic characteristics in Jimma University Specialized Hospital, Ambulatory Clinic, Jimma, January 31-March 14, 2013

Socio-demographic Characteristic	Description	Compliant Fill Rate (CFR)				
		25%	50%	75%	100%	Total
Sex	Male	42	29	24	62	157
	Female	27	34	22	25	108
Age in years	</=20	14	8	8	8	38
	21-30	17	47	23	15	102
	31-40	17	26	9	13	65
	41-50	19	10	9	5	43
	>/=51	8	4	2	3	17-
Marital Status	Unmarried	39	56	31	36	162
	Married	13	22	11	9	55
	Divorced	29	7	7	7	40
	Widowed	2	1	4	1	8
Educational Status	Tertiary	6	6	5	4	21
	Grade 8-12	12	10	8	10	44
	Grade 1-8	24	46	20	30	120
	No formal schooling	36	26	16	12	80
Occupational Status	Unemployed	12	14	6	10	42
	Employee	5	8	5	2	20
	Farmer	20	15	15	11	61
	Student	18	12	12	9	51
	Merchant	12	18	8	6	42
	Others	4	10	5	5	24
Religion	Orthodox	46	43	29	26	144
	Muslim	20	26	14	20	163
	Orthodox	23	28	18	15	71
	Protestant	6	3	2	2	25
	Other	3	5	5	3	6
Monthly income	>300	18	22	15	15	70
	200-300	23	20	14	11	68
	100-200	26	22	14	9	71
	< 100	22	28	18	17	85
	Unknown	9	12	6	14	41

The present study revealed that duration on antiepileptic medications treatment was significantly but negatively with adherence rate. From 74 patients who were on medications for only less than 2 years, 62 (83.8%) of them had adherence rate above 95%, but from 191 patients that were on AED for more than 2 year, only 53 (27.7%) had adherence rate of above 95%. This finding suggest that compared to patients with chronic conditions, patients with acute conditions have higher adherence rate, persistence among patients with chronic conditions was disappointingly low, dropping most dramatically after the first six-months of therapy. This finding is in agreement with other findings (5).

Forgetting 35 (31.8%) followed by being busy 23 (20.9%), were the major reasons to miss medications dose in this study. Similar to our finding, a study done by Abula et al. (10) in other parts of Ethiopia reported that forgetting, lack of Money, and occurrences of side effects were the major factors for missing the doses.

In present study communication between the patients and the health professional was high. Two hundred thirty five (88.3%) patients responded that they get information on their medication from their health care providers at each visit. The finding in the present study had shown that there was statistically significant association between quantity of medications taken and adherence rates. This may be due to an increase in number of medications misunderstanding may arise as a result of complex regimen and/or confusion of instructions from prescribers and other health care providers. Similar to our finding, a study done by Jones et al. (11) revealed that health care providers contribute to patient`s poor adherence by prescribing complex regimen, failing to provide adequate information on the benefits and side effects of medications. Although communication between patients and professionals were reported to be high, not only the communication but also the clarity of communication is very supportive in overcoming significant barrier to adherence because when misunderstanding occur treatment becomes complex and side effects go unmanaged.

In this study, patients' perception towards their illness was significantly associated with adherence rates. Majority of the patients in our study have no any idea about what their disease is about and nearly 20% the patients believe that the disease is spiritual. On the other hand, although few 33 (12.4%) in number, among the patients know that the disease is neurological, majority 25 (75.6%) had adherence rate over >80%. Contrary to our finding, in a study done in Pakistan 78% considered it to be a medical disorder (16). The main reason why most patients in our study had no idea or did think it is spiritual condition might be due to poor conversation between professionals and patients about the disease conditions.

Like other findings (13), the present study showed that patients with AED for more than two years and for 1-2 years duration had better improvement than patients on AED for 6 months to 1 year. On this study most 228 (86.04%) patients came for refill on due appointment. From the total 228 of patients who did not miss their appointment, 109 (47.8%) patients had adherence rate of above 95%. It was also found that missing of the appointment and adherence was significantly associated.

This study also showed that the presence of co morbid illness was significantly associated with adherence rate. It was demonstrated the effect of co morbidity adversely affected adherence and prognosis. This is in line with other findings (9).

The present study also revealed that age was significantly associated with adherence rate. It was found that majority (70%) of older people (age greater than 50) had adherence rate below 75%. Contrary to our finding, a study carried out in UK, reported that older patients (age greater than 60) were more likely to be compliant with their antiepileptic medication than patients under 60 years old (14). The inconsistency in the results and the main reason why older age patients were not adherent to their medications in our setting might be due to the fact that most of them were illiterate and might also prefer other alternative traditional practices at home than proper medication follow up.

Though other studies (15) demonstrated statistically significant association between variables such as marital status, occupational status, monthly income, ethnicity and type of seizure, all were not found to be significantly associated with adherence rate in our study.

In conclusion, the rate of adherence absorbed in this study was low, which highlights the pervasive problematic degree of antiepileptic medications adherence. The prescribers should negotiate about the treatment plan that the patient understands and to which he or she commits. Pill burden, co-morbid conditions and appointment missing were found to affect adherence. The pharmacist should provide appropriate counseling regarding importance of adherence to the patients as well as the family members. Moreover, close monitoring for any side effects and arranging between visits for any questions and problems. The high rate of non-adherence, in this study calls for further research and due consideration in planning appropriate strategies to improve the existing conditions.

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