



## Research paper

## Measurement and associative factors of adherence to epilepsy drug treatment among the elderly population in Tehran (Iran)



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## ABSTRACT

**Purpose:** The objective of this survey was to measure adherence and to identify correlation and prediction factors related to noncompliance among the elderly in Tehran, Iran.

**Methods:** A population-based survey was carried out among the elderly ( $\geq 60$  years of age) by using Tehran Epilepsy registry. All subjects were contacted by telephone and invited for face-to-face consultation. Questionnaires used were the following: Medication Adherence Rating Scale (MARS); Medical Prescription Knowledge (MPK); Abbreviated Mental Test (AMT). Along with customary descriptive statistics, a simple chi-square test (or Fischer exact test if value of cells was  $\leq 5$ ) was used for correlating; Cramer's V was used for strength of association, and prediction was by logistic regression. **Results:** Out of 104 subjects' approached, 23 subjects (median age 62.0, 95% CI 61.0–64.7, range 60–71; 73.9% males; 78.3% married and having a living partner; 54.5% epilepsy as supernatural; 21.7% with comorbid condition) participated. Most did not have a recent epilepsy onset ( $n = 20$ , 86.8%), or had active epilepsy ( $n = 22$ , 95.7%), convulsive seizures ( $n = 21$ , 91.3%), with no ( $n = 13$ , 56.5%) to low seizure number, and polytherapy ( $n = 12$ , 52.2%). Median MARS score was 8.0 (95% CI 6.0–8.0, range 3–10). Nonadherence was **correlated** to comorbidity ( $p = 0.003$ ) and widowhood or divorcehood ( $p = 0.04$ ) and **predicted** by the same factors. Treatment side effects altered behavior ( $p = 0.03$ ), and unsteadiness ( $p = 0.01$ ) was also associated with nonadherence. MPK was positive for all participants. Median AMT score was 9.0 (95% CI 9.0–10.0, range 6–10).

**Conclusion:** Elderly patients had a high treatment adherence and, as logically expected, were associated with comorbid state, divorce-widowhood, and drug-related behavioral side effects particularly behavioral and unsteadiness.

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## 1. Introduction

Epilepsy is a major neurological disorder with varying significance, opportunities, and challenges across different regions and countries.<sup>1,2</sup> Besides treatment coverage issues,<sup>2</sup> adherence to anti-seizure<sup>3</sup> medication treatment is a major issue of importance

among those with epilepsy, particularly among the elderly.<sup>4</sup> This ability and/or willingness to remain treatment compliant may not be always due to practical factors such as cost, distance, etc.,<sup>2,5–7</sup> but can also be culture-driven<sup>8</sup>; hence, it is a topic that merits assessment across different cultural set-ups.

There are a number of countries across geographical regions that continue to remain scientifically silent, less participatory, and internationally less vocal on epilepsy, be it in Asia,<sup>1</sup> Middle East, and North Africa (MENA)<sup>9</sup> or in Central America (currently unpublished, D Bhalla 2016). Among these, MENA also uniquely

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stands apart in its culture, religious and dietary aspects, etc. This is the region where elders are *by default* highly regarded and owe a special authoritative position in their family and communities. They are rarely preferred to be displaced to old age homes or other long-term care institutions.<sup>10,11</sup> In our example, MENA country i.e. Iran, similar cultural scenarios are noted where society is family-oriented and providing care to the elderly is considered a 'duty'.<sup>11</sup> Despite international anxieties,<sup>12</sup> Iran is an economically and culturally rich country and has a number of outstanding health and population-related aspects, be it near complete literacy of the population or liberal provision of 90.0% medical cost reimbursement to the country's population, among others. The population of Iran is predominantly young while the elderly constitute only about 5.0% of the population, which is growing<sup>13</sup> but not as dramatic or *sensationally* as often reported in the dementia literature (currently unpublished, D Bhalla 2016). Thus, with these different visions in mind, we conducted a population-based survey among the elderly ( $\geq 60$  years) epilepsy population of Tehran in order to measure treatment adherence and identify possible correlated and predictive factors related to nonadherence.

