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Correlation between adherence to antiepileptic drugs and quality of life in patients with epilepsy: A longitudinal study

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ABSTRACT

Objective: This study aimed to investigate whether the score of self-reported medication adherence using the Medication Adherence Report Scale (MARS-5) correlates with the serum level of antiepileptic medication, as well as whether the MARS-5 score can predict the quality of life (QoL) in patients with epilepsy.
Methods: A longitudinal study was carried out. The patients with epilepsy who were prescribed a minimum of one antiepileptic drug were recruited (n = 807). Each participant completed a background information sheet and the MARS-5 at baseline, followed by the Liverpool Seizure Severity Scale (LSSS) and Quality of Life in Epilepsy (QOLIE-31) questionnaire at 18-month follow-up. In addition, the serum level of antiepileptic medications was measured at the follow-up.
Results: The MARS-5 score was negatively associated with the LSSS score ($B = -0.089$, $SE = 0.009$, $p < 0.001$) and positively correlated with the serum level of antiepileptic medications ($B = 3.200$, $SE = 0.416$, $p < 0.001$), after adjusting for demographics and clinical characteristics. The serum level of antiepileptic drugs was significantly correlated with the overall QOLIE-31 score ($B = 3.118$, $SE = 1.417$, $p = 0.03$). The MARS-5 score was significantly correlated with the overall QOLIE-31 scores and all the scores in the subcategories. In addition, the MARS-5 score was in line with the correlation between the LSSS and QOLIE-31 scores ($Z = 4.20$, $p < 0.001$) and between serum antiepileptic medication levels and QOLIE-31 score ($Z = 3.98$, $p < 0.001$).
Conclusions: The MARS-5 score can predict the QoL in patients with epilepsy for up to 18 months. Therefore, healthcare providers may predict the QoL and drug adherence using the MARS-5 score, in order to design personalized interventions.

1. Introduction

Patients with epilepsy with poor seizure control often encounter various negative outcomes, including significant physical injuries, increased healthcare costs, decreased productivity, and even death [1,2]. It has been suggested that nearly one-fifth of people with epilepsy have attention-deficit hyperactivity disorder symptoms associated with increased psychosocial morbidity and lowered quality of life (QoL) [3]. Another study has reported that ~10% of the people with epilepsy may have neuropathic pain and nearly one-third may have depression [4]. Because of potentially fatal consequences and the high prevalence of epilepsy in developing countries, such as Iran (~5%) [5], healthcare providers should emphasize drug adherence among such patients. Importantly, it has been shown that nearly 60% of patients could achieve seizure control by adhering to prescribed antiepileptic drugs (AEDs) [6]. However, it has been reported that 30%–50% of patients with epilepsy were nonadherent with their AED treatment schedules [7–9]. Thus, nonadherence is a critical issue for patients with epilepsy [10].

Nonadherence highly correlates with the patients' QoL, an important outcome measure. Ettinger et al. [11] surveyed 1278 patients with epilepsy and found that 41% were nonadherent. Hovinga et al. [12] also found that the QoL was lower in those with poor AED adherence in the previous month compared with that in patients adhering to their AED. Similarly, a study by Martins et al. found a positive correlation between the level of medication adherence and QoL [13]. In addition, QoL is somewhat dependent on seizure control and seizure severity, as the level of QoL was found to be higher in patients who valued AEDs to control their seizures [14,15].

Abbreviations: AED, antiepileptic drug; CFI, comparative fit index; LSSS, Liverpool Seizure Severity Scale; MARS-5, Medication Adherence Report Scale; MEIA, microparticle enzyme immunoassay; QoL, quality of life; QOLIE-31, Quality of Life in Epilepsy; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; SEM, structural equation model; TLI, Tucker–Lewis index.

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However, the aforementioned studies on the correlation between AED adherence and QoL only employed a self-reporting method. Hence, the measurement of AED adherence may not be accurate because of potential and/or social desirability. Alternative objective measures are needed, such as AED serum level [16] and electronically recorded medication bottles [17]. Although these approaches are more accurate than the self-reporting method, the costs are much higher [2]. Therefore, there is the need for a reliable self-reporting instrument (e.g., the Medication Adherence Report Scale, MARS-5) which can provide relatively accurate information on AED adherence. Previous studies suggest that the MARS-5 failed to distinguish well-adherent and nonadherent patients with chronic obstructive pulmonary disease [18] and hypertension [19]. However, such poor efficacy may not occur in people with epilepsy because of different clinical characteristics. In addition, all the previous studies have adopted a cross-sectional study design with the correlation between self-reported adherence and actual blood AED level unknown. Therefore, in a cohort of patients with epilepsy, we used a longitudinal study to examine the relationship between self-reported MARS-5 score and the serum level of AED. False declaration on AED adherence may still exist because of the concerns of symptom control and resulting medical care [20], where a patient with severe seizures may falsely report they have good AED adherence.

Nevertheless, we hypothesized that the self-reported MARS-5 score can provide good indication of AED adherence in patients with epilepsy. Using an 18-month longitudinal follow-up design, this study aimed to investigate the following: (1) the correlation between MARS-5 score and serum AED level, (2) the correlation between AED adherence (both MARS-5 score and serum AED level) and the QoL, and (3) whether MARS-5 score can replace serum AED level to predict the QoL in patients with epilepsy.

