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Medication adherence status among patients with neurological conditions and its association with quality of life

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ABSTRACT

Background/Aim: Medication non-adherence may cause significant morbidity and mortality in patients with chronic diseases and may increase the economic burden on the healthcare system. The prevalence of neurological disorders is increasing in Malaysia; however, comprehensive data on medication adherence among Malaysian patients with these disorders is limited. This study was conducted to determine the association of medication non-adherence with quality of life in patients with neurological problems.
Methods: A cross-sectional survey was performed in 370 patients diagnosed with epilepsy, Parkinson's disease, stroke and Alzheimer's disease at Neurology clinic. Patients aged 18 years or older, without documented physical or psychiatric illness such as schizophrenia and major depression, were included. Patient-administered questionnaires, such as the Malaysian Medication Adherence Scale and Medication Possession Ratio were used to determine medication adherence. An established EQ-5D-3L questionnaire was used to determine quality of life. Data were analysed using descriptive and inferential analysis.
Results: The overall prevalence of medication non-adherence among patients with neurological disorders was 59.2%. Among these neuromedical diseases, 69.2% ($n = 9/13$) of Alzheimer's disease, 66.7% ($n = 98/147$) of epilepsy, 62.1% ($n = 36/58$) of Parkinson's disease and 48.7% ($n = 74/152$) of stroke patients were found non-adherent. There was a significant difference in EQ-5D index scores ($p = 0.041$) between adherent and non-adherent patients.
Conclusion: A high prevalence of medication non-adherence was found among patients with neurological disorders. The rate of non-adherence varied among different neurological conditions. There was a significant difference in quality of life between adherent and non-adherent patients.

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1. Introduction

More than 600 neurological disorders exist, including epilepsy, Parkinson's disease (PD), stroke and Alzheimer's disease (AD) (Siuly and Zhang, 2016). They are expected to become one of the Malaysia's leading causes of morbidity and mortality over the next decade (Abdullah et al., 2006). Approximately 50 million people worldwide, including up to 1% of the overall Malaysian population, have epilepsy (Arulsamy et al., 2014). Approximately 15,000–20,000 local Malaysian patients have PD (Oung et al., 2015). A total of 11,284 S cases were reported in the Malaysian stroke registry from 2009 to 2016 (National Neurology Registry, 2016). Alzheimer's disease is the most common type of dementia and currently affects about 50,000 local patients in Malaysia (Alzheimer's Disease Foundation Malaysia, 2018).

Chronic disorders commonly require long-term pharmacotherapies and non-pharmacological therapies. However, up to 50% of patients are non-adherent (World Health Organization, 2003). The worldwide rate of non-adherence to antiepileptic drugs (AEDs) is 25%–66% (Farrukh et al., 2018). Moreover, 64.1% of patients with epilepsy in Malaysia (greater than that of the Western population) have poor AED adherence (Tan et al., 2015). Medication non-adherence among stroke patients is 22%–53% (De Schryver et al., 2005, Cheiloudaki and Alexopoulos, 2019, Kim et al., 2018, Pan et al., 2017, Appalasamy et al., 2019). The medication non-adherence rate is 53% among stroke patients in Malaysia (Appalasamy et al., 2019). Data on the adherence rate among PD and Alzheimer's disease patients in Malaysia are limited. However, 67% of patients with PD in the southeastern part of the United States have shown suboptimal adherence to PD medications (Grosset et al., 2005). The medication non-adherence rate in patients with Alzheimer's disease is 42%–89.3% (Borah et al., 2010, Smith et al., 2017).