## 2. Methods

### 2.1. Source

In order to obtain participants, we relied on the population-based Tehran epilepsy registry (TER). This TER has now been established (current unpublished, D Bhalla 2016) to have more than 4800 epilepsy subjects of all ages, genders, and epilepsy types. The work to make this TER electronic in nature is also ongoing and so is the work to improve questionnaires for data collection. The registration for a patient with epilepsy (any age, epilepsy type) in this database is voluntary although encouraged through a number of public awareness and patient education campaigns (current unpublished, D Bhalla 2016).

### 2.2. Recruitment

From this population pool, all subjects 60 years and above, irrespective of gender and type of epilepsy, were identified as our possible participants. All such subjects were then invited by telephone for face-to-face consultation and collection of necessary data. In case of a nonresponse at the first invitation, a second attempt was made to encourage participation. Along with those who did not provide their consent to participate, those with any known physical and/or mental condition that could interfere with their ability to participate, and to understand and answer questions independently were simply excluded. As described below, Abbreviated Mental Test (AMT) was performed before other questionnaires.

### 2.3. Questionnaires

Data collection questionnaires included relevant socio-demographic, clinical and medication (chronic use) history, epilepsy, and seizure-related items. Apart from this, the following three questionnaires were used that have been previously used in Iran's population<sup>14,15</sup>: (a) Medication Adherence Rating Scale (MARS) for treatment adherence; (b) 3-question Medical Prescription Knowledge (MPK) questionnaire that tells us about the understanding of prescription by patients; (c) AMT, which provides rapid assessment among the elderly toward possibility of impaired cognition. AMT score of more than 6 was considered normal, 4–6 as moderate impairment, and 0–3 as severe impairment. MARS score of  $\geq 6$  was considered as being compliant to ASM.<sup>3</sup>

Tehran is the capital of Iran and has a population of 9 million within its metropolitan areas. The population is Persian-speaking and there are also large proportions of those with other ethnic origins such as Azerbaijanis, Armenians, Lurs, and Kurds. Tehran is divided into 22 municipalities with two important arrangements, universal health insurance and family physician program through primary health centers.<sup>16,17</sup>

In addition to customary descriptive statistics, a simple chi-square test (or Fischer exact test if value of cells  $\leq 5$ ) was used for correlating univariate categorical dependent (compliant/noncompliant) and independent variables, although it does intend to model dependent and independent variables. The strength of association (i.e. effective size of chi-square) after chi-square was determined by using Cramer's V test, which is better than Phi test because of nondependence on table size. Cramer's V test on its own is also appropriate for determining correlation between discrete variables. Prediction of a categorical binary outcome (dependent variable; compliant/noncompliant) *vis-à-vis* independent variables (i.e. **presence** of supernatural origin of epilepsy, polytherapy, active epilepsy, family history, comorbid state, female gender, convulsive epilepsy, night-time seizures, singlehood, lower-than-cutoff AMT score, and **absence** of acceptance of disease) was determined by logistic regression. In case where independent categorical variables had more than two levels (education, 30-day severity of seizures, and marital status), dummy coding was performed. Data were analyzed using STATA. A 95% confidence interval (CI) was adopted and a *p* value of  $< 0.05$  was considered statistically significant. All potential participants were requested to provide informed verbal consent prior to their participation. They were explained about the purpose of this survey prior to its start and the kind of data that would be collected. They had freedom to not choose or continue to participate. Ethical permission was obtained from the institutional review board of the University of social welfare and rehabilitation sciences. The authors are also aware that neither correlation nor other methods such as regression demonstrate 'causation' of any kind; hence, the effort is to identify associative factors.

