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Medication Non-Adherence in Essential Tremor

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Abstract

Background—There are numerous studies of medication adherence in a variety of chronic diseases including Parkinson's disease; however, there are no such studies in patients with essential tremor (ET). This study aimed to (1) present self-report data on medication adherence in ET cases, (2) examine the demographic and clinical factors that might be associated with lower medication adherence.

Methods—151 ET cases were enrolled in a clinical-epidemiological study at Columbia University. An 11-item medication adherence questionnaire, modeled after the Morisky medication adherence questionnaire, was administered.

Results—Seventy-three (48.3%) of 151 cases were taking daily medication for ET. One-third (24/73; 32.9%) of cases reported that they sometimes forgot to take their medication, and 1 in 5 (15/73; 20.5%) reported missed doses within the past week. Most striking was that nearly 1 in 4 (17/73; 23.3%) reported that there were whole days in the past two weeks in which they had not taken their medication. A factor analysis revealed four factors that captured different aspects of non-adherence. Higher non-adherence was associated with more depressive symptoms, younger age, and less severe tremor but was not associated with type or number of ET medications.

Conclusions—Approximately one in four ET patients reported whole days in the past two weeks in which they had not taken their medication. It is possible that this relatively high rate of

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non-adherence could be a function of the poor therapeutic efficacy of the medications currently available to treat ET.

Keywords

Essential tremor; Clinical; Epidemiology; Treatment; Adherence; Compliance

Introduction

There are numerous studies of medication adherence across a broad range of chronic diseases including Parkinson's disease (PD), epilepsy, rheumatoid arthritis, and asthma; however, there are no such studies in patients with essential tremor (ET) [1–5]. This is surprising, since ET is one of the most commonly encountered chronic neurological disorders [6–8]. Gauging medical adherence and understanding the factors that contribute to non-compliance is an important endeavor, which can enhance current treatment as well as direct future efforts in developing improved treatments. Medication compliance is a complex issue, and is related to a variety of factors, including the perceived efficacy of the medication [9, 10]. The current set of medications used for the treatment of ET certainly have limited efficacy [11, 12]. The presence of side effects may also decrease medication adherence [5], and unwanted side effects are a common occurrence among treated ET patients [13]. The two aims of the current study were to (1) present self-report data on medication adherence in ET cases, (2) examine the demographic and clinical factors that might be associated with lower medication adherence among patients with ET. It is hoped that these data will be of use to treating physicians as well as those interested in developing new therapies.

Methods

Participants

ET cases were enrolled in a study of environmental risk factors for ET at Columbia University Medical Center (CUMC) [14]. Upon enrollment, a trained tester obtained written informed consent, approved by the CUMC Institutional Review Board, from all participants. ET cases were identified from two primary sources: a computerized billing database of all ET patients who were seen at least once at the Center for Parkinson's Disease and Other Movement Disorders at CUMC over the past 5 years as well as the International Essential Tremor Foundation (IETF) [14]. IETF members lived in the New York metropolitan area and were mailed advertisements [14, 15]. All enrollees had received a diagnosis of ET from their treating neurologist and lived within a 2-hour driving distance of CUMC [14, 15]. After enrollment, all diagnoses were confirmed using published diagnostic criteria, as outlined below [14, 15].

Baseline recruitment began in 2000 and ended in 2009. In April 2009, a follow-up phase began, with the goal of enrolling at least 120 –130 ET cases. During the follow-up phase, the oldest cases were targeted first (i.e. those with the highest likelihood of loss to follow-up due to mortality). During recruitment for the follow-up phase, 41 ET cases (24 women, 17 men;

age 75.4 ± 13.0 years) refused to participate. At follow-up, 151 ET enrollees underwent the same in-person evaluation as at baseline (see below) [16].

Clinical Evaluation

Each case underwent an in-person evaluation consisting of a series of demographic and clinical questionnaires in which a variety of demographic and clinical factors that have been linked to medication non-adherence in other chronic diseases were assessed [1, 5]. An 11-item self-report medication adherence questionnaire was modeled after the Morisky medication adherence questionnaire, which is a simple, eight-question, self-reported tool [17]; however, three additional questions (questions 2, 4 and 7, Table 1) were added to try to capture additional non-adherence behaviors. In total, there were eleven items, 10 of which were scored as no (0) vs. yes (1) and one (question 11) that was scored with additional gradations (0, 1, 2, 3). The total score ranged from 0 – 13 (maximal non-adherence) (Table 1).

