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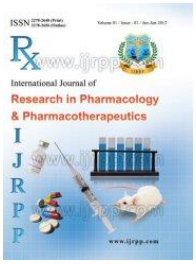

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Research article ***Open Access***

Assessment of factors influencing self reported drug adherence to anti-epileptic drugs at a tertiary care hospital

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ABSTRACT

Background

Epilepsy is one of the most common neurological disorders worldwide which requires incorporation of complex therapeutic regimens in daily routines. Success of the antiepileptic drugs (AEDs) regimen depends on the medication adherence. Non-adherence leads to recurrence, higher incidence of hospital admissions and imposes economic burden.

Objectives

To assess the factors contributing to self reported drug adherence of AEDs.

Materials and Methods

The study was conducted at the Neurology OPD, BMCRI for 6 months. 200 patients diagnosed with seizure disorder and prescribed AEDs were enrolled. Medication adherence was measured by patient self report using a single item question. The demographic and clinical variables of adherent and non-adherent patients were compared.

Results

Out of the 200 patients, 105 (52.5%) were males, mean age of the patients was 37.87±16.41 years and mean duration of epilepsy was 8.05±7.39 years. Most commonly prescribed AED was Carbamazepine (42%). About 11% of the patients reported adverse drug reactions (ADRs). 64.5% (129) of them were found to be adherent to AEDs and 35.5% (71) were non-adherent. Univariate Analysis showed that Age, education status, marital status, seizure burden, polytherapy and ADRs had a statistically significant association (p=<0.05) with self reported drug adherence. Regression analysis depicted that Marital status and ADRs best predicted non-adherence to AEDs.

Conclusion

35.5% of the patients were found to be non-adherent to AEDs. Non adherence was significantly higher among married patients and those who developed ADRs.

Keywords: Epilepsy, Antiepileptic drugs, Self reported drug adherence, Non adherence, Adverse drug reactions

INTRODUCTION

Epilepsy is the second most common neurological disorder next to headache, and is characterized by recurrent episodes of seizures. 50 million people in the world and an estimated 6-10 million people in India suffer from epilepsy which accounts for nearly 1/5th of global epilepsy burden. [1] Once diagnosed with epilepsy, the majority are treated with different Anti epileptic drugs (AEDs) and up to 70% can become seizure-free with optimum AED therapy. [2] However, approximately a third of patients continue to experience seizures despite the prescription of appropriate doses of AEDs. [3] Poor adherence to AEDs is one of the most important causes of poorly controlled epilepsy. [4]

The problem of adherence to drug regimes is prevalent across various chronic medical conditions [5] and has not spared epilepsy. A substantial proportion of patients with epilepsy experience inadequately controlled seizures because of non-adherence to AEDs. According to a patient survey by Cramer et al., 71 % of patients reported missing at least one dose of medication, with a mean of two missed doses per month and 45 % of respondents who had missed a dose of AED at least once monthly reported to have experienced a seizure thereafter. [6]

Individuals with epilepsy who are non-adherent to treatment are 21% more likely to experience seizures, [7] morbidity and mortality increases by 3 times, [8] experience 50% higher incidence of emergency room visits and 86 % higher frequency of hospitalization, incur higher inpatient costs, [9] experience decreased work productivity and low quality of life [10] compared with adherent patients.

Achieving complete adherence to AEDs remains an elusive objective due to the harmful consequences of non-adherence. Given the marked physical, psychological and social dysfunction associated with poorly controlled epilepsy, addressing the issue of non-adherence may well be a very cost effective addition to the better management of epilepsy. Hence the present study has been taken up to assess the factors influencing adherence to AEDs.

MATERIALS AND METHODS

This was an analytical, cross-sectional study conducted over a period of 6 months (July 2016- Dec 2016) at Neurology outpatient department of Victoria Hospital, attached to Bangalore Medical College & Research Institute, Bengaluru, India. Approval was obtained from the Institutional Ethics Committee (IEC) of Bangalore Medical College & Research Institute, Bengaluru. A consecutive sample of 200 patients who met the inclusion criteria and provided consent to participate in the study were recruited.