## 3. Results

### 3.1. Number of participants and nonparticipation

Overall, our population pool constituted 104 subjects', who were  $\geq 60$  years of age. Each of them was invited to participate in the survey. The reasons of nonparticipation were as follows: being in debilitated state ( $n = 41$ , 78.0%), distance and residence in another city ( $n = 4$ , 3.8%), pollution ( $n = 7$ , 6.7%), no one to accompany ( $n = 2$ , 1.9%), phone switched off, wrong phone number, or unreachable ( $n = 27$ , 34.6%).

### 3.2. Socio-demographics

Overall, 23 subjects participated with mean and median ages of 63.3 (SD 3.3, range 60–71) and 62.0 (95% CI 61.0–64.7, range 60–71) years, respectively. Majority of participants were males ( $n = 17$ , 73.9%) and their mean (63.4 versus 63.3) and median (62.0 versus 63.0) ages did not differ descriptively and statistically ( $p = 0.4$ ). Overall, 18 participants were married and had a living partner ( $n = 18$ , 78.3%) and the rest were widowed ( $n = 4$ , 17.4%) and divorced ( $n = 1$ , 4.3%). Only six participants had consanguineous marriage ( $n = 6$ , 26.1%). Only seven participants (30.4%) had family history of epilepsy. The majority had reported acceptance of epilepsy ( $n = 20$ , 90.9%) while 12 participants (54.5%) had reported epilepsy as supernatural, that is according to God's will. Only few had known comorbid condition ( $n = 5$ , 21.7%). Only one subject was an illiterate ( $n = 1$ , 4.3%) and only three participants ( $n = 3$ ,

13.0%) were living alone entirely. The family size was small (1–3 members) for 10 participants (43.5%) and large (4 and above) for 13 participants (56.5%). The mean (1.5) and median (2.0) family sizes were low.

### 3.3. Epilepsy description

For most of the participants, epilepsy was not a recent onset (>10 years ago for  $n = 14$ , 60.8%) and 5–10 years for  $n = 6$ , 26.0%) while only three had recent onset epilepsy ( $n = 3$ , 13.0%). Majority of the participants had active epilepsy ( $n = 22$ , 95.7%) and none were diagnosed by a traditional healer or religiously diagnosed. Majority ( $n = 21$ , 91.3%) had convulsive seizures and no circadian seizure pattern ( $n = 14$ , 60.9%), while most of the remaining participants had day-time seizures ( $n = 8$ , 34.7%), with only one subject having night-time seizures (10 AM–5 AM,  $n = 1$ , 4.3%). There was also no seasonal pattern with respect to season-based increase in seizure frequency ( $n = 18$ , 85.5%) in majority of the participants, and the remaining participants had summer ( $n = 4$ , 17.3%) and winter ( $n = 1$ , 4.8%) pattern. There was also no reported monthly moon pattern for seizure occurrence or change in frequency ( $n = 13$ , 56.5%) in the majority; the rest had no response ( $n = 9$ , 39.1%) while only one (4.3%) participant had reported seizure occurrence with relation to 1st moon quarter. Most patients had no seizure in the last 30 calendar days ( $n = 13$ , 56.5%) while low seizure number (1–3) was found in 6 (26.0%) patients and 3–5 seizures in 3 (13.0%) patients. Among those with seizures in the last 30 calendar days, the seizure severity was high in 5 (21.7%), moderate in 3 (13.0%) and low in 2 (8.6%) subjects.

### 3.4. Treatment description

Most participants were on treatment ( $n = 22$ , 95.7%) and nearly half of them were on polytherapy ( $n = 12$ , 52.2%); a variety of ASMs were being used for treatment, either single or in combination, as follows: carbamazepine ( $n = 14$ , 60.9%), valproic acid ( $n = 11$ , 47.8%), phenobarbital ( $n = 4$ , 17.4%), phenytoin ( $n = 3$ , 13.0%), primidone ( $n = 4$ , 17.4%), and lamotrigine, oxcarbazepine, levetiracetam, clonazepam, and acetazolamide ( $n = 1$ , 4.3%, each). The mean and median distances to nearest pharmacy were 1.2 KM (95% CI 0.6–2.0, range 0.05–5.0) and 1.0 KM (95% CI 0.2–1.8, range 0.05–5.0), respectively.