Medication adherence can be measured subjectively and objectively (Anghel et al., 2019). Multiple methods help compensate for putative weaknesses in study design and increase the accuracy of information captured for determination of adherence levels (Lam and Fresco, 2015). Quality of life (QOL) and adherence to medicines are interlinked. It is believed that patients who adhere to their treatment can experience an improvement in QoL and vice versa (Zioga et al., 2016). Most of the previous research demonstrates that patients with epilepsy experience poor QoL with additional psychosocial problems in comparison with the general population (Sillanpää et al., 2004). A study was carried out in Germany among epilepsy patients where anxiety was highly reported as compared to other domains of EQ5D (De la Loge et al., 2016). AED therapy reduces seizure frequency and enhances the quality of life. QOL was studied among PD patients in China and it was found that patients reported problems in all the domains (Fan et al., 2018). A study reported the Health-related quality of life in stroke patients and it was found that after treatments, the physiological quality of stroke patients increased, but the psychological quality remained low (Chen et al., 2019). QOL studies in other neurological disorders are limited. To achieve the optimal efficacy of the medication, patients should adhere to the regime prescribed by healthcare professionals The prevalence of disease-specific medication adherence is unknown among the Malaysian population. Although medication adherence and its associated factors have been extensively studied, less is known about the medication non-adherence rate among patients with neurological disorders in Malaysia and its association with the QOL. It is hypothesized that medication non-adherence is associated with poor QOL among patients with neuromedical illness. Thus, the objective of this study was to evaluate the prevalence of non-adherence and QoL among neuromedical patients in a tertiary care hospital in Kuala Lumpur, Malaysia.

2. Methods

2.1. Study design

A cross-sectional survey was carried out among patients diagnosed with neurological illnesses at the Universiti Kebangsaan Malaysia Medical Center (UKMMC) between March 2017 and November 2018.

2.2. Sample size calculation

The sample size of the study was determined by using Raosoft® Sample Size Calculator (Raosoft Inc, 2004), with a confidence interval of 95% and a margin of error of < 5%. A total of 370 patients were required for the study.

2.3. Study population and sampling method

The patients were recruited from the neurology clinic at the Hospital Universiti Kebangsaan Malaysia. Data was collected using simple random sampling. First the appointment list of patients was obtained from the clinic appointment record and then patients were randomly selected using a random number generator. Random Number Generator®, Android App developed by Ux Apps was used (Random Number Generator 2016). Patients were recruited based on the following criteria.

2.3.1. Inclusion criteria

Patients with epilepsy, PD, stroke and AD, who were 18 years or older, taking medications for at-least 6 months. The diagnosis was based on the diagnosis done by the physicians.

2.3.2. Exclusion criteria

Patients not fit to be interviewed determined by MMSE score < 12, Patients with a physical or psychiatric illness such as schizophrenia and major depression, critically ill patients and those who refused to participate in this study were excluded. Patients who were unable to communicate in English, Chinese and Malay language were excluded.

2.4. Data collection

Patients were approached in the physicians' rooms after completing their consultations. They were invited to take part in this study and briefed on the purpose of the study. Written informed consent was taken from the patients who agreed to fill in the self-administered questionnaires. When appropriate, nurses assisted the patients in filling out the questionnaires. CONSORT flow diagram showing participants recruitment process is presented as Fig. 1.

2.5. Survey items

The questionnaire consisted of 3 main sections. Section A consisted of patient's demographic data. Section B measured Medication adherence by using Malaysian Medication Adherence Scale (MALMAS) (Chung et al. 2015) (as shown in Appendix D) and Medication Possession Ratio (MPR) (Andrade et al., 2006). The MPR was determined from the pharmacy information system (PIS) by calculating the number of days' supply of medication dispensed divided by the number of days between the first and last prescription refill (Andrade et al., 2006). Poor adherence becomes clinically significant when MPR is<0.8 (Andrade et al., 2006) and MALMAS is<6 from a total score of 8 (Chung et al. 2015). If any of the two tools showed patient as non-adherent, patients were considered as non-adherent. Section C consisted of QoL which was measured by using validated Euro Quality of Life scale, EQ-5D-3L (EuroQOL Group, 1990). The EQ-5D-3L consists of descriptive system and the VAS. The descriptive system consists of the following 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression with three possible levels for each item (Level 1 = no problem, Level 2 = moderate problem, Level 3 = severe problem). The respondents were asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. A unique health state is obtained by combining 1 level from each of the 5 domains. The EQ VAS recorded the respondents' self-rated health status on a vertical visual analog scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. EQ-5D-3L
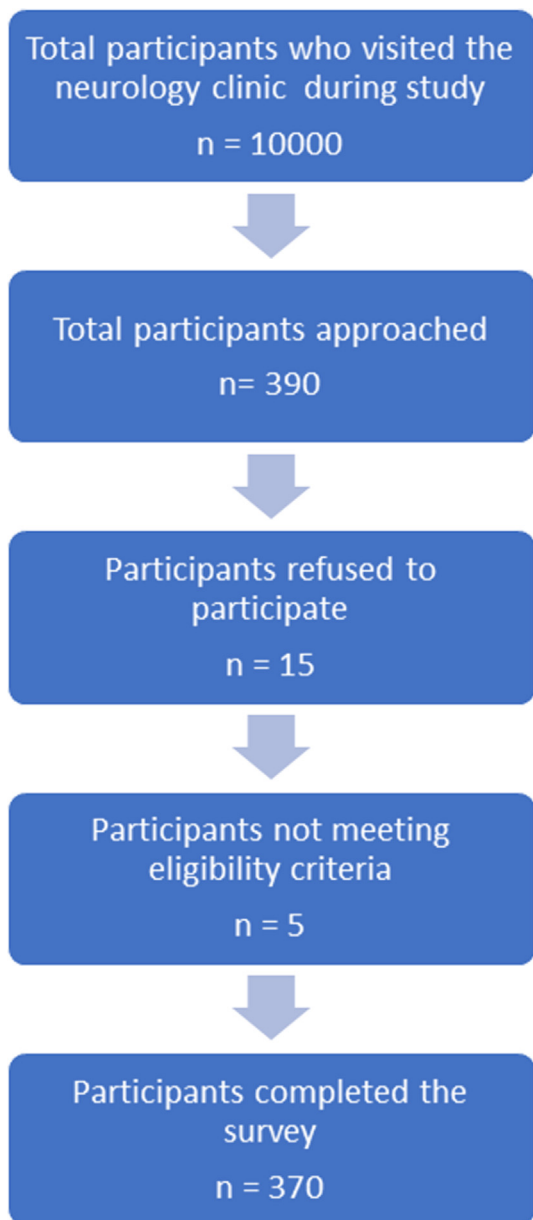
Fig. 1. CONSORT flow diagram showing participants recruitment process.