Medication adherence was measured by patient self report using a single item question used widely in clinical practice – "Did you forget or miss any of your medicine last week?". The patients were considered allegedly non-adherent if they answered "Agree" and adherent if answered "Disagree". Gomes and Filho et al [11] reported that single item question can consistently detect drug adherence in epilepsy. Wu et al [12] also validated that single-item question accurately predicted drug adherence in heart failure patients.

The influence of demographic and clinical variables on self reported adherence was evaluated. Study was conducted in compliance with the Declaration of Helsinki and Indian Good Clinical Practice Guideline.

Selection criteria and data collection

Patients with epilepsy aged 18 years or older, receiving AEDs for at least 6 months and willing to participate in the study were included in the study. Seizures were classified according to the definitions by The International League Against Epilepsy (ILAE). Patients with significant disability, major psychiatric disorders, severe medical co-morbidities confounding drug adherence and AED change in last 1 month were excluded.

A structured case record form was used to collect the data on socio-demographic, clinical and treatment parameters. Education status of <10 yrs means that the patient has not completed 10 years of school education. Education status of > 10 yrs means that the patient has completed his 10^{th} std in school or has any higher degrees. Patients were said to be seizure free if there was absence of seizure for more than 2 yrs. Patients with > 1 AED per prescription were said to be receiving polytherapy. Treatment data included generic names, daily dose, duration and adverse reaction profile after the administration of AEDs.

Statistical analysis

The data collected were subjected to descriptive analysis to evaluate the adherence of the AEDs. Results were expressed as percentages, as mean ±

standard deviation (SD) for continuous parametric variables. Comparisons between the adherent and non-adherent groups were performed using the chi-square (non-parametric variables) and t tests (parametric variables) as appropriate.

Univariate analysis was used to identify the association between the exploratory variables and adherence. Binary logistic regression analysis was used to determine the predictors of adherence to treatment. A p-value < 0.05 was considered statistically significant. Statistical analysis was done using statistical software R version 3.2.0.

RESULTS

Total of 200 patients were recruited in the study. Mean age of the patients was 37.87±16.41 years. 52.5% of the study population were male and 47.5% were females (Table 1). 31.5% had an education of >10 years and 65% were married. A total 53% of the patients were unemployed.

Table 1: Demographic and clinical profile

VARIABLES		NO (%)
Age groups		
18 – 59 years		175 (87.5%)
>60 years		25 (12.5%)
Gender		
Male		105 (52.5%)
Female		95 (47.5%)
Marital status		
Married		130 (65%)
Unmarried		70 (35%)
Education status		
<10 years		137 (68.5%)
>10 years		63 (31.5%)
Employment status		
Employed		94 (47%)
Unemployed		106 (53%)
Frequency of seizures	Seizure free	52 (26%)
	≤11 seizures per year	120 (60%)
	≥ 12 seizures per year	28 (14%)
Duration of seizures (mean ± SD in years)		8.05 ± 7.39
Monotherapy		109 (54.5%)
Polytherapy		91 (45.5%)
Drug Adherence		
Adherent		129 (64.5%)
Non adherent		71 (35.5%)

64.5% of them were found to be adherent to AEDs and 35.5% were found to be non adherent. Patients with lower mean age were found to be significantly adherent to AEDs. (p=<0.001), (Table-2). Patients with education status of >10 years were found to be significantly more adherent whereas married patients, patients who experienced ADRs and patients on polytherapy were found to be non adherent. Gender and employment status had no influence on adherence to AEDs.