The presence of direct treatment side effects varied as follows: **Physical:** weight loss ( $n = 3$ , 13.0%), loss of appetite ( $n = 5$ , 21.7%), weight gain ( $n = 5$ , 21.7%), headache ( $n = 6$ , 26.1%), malaise ( $n = 10$ , 43.5%), sleepiness/drowsiness ( $n = 11$ , 47.8%), unsteadiness/dizziness ( $n = 4$ , 17.4%), and hand tremors ( $n = 8$ , 34.8%); **skin-related:** dermatitis ( $n = 4$ , 17.4%); **gastro-intestinal:** upset stomach/nausea ( $n = 5$ , 21.7%), dry mouth, altered taste, and gum bleeding ( $n = 8$ , 34.8%); **vision:** disturbed vision ( $n = 11$ , 47.8%); **cognitive:** difficulty paying attention ( $n = 7$ , 30.4%) and decline in memory ( $n = 7$ , 30.4%); **behavioral:** altered behavior including anxiety, irritability, hyperactivity, nervousness, and agitation ( $n = 17$ , 73.9%); **sleep-related:** altered sleep ( $n = 7$ , 30.4%).

### 3.5. Compliance estimation, and correlated and predictive factors

Overall, most participants were found to be compliant ( $\geq 6$  MARS score), i.e.  $n = 18$ , 78.2%. The mean and median MARS scores were 7.0 (95% CI 6.2–7.8, range 3–10) and 8.0 (95% CI 6.0–8.0, range 3–10), respectively. For **correlation**, there was a correlation of nonadherence with having a positive comorbid state ( $p = 0.003$ ), as well as widowhood and divorcehood ( $p = 0.04$ ). These were also the **prediction** factors toward nonadherence i.e. having a positive comorbid state ( $p = 0.005$ ), widowhood and divorcehood (0.03); although to lesser statistical significance. Based on treatment side

effects, the **correlation** of nonadherence was found for altered behavior ( $p = 0.03$ ), difficulty paying attention ( $p = 0.01$ ), unsteadiness/dizziness ( $p = 0.02$ ), hand tremors ( $p = 0.07$ ), mouth- and gum-related changes ( $p = 0.07$ ), skin-related changes ( $p = 0.03$ ), upset stomach ( $p = 0.01$ ), loss of appetite ( $p = 0.03$ ), and weight gain ( $p = 0.01$ ). The **prediction** for nonadherence was found to be significant for unsteadiness/dizziness alone ( $p = 0.01$ ).

### 3.6. Medication prescription knowledge and abbreviated mental state

MPK was positive for all participants and none of them reported failure to recall the name of prescribed medicine, number of tablets to consume, and number of times a tablet is to be taken every day. For AMT, nearly all participants ( $n = 22$ , 96.0%) had reportedly a score of  $\geq 6$ . The mean and median AMT scores were 9.0 (95% CI 8.6–9.5, range 6–10) and 9.0 (95% CI 9.0–10.0, range 6–10), respectively.

## 4. Discussion

We performed an important survey on measuring adherence as well as identifying factors that are either correlated to or predict nonadherence among elderly subjects from Iran. There is not much regular and systematic data on epilepsy from Iran, which makes this effort of general importance. This survey is part of the last author's dedicated collaborative plans to activate epilepsy and research in this country, with systematic evaluations of epilepsy planned in one province.

Treatment adherence is an extremely intricate, inadequately defined, multidimensional, and culture-dependent subject, referred with various terms, including concordance, compliance, etc., each having its own intricate meanings, advantages, and objectives.<sup>18</sup> However, irrespective of the terms used, the central goal remains to determine how close a patient remains to his/her prescribed therapeutic regimen as practically feasible and what prohibits that goal.