health states can be converted to a single summary index ranging from 0 to 1 where the maximum score of 1 indicates the best health state. EQ-5d index values were obtained from a previous study done in Malaysia (Yusof et al., 2012). English and Malay versions of the tool were used after taking permission from the original authors.

2.6. Data analyses

The statistical analysis was conducted using version 23 of the IBM SPSS. Data were analyzed using inferential and descriptive analyses. Levels 2 and 3 of all five EQ-5D domains were merged to dichotomize the responses of patients into "level 1: no problem" and "level 2 or 3: some or extreme problem (Mubashra et al., 2018). Univariate analysis to study the relationship between the variables and medication adherence was done using pearson's correlation test, Chi-square test and Independent *t*-test where necessary. Association between adherence and sociodemographics and EQ-5D domains was analysed. Variables with p value < 0.1 in

the univariate amalysis were selected to be modelled using BLR with Backward-stepwise method (Lang, 2007). Variables with p < 0.05 was considered to have significant influence on adherence. Significant association between factors and adherence was described as statistical significant p value.

2.7. Ethical considerations

Ethical approval was taken from the Universiti Kebangsaan Malaysia Medical Centre's ethical committee, reference no. UKM PPI/111/8/JEP-2017–138. Written informed consent was obtained from all patients before participation in the study.

3. Results

3.1 . Sociodemographic characteristics of the respondents

For this survey, a total of 385 patients were approached and out of them 15 patients refused to participate. The response rate of the patients was 96.1%. The reasons given by the patients for not participating in this survey were time constraints (n = 8) and unwilling to participate (n = 7). A total of 150 female and 220 male patients aged 18 to 91 years participated in this study. Most of the patients were Malay ($n = 174$), followed by Chinese ($n = 158$) and Indian ($n = 38$). Majority of the patients went to secondary school as their highest education level ($n = 158$) and only a few ($n = 12$) had no formal education. The number of comorbidities varied among patients (range, 0–4). The prevalence of non-adherence determined by MALMAS and MPR was 54.6% and 41.9% respectively. However, overall prevalence of non-adherence to medication was 59.2% among patients with neurological disorders. Among these neuromedical diseases, 69.2% ($n = 9/13$) of AD, 66.7% ($n = 98/147$) of epilepsy, 62.1% ($n = 36/58$) of PD and 50% ($n = 76/152$) of stroke patients were found non-adherent. Single patients were more non-adherent than married and divorced patients. The average number of medications was significantly different between adherent and non-adherent patients ($p = 0.034$). Details of patients' sociodemographic characteristics and their medication adherence status are presented in Table 1.