Table 2: Comparison of demographic and clinical variables between the adherent and non-adherent groups of patients in epilepsy

Characteristics	Adherent n=129	Non-Adherent n=71	P Value *
Age, mean ± SD	33.99 ± 14.79	44.92±16.94	<0.0001#
Gender			
Male (n)	67	38	0.83

Female (n)	62	33	
Education status			
< 10 years (n)	74	63	<0.001
> 10 years (n)	55	8	
Marital status			
Married (n)	73	57	<0.001
Unmarried (n)	56	14	
Employment			
Employed (n)	62	32	0.68
Unemployed (n)	67	39	
Seizure burden			
Seizure free for ≥ 2 years (n)	47	5	<0.001
≤11 seizures per year (n)	77	43	0.9
≥ 12 seizures per year (n)	5	23	<0.001
Patients reporting ADR (n)	8	14	0.003
Polytherapy (n)	49	42	0.004

n=number of patients
P value < 0.05 considered as significant
*Pearson chi-square is used for significance
Unpaired t test

Carbamazepine (n=84) was the most commonly prescribed AED. Among 71 patients who were non adherent, 39 were treated with Phenytoin and 35 with Carbamazepine. (TABLE-3)

Table 3: Pattern and extent of AED use among epileptic patients

Drugs (Total number)	Adherent	Non adherent	P value*
Carbamazepine (84)	49	35	0.12
Phenytoin (77)	38	39	0.0003
Phenobarbitone (56)	33	23	0.34
Sodium Valproate (42)	28	14	0.74
Levetiracetam (26)	19	7	0.32
Clobazam (25)	17	8	0.86

P value < 0.05 considered as significant,
*Pearson chi-square is used for significance

Relationship between non adherence and clinical attributes

The predictors of drug non adherence were analyzed using multiple logistic regression analysis (Table 4). It showed that married individuals [OR=0.31, 95% CI = 0.07-0.95, p=0.04] and ADRs [OR=0.31, 95% CI = 0.08-0.91, p=0.04] were a significant predictor of non adherence.

Table 4: Determinants of Non-adherence to AEDs

Variables	Odd's Ratio	95% Confidence Interval	P Value
Age	0.98	0.94 - 1.02	0.39
Education>10 years	2.22	0.80 – 6.62	0.13
Married	0.31	0.07 - 0.95	0.04*
Seizure free	2.40	0.73-3.20	0.89
≤11 seizures per year	1.03	0.57-1.87	0.51
≥12 seizures per year	0.41	0.23-1.96	0.54
ADR	0.31	0.08-0.91	0.04*
Polytherapy (n)	0.71	0.14-3.63	0.68

*p<0.05 – significant

DISCUSSION

Chronic conditions such as epilepsy requires medication intake for long durations. Poor adherence to antiepileptic medications leads to poor control of seizures and non-responsiveness to AEDs. Factors influencing non-adherence should be identified at the earliest and measures should be taken to promote adherence to AEDs.

Carbamazepine was the most commonly used AED both as monotherapy and as polytherapy followed by Phenytoin. These findings differed from a study by Gurumurthy et al from south India, [13] who evaluated factors affecting adherence to AEDs in patients with epilepsy and reported Phenytoin as the most frequently prescribed AED as monotherapy.

35.5% of the patients self reported that they were non-adherent to AEDs. A study from New York conducted by Nakhutina et al [14] among ethnic minority low income patients showed that 63% of the patients were non adherent to antiepileptic treatment. Forgetfulness was the most often endorsed reason for non-adherence in many studies [13,14,15,16] which could be attributed to the chronic state of the disease and the need for frequent intake of the medications and complex medication regimens. Simplifying dosage regimen, decreasing the frequency of AEDs, use of pill dispensers or reminders and help from family members in reminding about medications would be helpful in reducing forgetfulness.

In univariate analysis, we found that patients with higher mean age (mean age 44.92$\pm$16.94) were more non adherent to the therapy. But multiple logistic regression model did not reveal age as a predictor for adherence. Literature search also shows conflicting results with regard to association between age and adherence. Gabr W M et al in Saudi Arabia did not find any association between age and adherence among 116 adolescent patients with idiopathic epilepsy. [15] Ferrari CMM et al from Brazil concluded that younger patients were less adherent to AEDs, [17] whereas Lusic I et al from Croatia observed that higher non adherence among elderly population. [18] However Cooper et al [19] concludes that age by itself is not the determining factor in medication non-adherence. Coping difficulties, immature attitudes, and irregular lifestyle may be related factors in younger individuals for non-adherence. Among elderly, longer duration of therapy, presence of co-morbidities or forgetfulness can contribute towards non-adherence. However, many factors may combine to render a person less able to adhere to their medication regimens; these include the specific illness, the treatment time frame, medication regimen, and the cognitive/affective status of the patient.