Good adherence is a health-promoting behavior<sup>19</sup> and, for those with epilepsy, is essential for preventing and minimizing seizures and their cumulative impact on day-to-day life.<sup>20</sup> Gross non-adherence may result in serious repercussions as well as avoidance and loss of feasible medication benefits.<sup>20</sup> Our population seemed to be conscious of these benefits since most participants (78.2%) were found to be adherent, while only two subjects were grossly nonadherent, i.e. MARS score of 3 or 4. Moreover, all participants had reported 100% prescription knowledge. This optimal adherence and prescription knowledge suggests 'concordance' between patient and doctor,<sup>21</sup> which is a method of positive health outcome.<sup>22</sup> Our population therefore reflects a traditional medical model wherein relationship between doctor and patient is of unequal power dynamics<sup>23</sup> and patient may not necessarily be the one who ultimately decides whether or not they adhere to the recommended regimen.<sup>24</sup> Although most patients had active seizures, 30-day seizure frequency and severity was low. Thus, it might be construed that patients were treated with right guidance and right medication, which might get reflected as medication adherence. Although no significant correlation or prediction was found, high knowledge and adherence could simply be due to the fact that most participants *theoretically* had active seizures, which may provide a greater sense of risk as well as an actual risk.<sup>25</sup>

Our survey demonstrates important results and also clarifies epilepsy-related issues that are often discussed unilaterally in the literature. Iran is a family-oriented society and elders may not necessarily be made to live alone<sup>11</sup> as can be seen from the fact that only few (13.0%) were alone altogether in our survey. This living alone could be for numerous unknown reasons; however living alone pose challenges for epilepsy patients, more so when they

would also be elderly.<sup>26</sup> Consanguinity, an important epilepsy risk factor,<sup>1</sup> was evident descriptively in this population as well since a quarter of participants had a consanguineous marriage. In spite of the fact that our population was elderly, this may still reflect today's scenario in Iran.<sup>27</sup> Although in Iran, as elsewhere, consanguinity is attributed to less-affluent individuals,<sup>28</sup> the fact that nearly all our subjects were literate indicates that this is rather a conscious choice, for multitude of reasons, in this society.<sup>27</sup> Consanguinity, like influential stigma, is probably an unresolvable issue and consanguinity along with family history of epilepsy will continue to act as major risk factors for epilepsy<sup>1</sup> as well as for nonadherence.<sup>29</sup>

In theory, supernatural belief on epilepsy would mean rejection of modern therapies. Although, in our survey, supernatural origin of epilepsy<sup>30</sup> was reported by nearly half of the population, yet most had reported 'acceptance of epilepsy'. Moreover, none of the participants were diagnosed by traditional or religious healer, even though Iran has a very strong and developed traditional healthcare system and a Muslim society.<sup>12</sup> This indicates that supernatural belief about epilepsy although erroneous may not necessarily pose *practical* restrictions. This is possibly the reason that no correlation or prediction was found for nonadherence with supernatural belief. This is also what has been demonstrated by the last author that scenarios regarding epilepsy-related stigma are of two different kind for numerous reasons, one where stigma is present but may not necessarily be influential **and** one where stigma is present but is also influential to independently modify people's *day-to-day* choices and decisions.<sup>5</sup> Having night-time seizures are important for many reasons, although no significant correlation or prediction was found *vis-à-vis* adherence in our survey since only one participant had reported night-time seizure.

