

Factors affecting adherence to antiepileptic drugs therapy in Malaysia

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Abstract

Poor adherence to antiepileptic drug (AED) therapy can lead to various undesirable complications. Identifying the contributing factors of poor adherence is beneficial in assisting health care professionals to provide optimal interventions to control the seizures. This study aimed to identify the prevalence and factors affecting the adherence level to AED therapy in a multiracial population with epilepsy. This cross-sectional study was conducted at the neurology clinic of a tertiary care setting. Researcher-assisted questionnaire was utilised. Adherence level was assessed using validated Modified Morisky Adherence Scale-8. A total of 145 patients with epilepsy were included in this study. The prevalence of poor adherence to AED therapy was 64.1%. Poor adherence level was significantly associated with younger age ($\chi^2 = 7.609$, $p = 0.022$), medication adverse effects ($\chi^2 = 5.075$, $p = 0.020$), shorter duration of epilepsy ($r = 0.180$, $p = 0.030$) and uncertainty about the necessity for AEDs ($\chi^2 = 11.803$, $p = 0.001$).

Conclusion, prevalence of poor adherence to antiepileptic drugs was high and factors associated with poor adherence to AEDs were identified for a multiracial population with epilepsy.

INTRODUCTION

Antiepileptic drugs (AEDs) therapy has been demonstrated to be effective in up to 70% of patients with epilepsy.¹ Issues that commonly hamper the success of AED therapy may be biological or non-biological in nature. These issues include drug resistance, poor adherence, drug-drug interactions and cost.^{2,3} In developing countries, the prevalence of poor adherence to AED therapy has been reported in up to 80%.⁴ In Malaysia, previous study documented that the prevalence of poor adherence to AED therapy was up to 78.8%.⁵

Adherence to medication is defined as the extent to which a patient's behavior taking the medication prescribed by the physician changes after therapeutic plan agreement is established between patient and physician.⁶ Common reasons for poor adherence include taking drugs with inappropriate dose and at inappropriate times, not following physician's instructions and taking other non-prescribed drugs without the physician's recommendation.⁷ In general, these reasons can be classified into five dimensions of factors namely socioeconomic, patient-physician relationship,

therapy-related, condition-related and patient-related.⁴

Poor adherence to AED therapy affects clinical and economic outcomes.⁸ Worsening of severity and seizure frequency is associated with increase hospitalizations, emergency care and appointments with physician, which contribute to the direct costs of epilepsy treatment. Low productivity and less income due to inability to work, poor quality of life and failed therapy expenses will contribute to indirect costs.⁸ Poor adherence to AED therapy is associated with higher risk of mortality compared to patients who adhere to their medication.⁹

Medication adherence can be assessed by either indirect or direct methods. Direct methods to measure adherence are attendance to direct observed therapy and measurement of the level of medication or metabolite and biological markers in the blood.⁶ Indirect methods include patient self-reporting, records of drug refills, pill counts, patient's treatment response assessment and the use of electronic medication-monitoring devices. Identifying the contributing factors of poor adherence will assist health care professionals to improve treatment plans and interventions which

will subsequently enhance adherence to AED therapy. There are limited studies regarding factors influencing adherence to AED therapy among non-Caucasian population. We postulate that these factors may be influenced by the population characteristics. Malaysians represent a culturally unique and diverse population with three major distinctive races namely Malay, Chinese and Indian. Thus, this study aimed to identify the prevalence and factors affecting adherence level to AED therapy among culturally diverse epilepsy patients in a tertiary teaching hospital in Kuala Lumpur.

METHODS

Study design

This was a cross sectional study conducted at the neurology clinic, Universiti Kebangsaan Malaysia Medical Centre.

Sampling method

The sampling method used in this study was universal sampling. The study was conducted from September to October 2013. Patients with epilepsy were invited to participate in the study while waiting for or after their clinical appointment at the neurology clinic. Consent was taken from the patients before the researcher-assisted questionnaire was administered. Telephone calls were made to clarify ambiguous information.

A list of patients who were taking AED such as carbamazepine, clonazepam, lamotrigine, phenytoin, sodium valproate, gabapentin, topiramate, levetiracetam, pregabalin, phenobarbitone, oxcarbazepine, zonisamide and clobazam at neurology clinic from 1st of January to 31st August 2013 was retrieved. After that, screening of their medical records was made in order to choose patients who met the inclusion and exclusion criteria. The inclusion criteria in this study were patients aged 18 years and above, and patients who received AED for epilepsy for at least 6 months. The exclusion criterion in this study was patients with documented psychiatric illness.