The most common items of MALMAS being reported by the patients were forgetfulness (48.1%), missing dose when away from home (37%), difficulty in taking medicine (28.6%), problem in remembering to take medicine (28.1%) and stopping medication after feeling better (27.6%). Patients response to MALMAS statements is shown in Table 2

Sixty four (31.7%) patients came to fill their prescriptions on time but were found non-adherent according to MALMAS scale. Seventeen (10.1%) patients over reported their adherence on MALMAS and were found to be non-adherent according to MPR. The association between MALMAS and MPR is presented in Table 3.

When the demographic characteristics of patients were evaluated against the QOL assessment scores, there was a significant negative correlation between age and EQ-5D index scores (r = –0.26, $p < 0.01$) and visual analog scale (VAS) scores (r = –0.34, $p < 0.01$). Single patients had higher EQ-5D scores and VAS scores than married patients. Those with fewer comorbidities had better QOL scores on both EQ-5D scales ($p < 0.01$). The mean VAS scores varied significantly among patients with epilepsy, stroke, AD and PD ($p < 0.01$). Based on EQ-5D index scores, male patients felt healthier than females (<0.01). The patient characteristics, EQ-5D scores and VAS scores are summarized in Table 4. Univariate analysis on association of medication adherence status and EQ-5D domains is shown in Table 5. Variables with p value < 0.1 in the univariate analysis were selected to be modelled using multivariate binary logistic regression analysis (BLR) as shown in Table 6.

Table 1
Sociodemographic characteristics of patients and their medication adherence status.

Item	Descriptive value	Adherence	Nonadherence	p-value
Age mean (SD)	53.52 (16.7)	53.8 (16.71)	53.28 (16.78)	0.74[†]
Gender, n (%)				0.280[*]
Male	220 (59.5)	95(43.2)	125 (56.8)	
Female	150 (40.5)	56 (37.3)	94 (62.7)	
Race, n (%)				0.017[*]
Malay	174 (47)	84 (48.3)	90 (51.7)	
Chinese	158 (42.7)	56 (35.4)	102 (64.6)	
Indian	38 (10.3)	11 (28.9)	27 (71.1)	
Marital status, n (%)				<0.01[*]
Single	103 (27.8)	31 (30.1)	72 (69.9)	
Married	245 (66.2)	102 (41.6)	143 (58.4)	
Divorced	22 (5.9)	18 (81.8)	4 (18.2)	
Diagnosis, n (%)				0.12[*]
Epilepsy	147 (39.7)	49 (33.3)	98 (66.7)	
Stroke	152 (41.1)	76 (50)	76 (50)	
PD	58 (15.7)	22 (37.9)	36 (62.1)	
Alzheimer's Disease	13 (3.5)	4.0 (30.8)	9.0 (69.2)	
Co-morbidities, mean (SD)	2.38 (1.2)	2.26 (1.16)	2.46 (1.24)	0.115[†]
No of medicines, mean (SD)	4.04 (1.9)	3.78 (1.7)	4.21 (2.02)	0.034[†]

[*] Chi-square test.
[†] Independent *t*-test.

Table 2
Patients response to MALMAS statements.

MALMAS statements	Patient response	
	Yes n (%)	No n (%)
Was there any time that you have forgotten to take your medicines during the past one month?	176 (47.6)	194 (52.4)
Was there any time that you took less of your medicines during the past one month?	98 (26.5)	272 (73.5)
During the past one month, was there time that you forgot to bring your medicines when you were away from home?	137 (37.0)	233 (63.0)
Did you take your medicines according to instructions yesterday?	291 (78.6)	79 (21.4)
During the past one month, did you stop taking your medicines when you feel better?	102 (27.6)	268 (72.4)
Do you think it is difficult to take your medicines?	106 (28.6)	264 (71.4)
Do you have any problem remembering to take your medicines?	104 (28.1)	266 (71.9)

Table 3
Association between MALMAS and MPR.

Item		MPR		
		Adherent	Non-adherent	p value
MALMAS, n (%)	**Adherent**	151 (89.9)	17 (10.1)	<0.05
	Non-adherent	64 (31.7)	138 (68.3)	

Single and married patients were found to be less adherent as compared to divorced. Patients who reported no problem in their usual activities were found to be more adherent.