Only few but logical factors were either correlated or predictive toward noncompliance in the elderly. Positive comorbid state, which influences lack of seizure control,<sup>31</sup> was found in 21.7% patients, which was the strongest correlated and predictive factor for nonadherence in our survey. Positive comorbid state is an important situation among elderly patients with epilepsy, and may make them hopeless/helpless about their life, render cognitive and mood changes, etc.<sup>32</sup> Our patients were cognitively intact as noted in high AMT scores for nearly all participants, page 7; however, drug-related behavior changes were found to be correlated with noncompliance in our survey. Behavioral issues are linked to nearly half of the chronic health problems,<sup>33</sup> including epilepsy.<sup>34</sup> This leads to another factor that was correlated to noncompliance i.e. widowhood and divorcehood. Divorce in Iran may bring shame<sup>35</sup> and, as reported, is related to psychological, cultural, and social factors.<sup>36</sup> Although it differs in each cultural context,<sup>37</sup> attitude toward epilepsy has improved in some while negative attitude toward epilepsy persists<sup>37</sup> with divorce rates among epilepsy being higher.<sup>38</sup> This although may quickly be attributed to epilepsy or stigma alone, this may not necessarily be a true approach. Marriage or separation should be seen from a practical point of view. For instance, discovering that a partner has epilepsy would mean requirement toward additional physical efforts, emotional support, as well as financial resources. In a union, there are other issues such as child rearing, limitation toward participation in *day-to-day* household chores, dietary restrictions, etc. This also depends upon seizure frequency, nature and coping capacity, or willingness of the partner. There are beliefs that epilepsy patients should not marry because offsprings might develop epilepsy too; however, the risk for developing epilepsy among offspring of two epilepsy subjects is not different from those between a union of epilepsy and a healthy individual. There is no reason why a person with epilepsy should marry only with a healthy individual? Based on these practical issues, a novel initiative '*Marryepilepsy*' has been on its implementation stage by the last author. Nevertheless,

marriage is related with overall happiness and has protective health effects,<sup>39</sup> more for men than women, while divorcehood and widowhood are difficult life situations and may lead to several physical and behavioral changes, negative consequences, as well as personal, domestic, and social disintegration,<sup>40</sup> especially for men.<sup>41,42</sup>

Although many were on polytherapy, an important situation among the elderly, this was neither correlated nor predictive for noncompliance in our survey. Both dizziness and unsteadiness are common complaints in patients with epilepsy<sup>43</sup> and is common with carbamazepine, phenytoin, levetiracetam, etc., the drugs used in our patients.<sup>44</sup> For this reason, a strong prediction of unsteadiness was found for noncompliance in our survey.

Lastly, adherence depends upon methods (direct and indirect) used for measuring it.<sup>45</sup> There are a number of methods, each having its advantages and disadvantages, but neither is ideal. The questionnaire methods that we used is one of such validated method for measuring adherence. Nevertheless, our survey did not look at consumption of medication over a certain time (ex. counting pills) but how a particular regime is likely to be followed.<sup>46</sup>

The limitations of our work include that many potential participants could not participate; although we invited them twice. Our work is based on low, selective population but interestingly provides results that correlate with other's results and also adds newer clarifications on certain issues that are widely reported in the literature.

## 5. Conclusion

Our work derived important conclusions. Traditional medical model of 'concordance' between patients and doctors is most likely present, which should not be unlikely in *culture-oriented* hierarchical societies, like ours. As demonstrated elsewhere, albeit infrequently, this can be a useful approach toward positive health outcomes. Noncompliance among the elderly epilepsy subjects in Iran is correlated to positive comorbid state and divorce-widowhood, and drug-related behavioral side effects. Prediction for noncompliance is related to unsteadiness. Looking from patient-practitioner's point-of-view, these risks are modifiable and should be looked-for (and addressed) during regular epilepsy patient management and follow-ups. Looking from the health system's point-of-view, there is a need to evaluate and find means to address epilepsy-based divorce in Iran. As, discussed above, the concept related to marriage among epilepsy has most likely been misunderstood with a unilateral *by default* point of view. A novel initiative '*Marryepilepsy*' has been on its implementation stage by the last author.

## Conflicts of interest

The authors have none to declare.

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