A total of 1,146 patients were identified at the neurology clinic from 1st January to 31st August 2013 and 922 medical records were available for screening. A total of 384 patients were excluded from this study because they were younger than 18 years old ($n = 21$), did not have epilepsy ($n = 351$) and had documented psychiatric illness ($n = 12$). From 538 epilepsy patients who met the

inclusion and exclusion criteria only 145 agreed to participate, the remaining 393 patients either refused to be interviewed ($n = 247$; response rate of 37%), had aphasia or speech difficulties or had their AEDs stopped by the physician.

Ethical approval

This study was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (UKM) with registration number UKM 1.5.3.5/244/NF-028-2013.

Study instruments

The questionnaires consisted of six dimensions: socioeconomic, disease condition, patient-physician relationship, therapy, patient and adherence scale. It was prepared in both Malay and English. The questionnaires were validated for content and readability by expert panels and pilot cohort, respectively.

The questions regarding appropriate dimensions were adapted from Buck *et al.*⁷ Questions pertaining to the socioeconomic dimension covered gender, age and educational level. Questions pertaining to disease conditions covered duration of epilepsy and frequency of attacks in one month. Questions pertaining to patient-physician relationship included how patients perceived his/her physician and whether patients had regular appointments to see his/her physician about epilepsy. Questions pertaining to therapy covered the number of prescribed drugs taken per day, frequency of taking AEDs per day, understanding of physician's instructions, adverse effects and cessation of AEDs after experiencing the adverse effects. Questions pertaining to the patient-related dimension included how the patients felt about the effectiveness and importance of his/her AEDs, whether the patients felt stigmatized by the epilepsy, whether the patients had altered drug-taking behavior due to fear of addiction to the AEDs and whether the patients changed their the dosing regimen to see if their seizures recurred.

The Validated 8-item Morisky Medication Adherence Scale (MMAS-8), a self reporting tool was used to assess the patient's adherence level to AED therapy.¹⁰ There were 8 questions evaluating the patient's forgetfulness, patient's understanding of the need for continued therapy and whether the patient felt it was inconvenient adhering to a daily medication treatment plan. For questions 1, 2, 3, 4, 6 and 7, a score of zero was given for

a positive response whereas a score of one was given for a negative response (Yes = 0; No = 1). Conversely, for item 5, a score of zero was given for a negative response whereas a score of one was given for a positive response (Yes = 1; No = 0). For item 8, a score of one was given for 'Never/Rarely' whereas a score of zero was given for 'Once in a while' / 'Sometimes' / 'Usually' / 'All the time'. The total score of MMAS-8 was 8. A Higher score indicated a higher level of self-reported adherence. Adherence level was categorized as high (Score: 8), medium (Score: 6 or 7) and low (Score: < 6).¹⁰Patients who had a MMAS-8 score of 8 were considered to have a good adherence level while patients who had a MMAS-8 score of less than 8 were considered as having a poor adherence level.

Data analysis and presentation

Data collected was analysed using Statistical Package for Social Science (SPSS) version 21. Associations between continuous variables were analysed using the Spearman's rank order correlation. Associations between categorical

variables were assessed using the chi-square (χ^2) test. A p-value of less than 0.05 was considered significant.

RESULTS

The socio-demographic characteristics of epilepsy patients are presented in Table 1. The 145 study subjects, 51% were men (n = 74), 66.2% of patients aged 18-39 years old (n = 96) and 59.3% of patients with secondary or lower educational levels (n = 86). The racial distribution was as follows: 54.5% of Malay (n = 79), 32.4% of Chinese (n = 47) and 13.1% of Indian (n = 19).

The prevalence of poor adherence to AED therapy was documented in 64.1% of the study subjects (n = 93). There was no significant association between the self-reported adherence level and gender, race and educational level. However, significant association was found between age and the self-reported adherence level ($\chi^2 = 7.609$, p = 0.022). The majority of patients with self-reported poor adherence level were below 40 years old (74.2%).