The Center for Epidemiological Studies Depression Scale (CESD-10), a self-report, 10-item screening questionnaire, was used to assessed depressive symptoms (range 0–30 [greater depressive symptoms]) [18]. The Folstein Mini-Mental Status test score (0 [most impaired] – 30) was used as a brief assessment of cognition [19].

Each case underwent a 20-minute videotaped neurological examination, which included an assessment of postural tremor, five tests of kinetic tremor, as well as assessments of head (neck), voice and jaw tremors [14]. Each videotaped examination was reviewed by E.D.L., who rated the severity of postural and kinetic arm tremors (range = 0 – 3) using a reliable and valid clinical rating scale, assigning a total tremor score (range 0 – 36) [14]. Diagnoses of ET were re-confirmed by E.D.L. using the videotaped neurological examination as well as published diagnostic criteria (moderate or greater amplitude kinetic tremor [tremor rating ≥ 2] during three or more tests or a head tremor, in the absence of PD, dystonia or another cause) [14].

Statistical Analyses

Data were analyzed in SPSS (Version 21). A factor analysis was performed, entering the 11 items in the medication adherence questionnaire. This analysis was performed using the principal component method, with orthogonal (varimax) rotation. This method was chosen to identify separable and independent clusters. Eigenvalues greater than 1.0 were used to select the factors, as is common practice [20]. The analysis identified four factors, and was used to create four non-adherence (NA) subscores and a total NA score. To do so, the responses to questions 7 and 8, had to be inverted. None of the NA subscores or the NA total score were normally distributed (Kolmogorov-Smirnov tests with all p values < 0.001); hence, nonparametric tests were used in assessing these scores. Associations between a range of demographic and clinical variables (age, gender, race, years of education, total tremor score, duration of tremor, mini-mental status test score, CESD-10 score, number of ET medications, taking vs. not taking particular ET medications) and each of the four NA subscores and total NA score were assessed using Spearman's correlation coefficients and Mann-Whitney tests.

Results

There were 151 enrollees (age = 71.7 ± 13.1 years, 78 [51.7%] female, education = 16.1 ± 2.6 years, total tremor score = 20.3 ± 6.1, tremor duration = 31.9 ± 18.8 years). The total number of prescription medications currently taken for any medical condition ranged from 1 – 15 (mean = 5.8 ± 3.2). Of these 151, 73 (48.3%) were taking daily medication for ET; the characteristics of these 73 (Table 2) were similar to those of the larger sample of 151.

Fifty (68.5%) of 73 were taking a beta-blocker (of whom 39 were taking propranolol), 31 (42.5%) were taking primidone, 9 (12.3%) were taking topiramate, 5 (6.8%) were taking gabapentin, and a small number were taking other medications. In addition, 17 (23.3%) were taking a benzodiazepine. Forty-seven (64.4%) of 73 were taking one ET medication, 23 (31.5%) were taking two, two (2.7%) were taking three, and one (1.4%) was taking four ET medications.

One-third of cases reported that they sometimes forgot to take their medication, and 1 in 5 reported missed doses within the past week (Table 1). Nearly 1 in 4 reported that there were whole days in which they had not taken their medication in the past two weeks (Table 1).

A factor analysis revealed four factors: Factor I (Questions 1, 2, 5, 6, Eigenvalue = 3.28, explaining 29.8% of the variance), Factor II (Questions 3, 10, 11, Eigenvalue = 1.93, explaining 17.5% of the variance), Factor III (Questions 7, 8, Eigenvalue = 1.43, explaining 13.0% of the variance), Factor IV (Questions 4, 9, Eigenvalue = 1.06, explaining 9.6% of the variance), which explained 69.9% of the variance. Each factor seemed to capture a different aspect of non-adherence. Factor II questions related to the nuisance of having to follow a routine medication schedule, factor IV questions captured behaviors such as the active self-management and even stopping of medications, factor I questions related to the occasional forgetting of a dose, and factor III questions related to recall of recent adherence.

Based on the four identified factors, four NA subscores and a total NA score were constructed. The NA subscores and total NA scores are shown (Table 3).

Associations between a range of demographic and clinical variables and each of the four NA subscores and total NA score were assessed. Higher total NA score was associated strongly with more depressive symptoms (Spearman's $r = 0.44$, $p < 0.001$) but not with other demographic or clinical factors. Additional analyses of NA subscores revealed more fine-grained associations (Table 4). Cases who were younger and had less severe tremor were more likely to actively manage and even stop medications (i.e., higher NA subscore 4, Table 4). Cases who had more depressive symptoms admitted to more occasional forgetting of doses (i.e., higher NA subscore 1) and greater perceived nuisance in having to follow a routine medication schedule (i.e., higher NA subscore 2) (Table 4). Higher education was associated with greater recent adherence (i.e., higher NA subscore 3) (Table 4). Gender was not associated with differences in adherence (all Mann-Whitney test p values > 0.05). There was a suggestion that white race was associated with greater adherence, although the number of non-white participants was so small that meaningful comparisons were not possible.

