Self-reported adherence in patients with epilepsy who missed their medications and reasons for nonadherence in China

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Abstract
Objectives: The objectives of this study were: (1) to evaluate self-reported adherence in adult patients with epilepsy in China who had missed taking their antiepileptic drugs (AEDs) at least once and (2) to determine why patients were not adherent to their medication to employ interventions targeted at barriers to adherence.

Methods: A questionnaire was used to collect the patients’ demographic data, disease information, and reasons for why the patients did not take their AEDs. Adherence was also included as measured using a four-item Morisky questionnaire (Morisky-4 questionnaire).

Results: Of the 131 patients, 4.6%, 70.2%, and 25.2% showed high, medium, and low adherence, respectively. The reasons for nonadherence included forgetfulness (54.2%), being seizure-free for a period (48.9%), and fear of adverse drug effects (27.5%).

Conclusions: Medium adherence was the predominant nonadherence pattern, and forgetfulness, being seizure-free for a period, and fear of adverse effects were the primary reasons for nonadherence to AEDs. To overcome barriers to nonadherence, it is essential to use tools that are sensitive to reasons for nonadherence.

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1. Introduction

Epilepsy is one of the most common neurological disorders worldwide, and the majority of people with epilepsy who live in developed countries manage their condition with anti-seizure medication [1]. For those patients who are treated, antiepileptics drugs (AEDs) are the mainstay of treatment [2]; however, many patients are unsuccessful at treating epilepsy with AEDs. Poor adherence to prescribed medication is considered to be the main cause of unsuccessful drug treatment for epilepsy [3,4]. Adherence to AEDs in patients with epilepsy is low and generally ranges from 20% to 80% [4], with nonadherence ranging between 30% and 50% [5]. Antiepileptics drugs nonadherence has been associated with increased resource utilization and costs [6,7]. Thus, nonadherence to AEDs is a critical problem that should be taken seriously, particularly in developing countries such as China, where the number of patients with epilepsy was 9 million in 2007 [8]. In developing countries, few patients with epilepsy receive adequate medical treatment. An estimated 75% to 90% receive no treatment at all; thus, epilepsy treatment in developing countries remains far from satisfactory [4,9], and adherence is an important problem to be solved.

Several measurements and interventions have been developed to assess and improve adherence. Although adherence in chronic and acute diseases has been reported in many studies [4,7,10–14], little is known regarding the extent of nonadherence [15] and even less is known in the Chinese population. Information about why patients are not taking their prescribed medications is important in designing appropriate interventions. Patient self-reports can simply and effectively measure adherence [10]. Self-report is considered to be the most appropriate method to use to monitor adherence and can distinguish between intentional nonadherence and unintentional nonadherence, which exhibit different underlying causes and may thus require different interventions [16]. Distinguishing between intentional and unintentional nonadherence may help to understand nonadherence so that effective interventions may be developed [17].

Thus, it is important to assess the extent of nonadherence and its underlying causes. To achieve this goal and to provide additional information on adherence in the Chinese population, we surveyed adult patients with epilepsy in China who had missed taking their AEDs at least once to examine the extent and reasons for nonadherence using the four-item Morisky questionnaire (Morisky-4 questionnaire).
2. Methods

2.1. Participants

Patients were recruited from HuaShan Hospital of Fudan University in Shanghai, China. This study was approved by the Research Ethics Committee of HuaShan Hospital. To achieve our research goal, we selected patients who: (1) were diagnosed with epilepsy, (2) were older than 16 years of age, (3) took AEDs for more than 6 months, (4) had missed taking their AEDs at least once, (5) could complete the questionnaire by himself/herself or understand it after having it explained by others, and (6) visited the outpatient clinic at the Hospital of HuaShan.

The exclusion criteria included: (1) treatment with traditional Chinese medicine (TCM), (2) communication language barriers, and (3) cognitive impairment that caused difficulty in understanding or communicating with the investigators.

In this study, 134 adult patients with epilepsy were eligible on the basis of these criteria, with 3 patients refusing to answer the questionnaire. Thus, a total of 131 questionnaires were obtained.

2.2. Questionnaire

Information was collected using the questionnaire, including the patients’ demographic data, disease characteristics, self-reported adherence, and reasons for why the patients had missed taking their AEDs.

Multiple reasons for nonadherence in the questionnaire included: forgetfulness, fear of adverse drug effects, being seizure-free for a period, discomfort after taking the AEDs, belief that the AEDs were ineffective, belief that it’s unnecessary to take AEDs, no access to refill medications at nearby hospitals, used-up AEDs, and “others.” The term “used-up AEDs” meant that the patients had run out of their AEDs and did not refill their medication despite being able to do so.