Table 1: Association between socio-demography factors and adherence level

Factor	Total (n=145)	Adherence level		χ^2 value; p-value ^a
		Good (n=52)	Poor (n=93)	
Gender				
Male	74 (51.0%)	28 (53.8%)	46 (49.5%)	0.256;
Female	71 (49.0%)	24 (46.2%)	47 (50.5%)	0.613
Race				
Malay	79 (54.5%)	26 (50.0%)	53 (57.0%)	0.742; 0.690
Chinese	47 (32.4%)	18 (34.6%)	29 (31.2%)	
Indian	19 (13.1%)	8 (15.4%)	11 (11.8%)	
Age (years)				
18-39	96 (66.2%)	27 (51.9%)	69 (74.1%)	7.609;
40 & above	49 (33.8%)	25 (48.1%)	24 (25.9%)	0.022*
Educational Level				
Secondary and below	86 (59.3%)	34 (65.4%)	52 (55.9%)	0.851;
Diploma or 1 st degree	53 (36.6%)	17 (32.7%)	36 (38.7%)	
High degree	6 (4.1%)	1 (1.9%)	5 (5.4%)	
Monthly income				
≤ RM2000	123 (84.8%)	45 (86.5%)	78 (83.9%)	1.713;
>RM 2000	22 (15.2%)	7 (13.5%)	15 (16.1%)	0.425

*Indicates significant difference between groups at p < 0.05

^aChi square

^bYates' chi square

^cRM, ringgit Malaysia, 1USD = 3.2 ringgit Malaysia

Table 2: Correlation between disease condition factor and adherence score

Factor	Observation	r for correlation to adherence score	p-value
Duration of epilepsy	12.21 ± 10.29 (mean ± SD)	0.180	0.030*
Frequency of seizure attacks in one month	0 (median)	0.013	0.873

*Significant at 0.05 level (two-tailed, $p < 0.05$)

Correlations between factors regarding disease conditions and adherence score are shown in Table 2. The mean (\pm SD) duration of epilepsy was 12.21 (\pm 10.29) years. A significant positive correlation was demonstrated between duration of epilepsy and adherence score (Spearman's $\rho = 0.180$, $p = 0.030$). The median frequency of seizures in one month was zero (range from zero to 30) and this factor was not significantly correlated with adherence score.

Associations between various potential influencing factors and adherence level are presented in Table 3. Most of the patients felt at ease when talking to their physician ($n=130$, 89.7%) and had regular appointments to see their physician to discuss their epilepsy ($n=144$, 99.3%). There was no significant difference between these two factors and the self-reported adherence level. A total of 63 patients (43.4%) received more than three prescription medications per day and 81 patients (55.9%) received monotherapy for their epilepsy. Most of the patients (78.6%, $n = 114$) took their AEDs twice daily and 130 patients (89.7%) understood their physician's instructions. The Percentage of patients reported to have experienced adverse effects after taking AEDs was 26.9% ($n = 39$), 7.6% ($n = 11$) of whom sometimes stopped taking their AEDs when they experienced adverse effects. Associations between treatment regimen complexity, understanding of physician's instructions and self-reported adherence level were not significant. However, there was a significant association between those who experienced side or adverse effects from AEDs and self-reported adherence level ($\chi^2_{\text{yates}} = 5.075$, $p = 0.020$).

A total of 69.7% ($n = 101$) patients felt that their seizures were well-controlled by AEDs. Out of 2.8% ($n = 4$) of patients who felt that AEDs did not have any effect on their seizures, 1.4% ($n = 2$) of patients stopped taking the AEDs prescribed. The Majority of the patients (79.3%, $n = 115$) felt that it was very important to take AEDs as

prescribed. Most patients did not feel stigmatized by their epilepsy (81.4%, $n = 118$) and were not worried about addiction to AEDs and thus did not alter their drug-taking behaviour (99.3%, $n = 144$). Some of the patients (15.9%; $n=23$) felt uncertain about the necessity for AED therapy and decreased or stopped their prescribed AEDs to see if their seizures recurred. A significant association was demonstrated between uncertainty about the necessity for AEDs and self-reported adherence level ($\chi^2 = 11.803$, $p = 0.001$).

DISCUSSION

The prevalence of self-reported poor adherence to AED therapy among our study subjects is higher than those reported in previous studies of the Western population.¹¹ However our finding is comparable with other local study.⁵ This showed that the prevalence of poor adherence to AED therapy among epilepsy patients in Malaysia is still high. In 2003, WHO reported that the prevalence of adherence to AEDs in developing countries ranged between 20% and 80%.⁴ Hence, our finding showed that the issue of poor adherence remains to be important for the past 10 years. As such, it is relevant to understand the factors affecting poor adherence to AED therapy.