The total number of prescription medications for any medical condition was not associated with the NA total score (Spearman's r = −0.02) or any of the subscores (for subscore 1, Spearman's r = −0.04, p = 0.77; for subscore 2, Spearman's r = 0.07, p = 0.55; for subscore 3, Spearman's r = −0.18, p = 0.14; for subscore 4, Spearman's r = −0.19, p = 0.12). More specifically, the number of ET medications was not associated to a significant degree with the NA total score (Spearman's r = −0.09, p = 0.43) or any of the subscores (for subscore 1, Spearman's r = −0.10, p = 0.38; for subscore 2, Spearman's r = −0.05, p = 0.68; for subscore 3, Spearman's r = −0.21, p = 0.08; for subscore 4, Spearman's r = −0.09, p = 0.44). Similarly, taking vs. not taking a particular medication (propranolol, primidone, topiramate, gabapentin) was not associated to a significant degree with the NA total score or any of the subscores.

Although this sample was in general highly educated, 13 (17.8%) cases only had a high school education. To assess whether the main findings were similar in this subgroup with relatively lower educational attainment, the analyses were repeated. The results were similar to those seen in the entire sample of 73 cases. Thus, one-third of these cases (4/13 or 30.8%) reported that they sometimes forgot to take their medication, 5/13 (38.5%) reported missed doses within the past week, and 4/13 (30.8%) reported that there were whole days in which they had not taken their medication in the past two weeks.

Discussion

The reasons for medication non-adherence in chronic diseases are multiple and varied. Compliance is related to the efficacy of the medication [9, 10] and is also related to the consequences of a failure to take a dose. For example, failure to take an oral contraceptive could result in an unplanned pregnancy [9]. Lower compliance may also be a function of greater medication side effects [5]. The current set of medications used for the treatment of ET certainly have limited efficacy [11, 12], failure to miss a dose has few consequences, and unwanted side effects are a common occurrence for ET patients [13].

In the current study, one-third (24/73; 32.9%) of cases reported that they sometimes forgot to take their medication, and 1 in 5 (15/73; 20.5%) reported missed doses within the past week. In a study of PD, 40.3% of patients reported sometimes forgetting to take their medication, which was similar to the current data in ET (32.9%) [5]. Perhaps most striking was that nearly 1 in 4 (17/73; 23.3%) ET cases reported that there were whole days in the past two weeks in which they had not taken their medication.

A factor analysis was performed and several discrete aspects of non-adherence were identified: non-adherence due to a perceived nuisance of having to follow a routine medication schedule, active self-management and even stopping of medications, and the occasional forgetting of a dose. Some patient subgroups seemed to be differentially susceptible to different aspects of non-adherence. For example, younger patients were more likely to be self-directed in terms of personalizing their medication usage patterns. Prior studies have also attempted to categorize non-adherence in movement disorder patients, although not using a factor analysis approach. For example, a study of PD patients distinguished between minor unintentional forgetting to take a dose of a medication vs.

major intentional changes in dosing [9]. Identification of such factors has potential utility in terms of lessening non-adherence in susceptible patients.

A number of specific factors were associated with an increase in non-adherence. Among the most robust was depressive symptoms, and this association has been reported in studies of patients with PD [5] and studies of patients with other chronic diseases as well [21].

These results should be interpreted in the context of the following limitations. First, a questionnaire was used to assess adherence. Questionnaires are highly imperfect and are known to under-estimate missed doses, as patients often do not admit to noncompliance [1]. To some extent, however, all forms of drug monitoring are imperfect [1]. Pill counts, for example, only identify under-dosing but not mistimed doses [1]. Electronic monitoring counts may fail if patients take out more than one dose at a time or if the bottle top is not properly replaced [1]. Nonetheless, future studies should assess non-adherence using a combination of such methods. Second, the questionnaire that was used was brief (11 items) and additional information might be obtained by using more elaborate assessments. Nonetheless, the questionnaire was actually an expansion of an 8-item self-report medication adherence questionnaire, the Morisky medication adherence questionnaire, which is a highly-cited tool in adherence research. Three additional questions were added to that tool to capture additional data. Third, studies have shown that the most common reason for stopping treatment is adverse events or side effects [5]. Unfortunately, data on side effects were not collected, so this could not be assessed. Fourth, the study sampled one group of ET cases, and it would be useful in future studies to sample other cases ascertained from different sources. All of our cases had attained a high school education or higher. It would be of additional value to assess whether non-adherence might be higher among cases with lower educational attainment (e.g., less than high school). Fifth, the sample size was small (n = 151 patients of whom 73 were currently taking medication); despite this, other studies of adherence in PD, for example, have typically sampled similar numbers of cases (e.g., n = 15 [9], n = 39 [1], 112 [22]).