2.3. Self-reported adherence

Self-reported adherence was measured by the Morisky-4 questionnaire, which was developed by Donald E. Morisky et al. in 1986. It is the most widely used multi-item questionnaire to measure self-reported adherence. The questionnaire’s validity has been previously demonstrated [18,19], and the questionnaire correlates well with the clinical outcomes in various chronically ill populations [15]. All of the items were translated into Chinese and were answered by a “yes” or a “no” response for each item as in the original scale. A lack of a “yes” response represented high adherence, 1–2 “yes” responses represented medium adherence, and 3–4 “yes” responses represented low adherence.

2.4. Statistical analyses

All of the data were analyzed using the IBM SPSS Statistics 19 software program. Descriptive analyses and graphs were used to describe the demographic data, disease characteristics, self-reported adherence, and nonadherence reasons of the patients.

Chi-square tests (p<0.05) were used to assess the differences between categories of gender, age, education, working status, type of seizure, and frequency of seizure.

3. Results

The demographic and disease characteristics of the 131 subjects (age 16–77 years) are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72 (55.0%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>31.2 (12.6)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>14 (10.7%)</td>
</tr>
<tr>
<td>Junior school</td>
<td>43 (32.8%)</td>
</tr>
<tr>
<td>High school</td>
<td>42 (32.1%)</td>
</tr>
<tr>
<td>Graduate</td>
<td>22 (24.5%)</td>
</tr>
<tr>
<td>Working status</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>23 (17.6%)</td>
</tr>
<tr>
<td>Full-time employed</td>
<td>57 (43.5%)</td>
</tr>
<tr>
<td>Part-time employed</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>41 (31.3%)</td>
</tr>
<tr>
<td>Retired</td>
<td>6 (4.6%)</td>
</tr>
<tr>
<td>Housewife</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Type of seizure</td>
<td></td>
</tr>
<tr>
<td>Partial seizures</td>
<td>82 (62.6%)</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>49 (37.4%)</td>
</tr>
<tr>
<td>Frequency of seizures</td>
<td></td>
</tr>
<tr>
<td>Yearly</td>
<td>73 (55.7%)</td>
</tr>
<tr>
<td>Monthly</td>
<td>41 (31.3%)</td>
</tr>
<tr>
<td>Weekly</td>
<td>17 (13.0%)</td>
</tr>
</tbody>
</table>

3.1. Patients’ self-reported adherence

Adherence, as measured by the Morisky-4 questionnaire, was classified into high, medium, or low levels. Of the 131 nonadherent patients with epilepsy, there were 6 patients with high (4.6%), 92 patients with medium (70.2%), and 33 patients with low (25.2%) adherence. The number and rate of “yes” responses to each item were the following: “Do you ever forget to take your medicine?”, 98 (39.7%) patients; “Are you careless at times about taking your medicine?”, 34 (13.8%) patients; “When you feel better do you sometimes stop taking your medicine?”, 75 (30.4%) patients; and “Sometimes if you feel worse when you take the medicine, do you stop taking it?”, 40 (16.2%) patients.

Because there were more than 2 groups in each category, several of the groups had been combined. The “high” adherence group was combined with the “medium” adherence group because it was lower than 5 after being divided into several categories. Importantly, the “high” adherence group was not truly high because some of the patients had missed their medications due to the AEDs being “used up.” There were no differences found between all of the categories. Further details are shown in Table 2.

3.2. Reasons for nonadherence

When the patients were asked why they had missed their AEDs, the primary reason reported in the questionnaire was forgetfulness (54.2%) followed by being seizure-free for a period (48.9%) and fear of adverse drug effects (27.5%). The responses for all of the reasons collected in the study are presented in Fig. 1.

Because the additional reasons for nonadherence reported by the patients were different from each other, it was difficult to classify the reasons into separated categories. In addition, some reasons that had been reported by a few patients could not be classified into a category. Thus, these reasons were combined into the category of “others.” The reasons for nonadherence that were reported by the patients for the category “others” (30, 22.9%) included: the use of several new antiepileptic drugs was too expensive (4, 13.3%); stress over the effects of the antiepileptic drugs on marriage or fertility (4, 13.3%); unawareness of taking the medications (3, 10.0%); misunderstandings about the disease (3, 10.0%), such as the needlessness of taking antiepileptic drugs after an operation and the idea that the patient had believed that they were cured; the patient would commonly
decrease or increase the dose when the patient did not feel good (2, 6.7%); the patient wanted to change the drug regimen (2, 6.7%); no medications were prescribed (1, 3.3%); laziness to refill their medications (1, 3.3%); and other reasons which were difficult to classify and describe (10, 33.3%).