Among the patients with neurological disorders, those with PD reported more problems in the four domains compared to those with other diseases. Anxiety was highly reported by patients with epilepsy and problems in self-care were reported more by those with Alzheimer's disease. The EQ-5D domain responses among patients with neurological disorders are shown in Fig. 2. Overall, the QOL was better among patients who adhered to their medications than among those who did not adhere to their medications (Table 7).

4. Discussion

Medication adherence in chronic diseases is recognized as an important public health problem because non-adherence to medicines can result in increased healthcare costs and poor health outcomes (Lam et al., 2015). This study aimed to determine the prevalence of medication non-adherence and its association with QOL among patients with neurological disorders. The prevalence of non-adherence was highest in AD patients, followed by those with epilepsy, PD, and stroke.

In this study Sixty four (31.7%) patients came to fill their prescriptions on time but were found non-adherent according to MALMAS scale. Seventeen (10.1%) patients over reported their adherence on MALMAS and were found to be non-adherent according to MPR. To overcome this issue, we categorized adherence status using a combination of MPR and MALMAS. In most studies, adherence is measured using only objective or subjective assessment methods. Patients who are considered adherent according to an objective method may be considered non-adherent when evaluated using subjective factors such as forgetfulness, dose skipping and complex therapeutic regimens (Vermeire et al., 2001).

The overall non-adherence rate among patients with neurological disorders was high compared to rates reported in previous studies conducted in western countries (Farrukh et al., 2018, Cheiloudaki et al., 2019, Appalasamy et al., 2019, Smith et al., 2017, Borah et al., 2010). This could be due to the differences in adherence assessment methods, study design, study populations and sample sizes across studies. Another reason for poor adherence

Table 4
Patient characteristics, EQ-5D scores and VAS scores.

Item	VAS score			EQ-5D Index score		
	Mean (SD)	95% CI	p-value	Mean (SD)	CI 95%	p-value
Age groups						
< 60 years	76.43 (10.71)	6.99, 12.35	< 0.01*	0.78 (0.17)	0.05, 0.13	< 0.01*
≥ 60 years	66.75 (15.41)			0.69 (0.19)		
Gender						
Male	71.10 (15.06)	−5.43, 0.31	0.081*	0.71 (0.19)	0.69, 0.74	< 0.01*
Female	73.66 (11.73)			0.78 (0.17)		
Race						
Malay	73.10 (13.91)	71.02, 75.18	0.408†	0.77 (0.17)	0.75, 0.80	< 0.01†
Chinese	71.06 (14.94)	68.71, 73.41		0.72 (0.19)	0.69, 0.75	
Indian	72.23 (7.23)	69.85, 74.61		0.66 (0.17)	0.61, 0.72	
Marital Status						
Single	77.23, (10.54)	75.17, 79.29	0.01†	0.78 (0.19)	0.74, 0.81	0.047†
Married	69.91 (14.70)	68.05, 71.76		0.72 (0.18)	0.70, 0.74	
Divorced	73.18 (11.60)	68.03, 78.32		0.76 (0.18)	0.67, 0.84	
Diagnosis,						
Epilepsy	77.99 (8.26)	76.64, 79.34	< 0.01†	0.76 (0.18)	0.73, 0.79	0.69†
Stroke	70.18 (13.82)	67.96, 72.39		0.74 (0.18)	0.71, 0.77	
PD	62.24 (18.54)	57.36, 67.11		0.68 (0.21)	0.63, 0.74	
AD	73.07 (9.47)	67.35, 78.80		0.77 (0.18)	0.66, 0.88	
Co-morbidities,						
≤ 2	74.65 (12.66)	1.41, 2.55	< 0.01*	0.77 (0.18)	0.03, 0.11	< 0.01*
> 2	69.31 (14.60)			0.70 (0.18)	0.03, 0.11	
Polypharmacy						
≤ 4	72.29 (14.04)	−2.57, 3.48	0.766*	0.76 (0.18)	0.013,0.09	< 0.01*
> 4	71.83 (13.50)			0.70 (0.19)		

 * Independent t-test.
 † One-way ANOVA.

Table 5
Association of adherence status and EQ-5D domains.