The study also had considerable strengths. This was the first study to examine adherence in ET. Second, patient self-report is an easily accessible, efficient, and economical method for assessing adherence, and is a commonly-used approach in adherence research [23]. Third, a standardized questionnaire was used in ET cases, which assessed multiple aspects of non-adherence. Fourth, a broad range of demographic and clinical data were collected, facilitating the evaluation of clinical factors that tracked with non-adherence.

In summary, approximately one in four ET patients reported whole days in the past two weeks in which they had not taken their medication. It is possible that this relatively high rate of non-adherence could be a function of the poor therapeutic efficacy of the medications currently available to treat ET.

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- There are no studies of medication adherence in patients with ET.
- 25% reported whole days in which they hadn't taken their medication.
- Higher non-adherence was associated with more depressive symptoms and younger age.
- The high rate of non-adherence may be due to the limited efficacy of current drugs.

Table 1

Medication adherence questionnaire in 73 ET cases who took daily medication for ET

	Question	Response data
1	Do you sometimes forget to take your ET medication?	24 (32.9)
2	Over the last week, did you miss any doses of your ET medication?	15 (20.5)
3	Over the past two weeks, were there any days when you did not take your ET medication?	17 (23.3)
4	In the past 2 weeks, have you sometimes stopped a dose of medication if you were feeling ok?	6 (8.2)
5	Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	6 (8.2)
6	When you travel or leave home, do you sometimes forget to bring your medications?	7 (9.6)
7	Did you take you last regularly scheduled dose of ET medication?	65 (89.0)
8	Did you take your ET medication yesterday?	66 (90.4)
9	When you feel like your tremor is under control, do you sometimes stop taking your medicine?	5 (6.8)
10	Do you ever feel hassled about sticking to your ET treatment plan?	7 (9.6)
11	How often do you difficulty remembering to take all your medication?	
	No difficulty	54 (74.0)
	A little difficulty	17 (23.3)
	Somewhat difficult	1 (1.4)
	Quite difficult	1 (1.4)

Values are numbers (percentages).

Table 2

Demographic and clinical characteristics of 73 ET cases who took daily medication for ET

Characteristic	Data
Age in years	73.0 ± 13.5
Female gender	39 (53.4)
White race	70 (95.9)
Years of education	16.2 ± 2.7
Total tremor score	21.9 ± 4.9
Duration of tremor in years	34.2 ± 18.3
CESD-10 score	7.4 ± 5.3
Mini-mental status test score	28.7 ± 1.7

Values are means ± standard deviations or numbers (percentages)

CESD-10 = Center for Epidemiological Studies Depression Scale

Table 3

Non-adherence subscores and total score

Subscore or Score	Data
Subscore 1 (Questions 1, 2, 5, 6)	0.71 ± 1.05 (0 – 4)
Subscore 2 (Questions 3, 10, 11)	0.63 ± 1.03 (0 – 5)
Subscore 3 (Questions 7, 8)	0.21 ± 0.55 (0 – 2)
Subscore 4 (Questions 4, 9)	0.15 ± 0.46 (0 – 2)
Total score (Questions 1 – 11)	1.70 ± 2.11 (0 – 9)

Values are mean ± standard deviation (minimum – maximum).

Table 4

Association between clinical variables each of the four NA subscores and total NA score

	NA subscore 1	**NA subscore 2**	**NA subscore 3**	**NA subscore 4**
Age in years	−0.004	−0.03	0.03	**−0.25**[2]
Total tremor score	0.14	−0.002	−0.19	**−0.21**[1]
Years of education	−0.13	−0.10	**−0.24**[2]	0.03
Duration of tremor in years	0.08	0.10	0.17	−0.06
Mini-mental status test score	−0.14	−0.03	0.01	**0.27**[2]
CESD-10 score	**0.30**[2]	**0.34**[3]	0.12	−0.04

All values are Spearman's correlation coefficients (r).

[1] $p < 0.10$,

[2] $p < 0.05$,

[3] $p < 0.01$.

Bolded values are significant ($p < 0.05$) or marginally significant ($p < 0.10$).