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ORIGINAL ARTICLE

Drug adherence of patients with epilepsy in Iran: the effects of the international economic sanctions

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Abstract Drug adherence of patients with epilepsy was investigated to determine the reasons behind poor adherence. In this retrospective chart review study, all patients with a clinical diagnosis of epilepsy were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences. We routinely asked about the patient's drug adherence and reasons behind poor drug adherence in every office visit. We defined drug adherence adequate if the patient reported less than or equal to one missed dose per month. Patients' drug adherences were investigated during two time periods: March 2010–2011 (before intensification of the international economic sanctions against Iran), and September 2012–2013 (during intensified international economic sanctions). One hundred and ninety-nine patients were studied. Drug adherence was satisfactory in 139 patients (69.8 %) during the first time period. Drug adherence was satisfactory in 146 patients (73.4 %) during the second time period. The most common reasons for poor drug adherence was carelessness, followed by cost and lack of drug availability (1.5 % in the first time period and 4 % in the second time period; $P = 0.07$). About one-third of patients with epilepsy had poor drug adherence. To overcome the problem, it is important to find the reasons behind poor drug adherence in each patient and try to overcome the cause. Purely from a clinical and patient care perspective, it seems necessary that politicians should facilitate decisions that make the health and well-being of ordinary people more affordable and without hardship.

Keywords Drug adherence · Epilepsy · Cost · Economic sanctions

Introduction

Drug adherence is the extent to which a person's behavior coincides with medical or health advice and recommendations [1]. This adherence then depends on the specific clinical situation, the nature of the illness and the treatment program, to name a few. The reasons for poor drug adherence may include discomfort or adverse effects resulting from treatment, patient's state of health, cost of treatment or therapy, maladaptive coping styles and other factors or situations that might affects a person's behavior with regards to the medical advice [1–3].

Epilepsy is a common chronic neurological disorder. The mainstay of treatment in patients with epilepsy is antiepileptic drug (AED) therapy [4]. Many patients with epilepsy often show good adherence with their medication because a neglect of medical treatment may cause epileptic seizures. However, a significant proportion of people with epilepsy may show poor drug adherence for a variety of reasons [2, 3], despite potentially grave consequences. Non-adherence is a frequent precipitator of status

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epilepticus in patients with epilepsy. This is one good reason for the significance of measuring drug adherence in patients with epilepsy [5]. Besides, poor drug adherence is a possible cause for pseudointractability in patients with uncontrolled seizures [4].

In the current study, drug adherence of patients with epilepsy was investigated over a long period of time to determine the reasons behind poor drug adherence. We tried to specifically analyze the effects of the international economic sanctions on drug adherence of patients with epilepsy in Iran. These sanctions caused significant socio-economic hardship for the general population of the Iranian people. This is the first study to investigate the consequences of the economic sanctions imposed on a country due to political reasons on health and well-being of the ordinary people.

Materials and methods

In this longitudinal retrospective chart review study, all patients with a clinical diagnosis of epilepsy were recruited; these patients referred to the outpatient epilepsy clinic at Shiraz University of Medical Sciences for the management of their epilepsy. This is the only epilepsy clinic in South Iran, which was established in 2008. Patients are being referred to this clinic from all over the country. The diagnosis of epilepsy was made exclusively by the only epileptologist working at this institution (the first author); it was based on clinical grounds and electroencephalographic (EEG) findings. All patients were under the care of the epileptologist at our institution for at least four-and-a-half years. We excluded those who did not have enough follow-up visits (i.e., at least two office visits per year during the study period); all patients from period one were followed up in period two of the study. There was no age limit to enter the study. This was a retrospective chart review study and no written consent was needed. However, the patients routinely consent orally at the first visit that their information will be used anonymously in the future studies, like this one, at our clinic; if they do not agree, their charts will not be used in studies.

I (the first author) routinely ask about the patient's drug adherence in every office visit; "how many doses of your antiepileptic drug have you missed during past month?" I personally ask the patients or their care-givers (in case of children and mentally ill patients); this is a self-reported outcome. I also ask an open question about reasons behind poor drug adherence if the patient admits that he/she had missed any doses. We arbitrarily defined drug adherence as adequate if the patient reported less than or equal to one missed dose per month, and poor if there was more than one missed doses per month. Age, gender, age at seizure onset, epilepsy risk factors, drug regimen, and seizure control [i.e., history of any seizures (type and frequency) since their last visit; a self-reported outcome] of all patients were registered routinely. Patients' drug adherences were investigated during two time periods: March 2010–2011 which was before intensification of the international economic sanctions against Iran, and September 2012–2013 which coincides with the intensified suffocating international economic sanctions. Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. Statistical analyses were performed using Chi square, Fisher's Exact and Mann–Whitney U tests to determine potentially significant differences, and a P value less than 0.05 was considered significant. This study was conducted with the approval by Shiraz University of Medical Sciences Institutional Review Board.