4. Discussion

4.1. Adherence in patients with epilepsy and the Morisky-4 questionnaire

Medication nonadherence among patients with chronic conditions is a significant barrier to achieving therapeutic outcomes [20]. Nonadherence affects 30% to 50% of patients with epilepsy [5,21]. Compared with adherent periods, nonadherence to AEDs was associated with a 50% higher incidence of emergency department visits, an 86% higher incidence of hospitalizations, and a threefold increase in mortality risk [22]. In adults, AEDs nonadherence was associated with increased inpatient and emergency room costs of $1799 and $260, respectively, per patient per year [6].

The self-reported measure is the most common measurement of medication adherence [23]. It is easy to use, noninvasive, relatively quick [24], inexpensive, and adaptable to a target population [1]. There are many self-reported measures developed to measure adherence, such as the Morisky-4 questionnaire [18], the Self-Reported Medication-Taking Scale [25], the Medication Adherence Rating Scale [26], and others [27–30]. The most widely used multi-item measure is the Morisky-4 questionnaire, which inquires into whether patients miss doses due to forgetfulness, carelessness, feeling better, or feeling worse [31]. Since its introduction, the Morisky-4 questionnaire has been validated and used in many studies [11,12,32]. Its validity has been demonstrated on the basis of its relationship with the clinical outcomes in various chronically ill populations [15] and was renewed in 2008 [33].

An indirect measurement is often desirable because it can provide information on why the patient is not taking his/her medications, and the self-report is able to distinguish between intentional and unintentional nonadherence [16], which is an additional reason for the selection of the Morisky-4 questionnaire as a measurement to assess adherence and to determine the underlying reasons for nonadherence.

In China, the validity and reliability of the Morisky-4 questionnaire were confirmed by WeiHua Xu et al. [34] and Kun Li et al. [35] in patients with hypertension and was tested in 200 Chinese immigrants in America [19]. Because it is a widely used scale, the Morisky-4 questionnaire has been applied in many previous studies [36–38], and it has also been used on patients with epilepsy [39]. It means that, though China has a different health care system and cultural perspective on medications, the Morisky-4 questionnaire was applicable, acceptable, and has a good reliability in China.

4.2. Self-reported adherence of nonadherent patients with epilepsy in China

There have only been a few studies that provide clinically relevant findings concerning nonadherent patients with epilepsy and even fewer studies in Chinese patients. To the best of our knowledge, our study is the first to examine nonadherent patients with epilepsy in...
China. The self-reported adherence detected by the Morisky-4 questionnaire was 4.6%, 70.2%, and 25.2% for high, medium, and low adherence, respectively. This indicates that the most prevalent extent of adherence in adult patients with epilepsy who missed taking their AEDs was medium adherence, which was similar to the results reported by Robin Mathews [13] where medium and low adherence was 21% and 4%, respectively. The number of patients with low adherence was lower than the number of patients with medium adherence. Thus, the adherence of nonadherent patients with epilepsy in China was not very poor. However, due to the limited reasons listed on the Morisky-4 questionnaire, the adherence of patients who missed their medications because of “used-up AEDs” in our study was identified as high. In fact, these patients were nonadherent, and thus, they were categorized as patients with high adherence as measured by the Morisky-4 questionnaire, which did not indicate that the patients perfectly adhered to their drug regime. Most of the patients had 1 to 3 forms of nonadherent behavior. The most common form of nonadherence was “forgetfulness,” which was followed by “stopped taking AEDs when they felt better,” and “stopped taking AEDs when they felt worse.”

The lack of significant differences between all of the adherence categories indicated that regardless of age or seizure type or whether the patients were employed, were seizure-free, or had a high educational background, the extent of the nonadherence was the same. This may be due to the gaps in medical information between medical science and non-medical science. It may be potentially helpful to identify the reasons for and the underlying barriers to nonadherence in individual patients.

4.3. Reasons for nonadherence in patients with epilepsy in China

Forgetfulness and adverse effects have been reported in many surveys as the main reasons for nonadherence and are significantly associated with nonadherence [14,20,40]. As shown in Fig. 1, “forgetfulness” was the first major reason for nonadherence in patients with epilepsy in China, which was reported by over half of the patients.

In contrast to other findings, “being seizure-free for a period” was a unique reason for nonadherence in patients with epilepsy. We also found that patients became nonadherent because of “discomfort after taking the AEDs” (15.3%), the “belief that the AEDs were ineffective” (15.3%), and the “belief that it was unnecessary to take the AEDs” (9.2%). This indicated that the patients who did not understand their medications potentially became nonadherent.