Item		Non-Adherent	Adherent	P value
Mobility	No problem	124 (56.4)	96 (43.6)	0.286[a]
	Some Problem	93 (62.0)	57 (38.0)	
Self-care	No problem	123 (54.7)	102 (45.3)	0.053[a]
	Some Problem	94 (64.8)	51 (35.2)	
Usual Activity	No problem	91 (52.0)	84 (48.0)	0.014[a]
	Some Problem	126 (64.6)	69 (35.4)	
Pain	No problem	91 (54.8)	75 (45.2)	0.177[a]
	Some Problem	126 (61.8)	78 (38.2)	
Anxiety	No problem	70 (53.0)	62 (47.0)	0.102[a]
	Some Problem	147 (61.8)	91 (38.2)	

a = Chi-square test.

Table 6
Binary logistic regression on medication adherence.

Items	B	S.E.	Wald	df	p value	Exp(B)	CI
Marital Status,							
Divorced (R)	1.00	-	-	-	-	-	-
Single	−2.356	0.602	15.327	1	<0.05*	0.95	0.02, 0.30
Married	−1.854	0.577	10.332	1	<0.05*	0.157	0.05, 0.48
No of medicines	−0.114	0.62	3.41	1	0.06	0.89	0.79, 1.00
Usual Activities							
Some Problem	1.00	-	-	-	-	-	-
No Problem (R)	0.514	0.222	5.369	1	0.020*	1.671	1.08, 2.58
Selfcare							
Some Problem	1.00	-	-	-	-	-	-
No Problem (R)	0.123	0.282	0.191	1	0.662	1.131	0.65, 1.96

(R) = Reference, *Means the values are statistically significant at p < 0.05.

could be that people residing in developing countries have different cultural norms and may prefer traditional medicines over modern allopathic medicines (Farrukh et al., 2018).

Patients taking a large number of medications were found to be non-adherent. The number of medications may determine the complexity of treatment regimens. The complexity of medication regimens was associated with reduced treatment adherence (Ferrari et al., 2013, Ahmad et al., 2013a,b) Polypharmacy potentially contributes to patient forgetfulness in taking medicines and skipping doses, which leads to non-adherence. The overall QOL
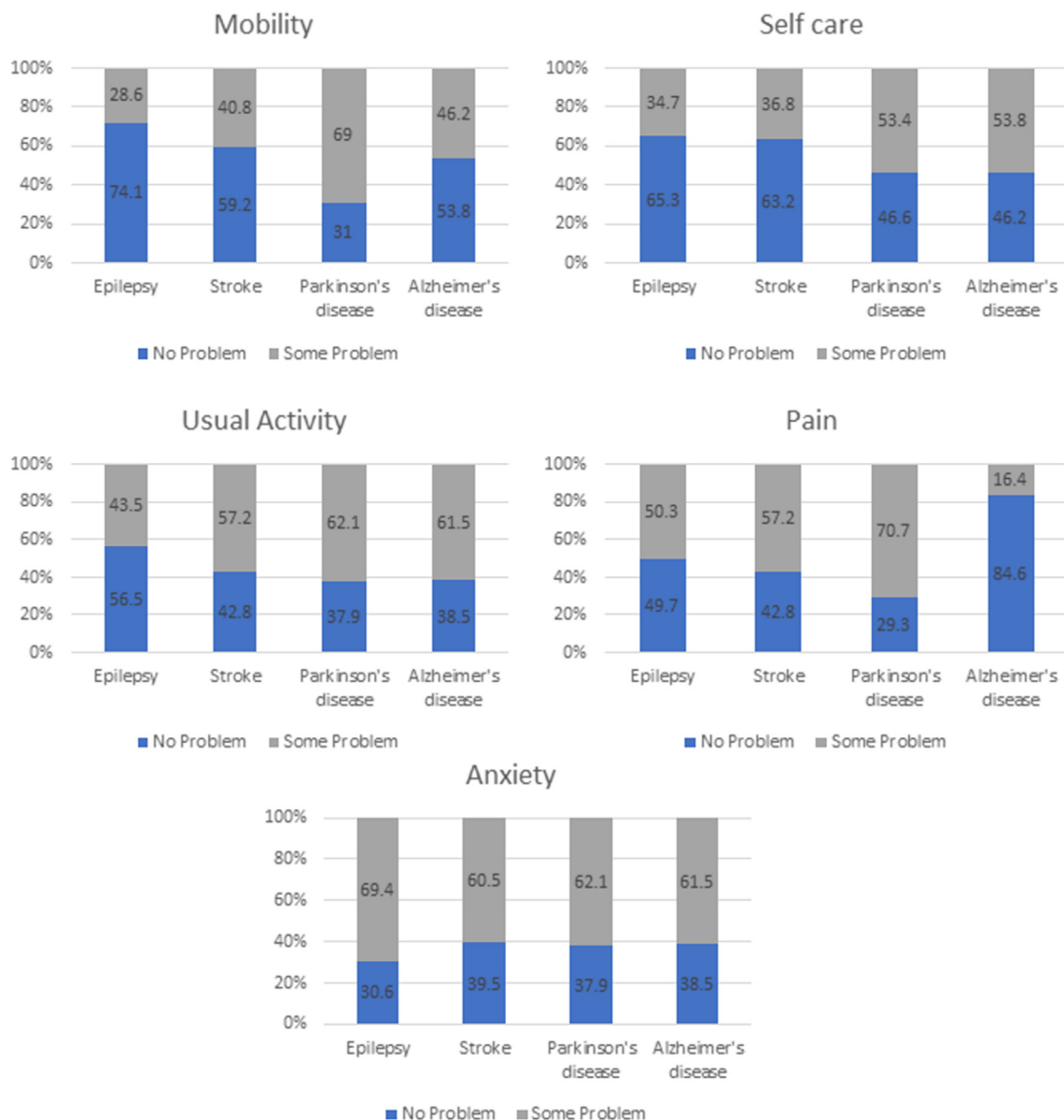
Fig. 2. EQ-5D domain responses among patients with neurological problems.