2. Methods

This study was approved by the Medical Sciences Ethics Committee of Qazvin University (February 2014), and the data were collected between March 2014 and December 2015.

2.1. Participants

The participants were recruited by convenience sampling of patients with epilepsy who were referred to 6 neurology clinics in Iran (2 in Qazvin and 4 in Tehran). Inclusion criteria were the following: being diagnosed with epilepsy (according to the International League Against Epilepsy criteria, 1989), being prescribed a minimum of one AED, ≥18 years of age, understanding Persian language, and agreeing to sign the consent form. The patients were excluded if they could not live independently and relied on the carers for medications. Moreover, the patients with cognitive impairments (score < 23 in the mini-mental state examination), intellectual disabilities, uncontrolled psychosis, and substance abuse were excluded from this study.

2.2. Instruments

2.2.1. Background information sheet and medical records

Demographic data including age, gender, marital status, employment status, and monthly income (*good and above* > USD 2000; *fair* = USD 1000–2000; *poor* < USD 1000) were recorded in the background information sheet. The information on epilepsy classification and the course of disease was collected from patients' medical records.

2.2.2. Medication Adherence Report Scale (MARS-5)

The MARS-5 (Table 1), a self-reported five-item questionnaire, was completed by all participants at baseline. All five items in the MARS-5 were answered on a 5-point Likert scale (from *never* to *always*) with the overall score range between 5 and 25. A score ≥20 suggests a high adherence [19]. In addition, the internal consistency of the MARS-5 is acceptable ($\alpha = 0.78$), and its concurrent validity is supported [21].

Table 1
Descriptions of the MARS-5.

1.	I forgot to take my antiepileptic medicine.
2.	I altered the dose of my antiepileptic medicine.
3.	I stopped taking my antiepileptic medicine for a while.
4.	I decided to miss out a dose of my antiepileptic medicine.
5.	I took less antiepileptic medicines than prescribed.

MARS-5 = Medication Adherence Report Scale.

2.2.3. Liverpool Seizure Severity Scale (LSSS)

The LSSS, a 20-item questionnaire, was completed at 18-month follow-up. Each item was answered on a 4-point Likert scale, and a higher score represents more severe seizures. Both test–retest reliability ($r = 0.72$ to 0.96) and internal consistency ($\alpha = 0.62$ to 0.86) are acceptable. The known-group validity of the LSSS has also been supported by the significantly different LSSS scores between people with severe seizure symptoms and those with minor seizure symptoms [22]. The Persian version of the LSSS has been linguistically validated by us using a different cohort of patients with epilepsy. We have examined the internal consistency ($\alpha = 0.90$), test–retest reliability within two weeks (intraclass correlation coefficient = 0.96), criterion-related validity ($r = -0.43$ with QoL), and known-group validity. The known-group validity was examined using the LSSS score in three groups of participants with different seizure severities. The severity was classified using the number of seizures in the last 3 months as follows: mild (≤3 times), moderate (4–8 times), and severe (≥9 times). The LSSS scores were significantly different among the mild (19.62 ± 5.36), moderate (42.62 ± 20.01), and severe (73.19 ± 22.39) groups ($F = 8.21$, $p < 0.001$).

2.2.4. Quality of Life in Epilepsy (QOLIE-31)

The QOLIE-31, a 31-item questionnaire, was measured at 18-month follow-up. There are seven domains in the QOLIE-31: seizure concerns, cognitive function, energy/fatigue, emotional wellbeing, social function, medication efficacy, and overall QoL. The QOLIE-31 was developed based on several instruments and studies, including the RAND 36-item Health Survey 1.0, Medical Outcomes Study, and Epilepsy Surgery Inventory—55 [23]. The raw scores in all domains were converted into a 0–100 scale based on the developers' instructions, and a higher score represents better QoL [23]. The test–retest reliability ($r = 0.64$ to 0.89) and internal consistency ($\alpha = 0.77$ to 0.93) are all acceptable [23]. The QOLIE-31 was translated into Persian using a published protocol [24], with satisfactory test–retest reliability ($r = 0.68$) and internal consistency ($\alpha = 0.90$).

2.2.5. Serum AED measurement

Serum AED level was measured at 18-month follow-up using a microparticle enzyme immunoassay (Abbott Axsym®, Abbott Laboratories, Abbott Park, IL, USA). All blood samples were taken prior to the next routine dose of drug. The AEDs used have been reported in detail previously [25]. The results were reported in two groups based on the reference ranges: below the therapeutic range (i.e., nonadherent) and within and above the therapeutic range (i.e., adherent) [16].

2.3. Statistical analysis

All the demographic data were analyzed using descriptive analyses, including mean (SD) for continuous variables (e.g., age) and n (%) for categorical variables (e.g., gender). The correlation between the MARS-5 score and serum AED level was analyzed using biserial correlation where serum levels were categorized into two groups: equal to or above the therapeutic range and below therapeutic range. Additionally,