Factors found to be associated with poor adherence to AED therapy were younger age, shorter duration of epilepsy, medication side or adverse effects and uncertainty about the necessity for AEDs. A similar observation was reported earlier in which a higher adherence level to AED therapy was associated with elderly patients.⁷ The possible explanation to this observation is that younger patients are pre-occupied with an active social life, academic studies or jobs causing them to sometimes forget to take their medication, and they may also think that they are healthier and do not require any treatment. WHO also reported that patients with busy lifestyles commonly do

Table 3: Association between various factors and adherence level

Item	Total (n=145)	Adherence level		χ^2 value; p-value
		Good (n=52)	Poor (n=93)	
Patient-Physician Relationship Factor:				
Patient's perception on the physician:				
Easy to talk to	130 (89.7%)	47 (90.4%)	83 (89.2%)	0.078;
Not easy to talk to	5 (3.4%)	1 (1.9%)	4 (4.3%)	0.960 ^a
Not sure	10 (6.9%)	4 (7.7%)	6 (6.5%)	
Regular arrangement for physician visit on epilepsy.				
Yes	144 (99.3%)	52 (100%)	92 (98.9%)	0.088;
No	1 (0.7%)	0 (0%)	1 (1.1%)	0.767 ^a
Therapy-related Factor:				
Number of prescription medication taken per day				
One	21 (14.5%)	5 (9.6%)	16 (17.2%)	6.207;
Two	43 (29.7%)	11 (21.2%)	32 (34.4%)	0.102
Three	18 (12.4%)	7 (13.5%)	11 (11.8%)	
Four and more	63 (43.4%)	29 (55.8%)	34 (36.6%)	
Antiepileptic drug regimen received				
Monotherapy	81 (55.9%)	25 (48.1%)	56 (60.2%)	1.993;
Polytherapy	64 (44.1%)	27 (51.9%)	37 (39.8%)	0.158
Frequency of antiepileptic drugs taken per day				
Once daily	26 (17.9%)	10 (19.2%)	16 (17.2%)	0.085;
Twice daily	114 (78.6%)	40 (76.9%)	74 (79.6%)	0.958 ^a
Thrice daily	5 (3.4%)	2 (3.8%)	3 (3.2%)	
Knowledge on antiepileptic drugs intake as instructed by the physician				
Yes	130 (89.7%)	47 (90.4%)	83 (89.2%)	0.047;
No	15 (10.3%)	5 (9.6%)	10 (10.8%)	0.829
Experience of side or adverse effects after taking antiepileptic drugs				
Yes	39 (26.9%)	9 (17.3%)	30 (32.3%)	3.791;
No	106 (73.1%)	43 (82.7%)	63 (67.7%)	0.052
Ever stop taking antiepileptic drug when experienced side or adverse effects of antiepileptic drug.				
Yes	11 (7.6%)	0 (0%)	11 (11.8%)	5.075;
No	134 (92.4%)	52 (100%)	82 (88.2%)	0.020 ^a
Patient-related Factor:				
Control of seizure by antiepileptic drug.				
Very well	101 (69.7%)	39 (75.0%)	62 (66.7%)	1.244;
Fairly well	34 (23.4%)	9 (17.3%)	25 (26.9%)	0.742 ^a
Not very well	6 (4.1%)	3 (5.8%)	3 (3.2%)	
Not at all	4 (2.8%)	1 (1.9%)	3 (3.2%)	
Stop taking antiepileptic drug when I feel it is not effective.				
Yes	2 (1.4%)	0 (0%)	2 (2.2%)	0.205;
No	2 (1.4%)	1 (1.9%)	1 (1.1%)	0.903 ^a
Not sure	141 (97.2%)	51 (98.1%)	90 (96.8%)	

Importance of taking antiepileptic drugs as prescribed.

Very important	115 (79.3%)	44 (84.6%)	71 (76.3%)	0.661;
Fairly important	22 (15.2%)	6 (11.5%)	16 (17.2%)	0.882 ^a
Not very important	7 (4.8%)	2 (3.8%)	5 (5.4%)	
Not at all important	1 (0.7%)	0 (0%)	1 (1.1%)	

Feels stigmatized by your epilepsy.

Yes	27 (18.6%)	7 (13.5%)	20 (21.5%)	1.424;
No	118 (81.4%)	45 (86.5%)	73 (78.5%)	0.233

Alter drug-taking behaviour because of fear of addiction to antiepileptic drug.

Yes	1 (0.7%)	0 (0%)	1 (1.1%)	0.088;
No	144 (99.3%)	52 (100%)	92 (98.9%)	0.767 ^a

Test the seizure control status by decreasing or ceasing the intake of the prescribed antiepileptic drug.