Results

One hundred and ninety-nine patients (101 women and 98 men) were studied. Age of patients at referral was 19 ± 11 years (minimum = birth day and maximum = 47 years) and age at seizure onset was 10 ± 8.7 years (minimum = birth day and maximum = 45 years). Eighty-nine patients (44.7 %) were taking one AED and the rest (110 patients, 55.3 %) were taking two or more drugs during the first time period. Drug adherence was satisfactory in 139 patients (69.8 %) during the first time period (March 2010–2011). Drug regimen (monotherapy vs. polytherapy) did not have a significant relationship with drug adherence ($P = 0.2$). Ninety-seven patients (48.7 %) were taking one AED and the rest (102 patients, 51.2 %) were taking two or more drugs during the second time period. Drug adherence was satisfactory in 146 patients (73.4 %) during the second time period (September 2012–2013). Drug regimen (monotherapy vs. polytherapy) did not have a significant relationship with drug adherence ($P = 0.4$). The difference between the number of patients receiving monotherapy with an AED between the first time period (89 patients) and the second time period (97 patients) was not significant ($P = 0.4$). The difference between the number of patients who had good drug adherence between the first time period (139 patients) and the second time period (146 patients) was not significant ($P = 0.4$). The difference between the number of patients who were seizure free between the first time period (106 patients) and the second time period (111 patients) was not significant ($P = 0.6$). The reasons for poor drug adherence of patients are shown in Table 1.

In the second phase of the study, we compared the patients with good drug adherence (146 patients, 73.4 %)

Table 1 Reasons for poor drug adherence in patients with epilepsy

Reason for poor adherence	Time period		*P* value
	March 2010–2011	September 2012–2013	
Carelessness/forgetfulness	35 (17.6 %)	38 (19.1 %)	0.1
Price/not being available in the market	3 (1.5 %)	8 (4 %)	0.07
Adverse effects	4 (2 %)	2 (1 %)	0.6
Other reasons	14 (7 %)	4 (2 %)	0.02
Missing data	4 (2 %)	1 (0.5 %)	–

Table 2 Comparison of patients with epilepsy and good drug adherence with those who had poor adherence

Clinical variable	Patients with good adherence ($N = 146$)	Patients with poor adherence ($N = 53$)	*P* value
Age (mean ± standard deviation)	18.2 ± 10.6	21.1 ± 11.7	0.1
Age at seizure onset (mean ± standard deviation)	9.7 ± 8.7	10.8 ± 8.6	0.4
Sex ratio (female/male)	74/72	27/26	0.9
Neurocognitive development (normal/abnormal)	104/41	41/11	0.3
Family history of epilepsy	47 (32.1 %)	16 (30.1 %)	0.8
Drug regimen (monotherapy/polytherapy)	69/77	28/25	0.4
Poor previous drug adherence (March 2010–2011)	36 (24.6 %)	23 (43.3 %)	***0.02***
Seizure free state	91 (62.3 %)	20 (37.7 %)	***0.002***
Medical comorbidity	24 (16.4 %)	10 (18.9 %)	0.6

Significant *P* values are in bold and italic

with those who had poor drug adherence (53 patients, 26.6 %) in the time period September 2012–2013. This comparison is presented in Table 2.

Discussion

Daily antiepileptic drug (AED) medication is the mainstay of epilepsy treatment. Since epilepsy is a common chronic neurological disorder, there are significant consequences (e.g., status epilepticus, sudden unexpected death in epilepsy, etc.) for any systematic treatment failure [5]. If one accepts the premise that AEDs are effective, then the daily medication regimen is critical and nonadherence to this strategy may have consequences [5, 6]. In the current study, we observed that about one-third of patients with epilepsy had poor drug adherence. In previous studies with variable methodologies it has been reported that 21–50 % of patients with epilepsy had poor adherence to their drug regimen [6, 7]. Therefore, nonadherence is a significant challenge for the treating physicians and also for patients with epilepsy and their care-givers. Poor drug adherence may increase the risk of uncontrolled seizures (pseudointractability) or even status epilepticus [4, 5]. In this regard, the implementation of strategies to promote AED adherence could be helpful [3, 8]. One important strategy is to find the reasons behind poor drug adherence in each patient and try to overcome the cause. In other words, to overcome the barriers to nonadherence, it is necessary to use individualized tools that are sensitive to reasons for nonadherence. In this study, we observed that the most common reason for poor drug adherence was carelessness or forgetfulness and this did not change with the passage of time. In a study from China, similar results were observed [9]. Patient education, particularly by providing patients with written information increases their medication knowledge and probably enhances their drug adherence [10]. The treating physician has a significant role in patient education, but there are many opportunities for pharmacists as well. The role of pharmacists extends beyond dispensing medications. The pharmacists have a significant role in educating patients about the disease and therapy and encouraging good drug adherence [11].