In the present study, we did not find any significant differences in rates of non-adherence between the genders. This finding is similar to that of a study by Liu et al, [16] in which the authors did not find any influence of gender on adherence to AEDs. Married patients were found to be significantly non adherent as compared to unmarried patients. Epilepsy, in India is still a social stigma. Patients may try to hide the fact that they are epileptic before getting married. Incidences of separation or divorce after marriage were more if the women were epileptic. It might be due to false belief that the disease would be transmitted to the children making them physically or mentally retarded resulting in a financial burden to the parents. Patients with epilepsy may become non-adherent to treatment in-order to hide the fact after marriage. We found that patients who were seizure free were 2.4 times more adherent. This was also shown in a study done by Gabr et al [15] which showed that patients with lesser seizure frequency were more adherent. There was an increase in the frequency of seizure among non-adherent patients and this may be attributed to their non-compliance with the prescribed medications. 49 out of 129 adherent patients and 42 out of 71 non adherent patients were on polytherapy. We found that patients on polytherapy were more non adherent which matches with the study conducted by Bautista et al from United States. [19] However Sweileh et al [21] from Palestine reported that polytherapy does not influence medication adherence. The reason for increase in non-adherence among patients with polytherapy can be attributed to the high pill burden and cost of the drugs. A total of 22 (11%) ADRs were reported. 8 out of 129 adherent patients had ADRs, whereas 14 out of 71 non adherent patients had ADRs. Most of the ADRs were mild. The most common ADR was gastritis and the most common drug causing it was Phenytoin. One case of serious ADR (Carbamazepine induced fulminant hepatitis) was reported. The underlying mechanisms behind hepatotoxicity induced by AED are not clear. Reactive metabolites from AED can lead to hepatocyte necrosis and cytotoxicity, and in some other cases this results in antigen mediated

immunoallergic reaction. [22] ADRs was associated with non adherence which was also shown by Uthman et al from Qatar, UAE. [23] Martins et al from Brazil found a statistically significant association between occurrence of ADRs and adherence to AED among 43 patients with juvenile myoclonic epilepsy. [24] Occurrence of ADRs may influence irregular consumption of drugs leading to poor adherence or discontinuation of the therapy.

The results are difficult to generalize as the study was conducted in a single centre. The sample size was relatively small. It is possible that significant results were not detected due to an insufficient sample size. Self reported adherence to medication is a crude approximation of the patient's behavior, but defining adherence by itself is noted to be primarily difficult by many researchers in the past. Self reported adherence has been criticized for its suboptimal accuracy because of recall bias which may overestimate drug adherence. However, Stephenson BJ et al [25] noted that self reported adherence has 55% sensitivity, 87% specificity and 4.4 likelihood ratio in cases of positive tests. Therefore, whenever possible, in order to reduce the bias related to the assessment of adherence, we always cross verified with the patient attenders, their prescription refills and the date of last appointment. It was not possible in this study to corroborate the reports of adherence by other means which would have added precision to the results.

CONCLUSION

35.5% of the patients self-reported that they were non-adherent to AEDs. Married patients were found to be significantly non adherent as compared to unmarried patients. Development ADRs had a significant association with non-adherence to AEDs. Age, gender, educational status, seizure free period and polytherapy were not significantly associated with non-adherence to AEDs. Given the marked physical, psychological and social dysfunction associated with poorly controlled epilepsy, and the considerable financial impact on health services, addressing the issue of non-adherence may well be a very cost effective addition to the better management of epilepsy. Assessment of adherence to AEDs should hence be a routine part in management of epilepsy.

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