Due to differences in economic and medical practices between Chinese provinces and cities, it was not surprising that in some areas, the patients could not refill some types of AEDs after their physicians had prescribed these medications. Difficulties in medication access were reported as a reason for nonadherence in a few studies [40]. This included difficulty in paying for medications and the inability to obtain transportation to medical appointments. However, this may be a unique problem associated with the Chinese health care system in our study. We observed that 6.1% and 5.3% of patients stopped or reduced taking their AEDs, respectively, due to “no access to refill medications at nearby hospitals” or having “used-up AEDs,” respectively. We believe that, for those patients who cannot refill their prescriptions at nearby hospitals, the government should take its responsibility to ensure appropriate access to refill medications for patients, such as building a community pharmacy in every city where all of the medications can be refilled.

4.4. Intentional and unintentional nonadherence

Nonadherence to medication may be divided into intentional and unintentional nonadherence. Unintentional nonadherence is defined as being careless or forgetful. Unintentional interruptions may be categorized as unintentional nonadherence, such as the inability to access medications, an interruption in routine, or a lack of reminders that caused the patients to miss their medications. Intentional nonadherence was dependent on the patient’s intentional decision to miss or alter the drug doses to suit his/her needs [41,42].

In this study, “forgetfulness” and “no access to refill medications at nearby hospitals” were considered reasons for unintentional nonadherence. The other reasons for nonadherence were intentional. The major features that differentiated intentional domains from unintentional domains were associated with the individual’s cognitive and noncognitive processes in relation to taking their medications [42]. This included the difference between “used-up AEDs” and “no access to refill medications at nearby hospitals” where the difference was not whether the patient could refill his/her prescription, but whether refilling his/her prescription was dependent on his/her knowledge and attitude about the AEDs.

Many studies have confirmed poor adherence, with the respondents self-reporting having missed 30% or more of their medication within the past week or past month [40]. However, we believe that with the exception of a number of medications omitted by the patients, another determinant of adherence was whether the patients were intentionally nonadherent because only patients who took all of their medications at the right time with the right dosage were defined as perfectly adherent. Patients who unintentionally missed as little as 20% of their medication may be adherent; however, those patients who intentionally missed 1 pill were nonadherent because patients who intentionally missed one dosage may miss another in the future.

4.5. Limitations of the study

There are several limitations that exist in this study. First, self-reported measures pose a disadvantage; there may be over-reported adherence because of the patients’ misperceptions or the tendency to provide socially desirable responses [1]. Another limitation is the use of the Morisky-4 questionnaire, which specifies reasons for nonadherence [15]; some patients may have missed their medications because the medications were used up; however, high adherence was still estimated in our study.

Second, there may have been a bias in participant selection. All of the participants were screened by Dr. Zhu. The patients were recruited only if they had missed taking their medication at least once according to the chief complaints or after being asked whether they had missed their medication. Thus, this selection relies on the ability of the physician to recognize nonadherence, which may be poor [10] and unreliable [43]. Thus, it is necessary to use screening instruments that are sensitive in detecting nonadherence. In addition, the patients who admitted to nonadherence may be different from the nonadherent patients who deny their nonadherence.

Third, as there are no other reliable measures and databases available in China, such as a uniform administration of patient medical information, refill recordings, and electronic monitoring devices, we lack reliable measurements that are required to accurately assess adherence in real life.

Finally, traditional Chinese medicine (TCM) is a traditional and unique issue in China, which may potentially affect adherence in patients with epilepsy. Due to some limitations, TCM was not involved, which was a loss to this study. The reasons for not involving TCM included: the discontinued recommendation of TCM by Chinese experts [44]; TCM was a treatment used by some small populations of traditional Chinese physicians; at the Hospital of HuShan, the patients were treated with chemical medicines — AEDs; and the next plan of this study was to perform targeted interventions as a pharmacist, and as it was impossible to track adherence to TCM, we focused only on patients who took AEDs as their doctors had prescribed.
5. Conclusions

Taken together, our investigation revealed four main key points. First, regardless of the reasons for nonadherence, medium adherence was the major nonadherence pattern observed in adult patients with epilepsy who missed taking their AEDs at least once. Second, “forgetfulness,” “being seizure-free for a period,” and “fear of adverse effects” were the primary reasons for AED nonadherence. Third, interventions such as providing education for patients who are nonadherent because of a lack of understanding of their drug regime and increased access to refill medication to improve adherence should be implemented in China. Finally, enhanced accuracy and easy-to-administer measurements of adherence should be developed. Moreover, the Morisky-4 questionnaire may be used as a routine tool in a chronic disease setting to screen for nonadherent patients so that appropriate interventions may be individually administered to help patients overcome targeted barriers to adherence. To provide information on the target interventions, further studies identifying behaviors and factors associated with nonadherence, particularly in TCM in Chinese populations, are needed.

Our study revealed that the natural behaviors of nonadherence in patients with epilepsy in China were not serious and that the patients were nonadherent because of unintentional rather than intentional reasons. Thus, to identify targeted interventions, the use of the Morisky-4 questionnaire as a screening tool to identify nonadherence and its underlying reasons may be used.

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References