Ever	23 (15.9%)	1 (1.9%)	22 (23.7%)	11.803;
Never	122 (84.1%)	51 (98.1%)	71 (76.3%)	0.001

^a Yate's χ^2 test

not adhere to medication.⁴Patients with a longer duration of epilepsy perceived taking AEDs as part of their daily routine which resulted in better adherence level. This suggested that patients realized the benefits of adherence as time passed because they learn from their personal experience.¹¹

Frequency of seizures prior to the current survey was not correlated with the adherence score. This finding is comparable to a previous study.¹²Patients may question the need of adhering to AED therapy if they miss a dose of their AED with no occurrence of a breakthrough seizure. No significant association was identified between patient-physician relationship and adherence level in this study. Patients who felt at ease when talking to their physician and those who had regular appointments with their physician to discuss their illness remained non-adherent. This observation may be due to the limited contact time with the physician despite regular appointments as claimed by some patients. Longer contact time between patients and physician provided greater opportunity for patients to discuss any drug-related problems that they experienced. In addition, the physician may use this opportunity to emphasize the importance of good adherence to AED therapy in order to control the seizures.⁷

Patients sometimes stopped taking their AED when they experienced the intolerable adverse effects of AED. The common adverse effects of AEDs experienced by the study subjects were hair loss, weight gain, memory problems, fatigue and dizziness. These common adverse effects were the most frequent complaints from epilepsy patients on AEDs.¹³Concern about the safety of medication

was reported as one of the factors affecting adherence level.⁷In addition, misconception about the potential adverse effects of AEDs may also result in poor adherence level.

Adherence level was significantly associated with the feeling of uncertainty about the necessity for AEDs as was observed earlier.¹⁴Possible reasons for this uncertainty may include curiosity of patients about the effectiveness of the AED regimen and insufficient counseling given on the AED therapy by the health care professionals. One study reported that more than half of the epilepsy patients thought that they could reduce or cease taking the AEDs just to see what would happen.¹²This shows that poor understanding about the nature of, and need for the AED therapy could lead to poor adherence level.

No significant association was demonstrated between treatment regimen complexity and adherence level. In contrast, a study earlier reported that AED polytherapy is associated with better adherence, as polytherapy often implies history of more frequent and severe seizures, reinforcing the need for good adherence.⁷Nevertheless, the need for good adherence may have been hampered by complex medication regimens such as increased frequency of AED intake which may cause confusion and forgetfulness in some of the patients.¹⁵This may be one possible explanation for our current finding.

No significant association was identified between adherence level and understanding of instruction on how to take the AED. This indicates that good understanding of how to take the AED does not guarantee good adherence to medications. Some of the patients changed the dosing frequency

of AEDs themselves without consulting their health care professionals. The possible reason for this self-adjusted dosing frequency is the desire to assess the need for therapy or the seizure status as reported in a previous study.¹⁴

Previous studies showed that patients with higher adherence level were those who perceived taking medication as important.⁷In our findings, however, no significant association was found between the perception on the importance of taking AEDs and adherence level. Most of the patients who felt the importance of taking AED practiced poor adherence. The conflicting findings may be explained by forgetfulness of the patients in taking their AED.⁴

In the current study, the feeling of being stigmatized by the epilepsy was not significantly associated with adherence level. In contrast, the feeling of being stigmatized was reported in one study to promote poor adherence to medication so as to prevent disclosure of the illness to the public.⁷Taking AEDs in public or in front of relatives and friends family members could expose the patient's illness. Most of our patients, however, did not feel stigmatized by their epilepsy, and some of them rationalized that their seizures had not occurred in public or they had disclosed their epilepsy to their friends.

This study has highlighted several important findings. Nevertheless, these findings should be inferred with caution due to several limitations such as limited sample size, possible patients' misunderstanding of the questionnaires, self-reported adherence may not reflect actual adherence of the respondents and the nature of the study which reflects the current situation. All possible preventive actions have been taken to reduce the effects of these limitations on the results presented.

Our study indicates that health care professionals should spend sufficient time in educating the patients to improve the adherence level especially for newly diagnosed and younger epilepsy patients. The educational topics should include the potential consequences of poor adherence, the necessity for AED therapy and the safety profile of the AEDs.

In conclusion, the prevalence of poor adherence to AED among epilepsy patients in the study cohort was 64.1%. Factors associated with poor adherence to AED therapy were younger age, short duration of epilepsy, medication adverse effects and uncertainty about the necessity for AEDs.

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DISCLOSURE

Conflict of interest: None

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