Table 7
Difference between the EQ-5D index/VAS score and the adherence status.

Item	Adherent Mean (SD)	Nonadherent Mean (SD)	p-value
EQ-5D Index	0.76 (0.19)	0.72 (0.18)	0.041[*]
VAS score	73.7 (14.2)	71.01 (13.4)	0.062[*]

[*] Independent *t*-test.

was better among adherent patients than among non-adherent patients. The mean QOL index scores between adherent and non-adherent patients were significantly different. Similar results were reported in a previous study conducted among patients with diabetes and epilepsy in which QOL and medication adherence were found to be interrelated. Patients who adhered to their treatment experienced an improvement in QOL and vice versa (Zioga et al., 2016, Ahmad et al., 2013a,b, Mubashra et al., 2018). This implies that good adherence to AEDs can provide good seizure control, resulting in an improved QOL.

There were some variations in QOL scores among the different types of neurological disorders. Anxiety was highly reported by patients with epilepsy. Patients experiencing seizures rated their anxiety levels higher than those without seizures (Simms et al., 2008). A common cause of anxiety in patients with epilepsy is the fear of experiencing seizures. A seizure can occur at any time and place without much warning is a major cause of anxiety for many patients. Some patients are also anxious about social rejection because of their disease (Epilepsy Foundation, 2019). Patients with PD reported higher problems in the four EQ-5D domains compared to those with other diseases. In this study, The prevalence of problems reported by patients with PD was similar to that reported in a previous survey conducted in China (Fan et al., 2018). In PD the most visible manifestations of the disease were motor symptoms, such as slowness and tremor. They can increase distress and social isolation. Besides, additional difficulties like wearing-off phenomena and morning akinesia may affect QOL (Stocchi et al., 2014).

5. Strengths

This study determined the prevalence of disease specific medication non-adherence and its association with QoL among neuromedical patients in Malaysia with multiethnic backround.

6. Limitations and future research

Although the current study has highlighted a number of significant findings, there are some limitations and our results should be interpreted with caution for several reasons. We did not record the type of medications that patients were taking and the clinical characteristics of diseases was not recorded so it could not be related to medication non-adherence. A substantial number of patients refused to take part in the survey or were excluded due to critical condition and not fit to be interviewed. Patients with AD were less that might have contributed to their high rate of non-adherence. It was single centered study with its own practices and education system for patients Further research is needed to generalise these results to different clinical settings and on a larger sample size.

7. Conclusion

Thus, to conclude, a high prevalence of medication non-adherence was found among patients with neurological disorders. The rate of non-adherence varied among different types of neurological disorders. The most common causes of non-adherence were forgetfulness, missing doses when away from home and difficulty taking medications. Patients who were non-adherent had low QoL scores. This comprehensive data may help to develop disease-specific interventions to enhance medication adherence.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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