Other important reasons for poor drug adherence in our study were high drug price and lack of drug availability in the market place. These factors could reflect the hardship caused by the international economic sanctions imposed on the Iranian people. There was an increase in the number of patients who reported poor drug adherence for these reasons (i.e., high drug price and lack of drug availability), directly associated with the increase in the intensity of the international economic sanctions against Iran. This increase was not statistically significant, but it showed a trend ($P = 0.07$). Besides, the observed increase in poor

drug adherence could have been worse if some of the antiepileptic drugs were not subsidized by the Iranian government. Compared to the first time period, the price of some antiepileptic drugs (e.g., levetiracetam) increased up to 300 % in the second time period and after intensifications of the international economic sanctions against Iran. Besides, some other antiepileptic drugs were not available (e.g., zonisamide and nitrazepam) or difficult to be accessed (e.g., vigabatrin and oxcarbazepine) in the second time period. In one study from Canada [12], cost-related nonadherence was reported by 9.6 % of people who had received a prescription in the past year. The authors found that people in poor health (odds ratio [OR] 2.64, 95 % CI 1.77–3.94), those with lower income (OR 3.29, 95 % CI 2.03–5.33) and those without drug insurance (OR 4.52, 95 % CI 3.29–6.20) were more likely to report cost-related nonadherence [12]. Predicted rates of cost-related nonadherence ranged from 3.6 % among people with insurance and high household incomes to 35.6 % among people with no insurance and low household incomes [12]. In our study, 4 % of the patients reported cost-related nonadherence, which is less than the Canadian study (i.e., 9.6 %). However, this does not mean that the economic situation is better in Iran. Some drugs (e.g., phenytoin, carbamazepine, lamotrigine, and valproate) are subsidized and available at low cost in Iran. Therefore, even during the first time period we had the inclination to prescribe these subsidized drugs, at least as our first choices. We prescribed other antiepileptic drugs, such as levetiracetam, vigabatrin, or nitrazepam, in a minority of patients and under special circumstances (e.g., vigabatrin for infantile spasms associated with tuberous sclerosis and levetiracetam for juvenile myoclonic epilepsy unresponsive to lamotrigine in a young girl). These factors (i.e., cost, availability and accessibility of drugs) are often influenced by the governments' policies and the political situation of the countries. Purely from a clinical and patient care perspective, it seems necessary that politicians should facilitate decisions that make the health and well-being of ordinary people more affordable and without hardship.

In our study, poor drug adherence among patients with epilepsy did not have a significant association with age, gender, neurocognitive development, family history of epilepsy, complexity of the drug regimen, and existence of other medical comorbidities. In contrast, seizure-free state was significantly more frequent among those with good adherence compared to that in patients with poor adherence. This finding does not necessarily establish a cause and effect relationship. It is probable that patients with good drug adherence remain seizure free because they take their medication or alternatively, those who are not seizure free do not take their drugs because they have lost their faith in their routine therapy. In addition, these findings are not consistent among different studies. In a previous study, adherence was positively and significantly correlated with age and duration of illness, while no significant difference in adherence was found between patients with well-controlled and those with poorly controlled seizures [13]. Factors affecting drug adherence in patients with epilepsy should be further explored in future studies.

Study limitations

1. We assessed drug adherence in a qualitative manner by self-reporting, that is prone to bias (e.g., recall bias, under-reporting, etc.).
2. We did not use confirmatory measures (e.g., drug serum levels) to assess the drug adherence.
3. The study setting was a referral university clinic and the patients may not represent the whole population of patients with epilepsy. However, this was the only epilepsy clinic in South Iran.
4. Although we included all patients of the clinic, whether a sample of 199 patients is adequate to detect a difference between the two periods cannot be confirmed without a sample size calculation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was conducted with the approval by Shiraz University of Medical Sciences Institutional Review Board.

Informed consent This was a retrospective chart review study and no written consent was needed. However, the patients routinely consent orally at the first visit that their information will be used anonymously in the future studies, like this one, at our clinic; if they do not agree, their charts will not be used in studies.

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