Published in final edited form as:
Parkinsonism Relat Disord. 2010 November ; 16(9): 604–607. doi:10.1016/j.parkreldis.2010.07.011.

Survey of Medication Usage Patterns Among Essential Tremor Patients: Movement Disorder Specialists vs. General Neurologists

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Abstract

Background—Although small treatment trials have examined the efficacy of front-line medications in tremor reduction in essential tremor (ET), an overall survey of pharmacological management has not been undertaken in a large sample of ET cases.

Objectives—To conduct a survey of medication usage among several hundred ET patients.

Methods—A computerized database at the Neurological Institute of New York was used to identify 223 ET patients cared for by movement disorder neurologists and 37 cared for by general neurologists. Each had been seen one or more times within past five years. Lifetime treatment data were abstracted from clinical records.

Results—One-hundred-sixty-three (73.1%) of 223 patients cared for by movement disorder neurologists had taken medication for ET during their lifetime; 53/163 (32.5%) had taken ≥4 medications; 31/163 (19.0%) had taken ≥5 medications; and 3 (1.8%), ≥10 medications. Nearly three-quarters (158/223 [70.9%]) had taken primidone or propranolol, yet 89/158 (56.3%) had discontinued both. Among 11 patients who had undergone ET surgery, the mean number of ET medications tried was 6.0±2.8 (range = 3–12). Medication usage by general neurologists was less than by movement disorder specialists ($p<0.001$). One-third of general neurologists' patients (14/37 [37.8%]) had taken primidone or propranolol at some point and 6/14 (42.9%) had discontinued both.

Conclusions—In this large survey, a substantial proportion of ET patients failed treatment with both front-line medications. Among patients seeing movement disorder specialists, the number of medications they had had to try was sizable. These data demonstrate the limitations of current pharmacological options for ET.

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Keywords

Essential tremor; clinical; epidemiology; treatment; medication

Introduction

Essential tremor (ET) is one of the most commonly-encountered movement disorders [1,2], yet pharmacotherapeutic options are limited [3,4]. There are only two front-line medications, propranolol and primidone. There is an anecdotal impression that only 50% of patients benefit from medications, although large surveys have not provided detailed treatment response data [5]. Aside from poor efficacy, bothersome side effects limit medication usage. Although small treatment trials (number of subjects = 11–22)[6–9] have examined the efficacy of front-line medications during the brief clinical trial period, a more general appraisal of pharmacological management has not been undertaken. Interestingly, there has been no larger-scale survey of basic medication usage patterns in ET patients. What proportion of ET patients is treated with any medication? What proportion, with >1 medication? What is the average number of medications tried? What percentage has used a front-line medication at some point? What proportion has discontinued medication? To what extent does poor efficacy vs. intolerable side effects underlie these decisions? To address these questions, we reviewed the clinical experience of several hundred patients followed at our treatment center in New York. Two groups of patients, those followed by general neurologists and those followed by movement disorder neurologists, provided complementary data on treatment patterns.

Methods

The computerized billing database at the Neurological Institute of New York (NI), Columbia University Medical Center, was used to identify patients with the International Disease Classification (ICD)-9 diagnostic code 333.1 (essential and other specified forms of tremor). The search was open to both the Center for Parkinson's Disease and Other Movement Disorders and the Division of General Neurology and was limited to patients seen ≥1 times within past five years by any of eight physicians. Ethical approval was obtained from our institutional review board. Forty-four of 550 charts could not be located. Of the remaining 506 patients, 260 had been diagnosed with ET by their treating physician. The remaining 246 patients were excluded because they had Parkinson's disease (PD, with our without co-occurring ET, N=49), physiological tremor (N=33), dystonic tremor or ET with dystonic tremor (N=25), and psychogenic tremor (N=22).

The 260 clinical charts were reviewed by a movement disorders fellow (N.D.) and data were entered into a computerized database (SPSS version-17.0). Data fields were created for the following items: gender, education, family history of ET, age when tremor was first noticed by patient, age at first neurological visit, age at ET diagnosis, age when ET medications were first used, number of neurologists seen in their lifetime, number of visits to our center, presence of head tremor on examination, and presence of voice tremor on examination. Current and previous use of oral ET medications was documented along with the number of trials. Reasons for discontinuation of each medication were noted (side effects, lack of efficacy, both, unknown). Botulinum toxin injections and ET surgeries (e.g., deep brain stimulation [DBS]) were documented. The severity of tremor (on the hand-drawn spiral at the initial visit to our center) was rated (N.D.) using a 0–4 clinical rating scale [10].

Proportions were compared using chi-square tests. The total number of medications was not normally distributed (Kolmogorov-Smirnov $z=3.17$, $p<0.001$); therefore nonparametric tests (Spearman's rho, Mann-Whitney test) were used for this variable.

Results

There were 260 ET patients; 37 (14.2%) were followed by general neurologists and 223 (85.8%), by movement disorder neurologists at our center (Table 1).

Patients Cared for By Movement Disorder Neurologists

During their lifetime, these ET patients had seen 2.2±1.1 (range 1–7) neurologists for their tremor and had visited our center 3.5±4.4 times (range 1–33 times). The mean age at their most recent visit to our center was 64.3±17.5 years and the mean age at which they first noticed tremor was 44.0±21.6 years. On average, they had been under neurological care for 6.8±9.4 years (i.e., 6.8 years had elapsed between their first neurological visit to any neurologist and their most recent visit to our center). If we excluded those patients who had had only one visit to a neurologist, this value was 9.1±9.8 years.

One-hundred-sixty-three (73.1%) patients had at some point in their lifetime taken ≥1 medications for ET. The mean number of medications taken for ET was 2.2±2.2 (median 2, range 0–12) and, among the 163 who had taken ≥1 medications, the mean number was 3.0±2.0 (median 2, range 1–12). Fifty three of 163 (32.5%) had taken ≥4 medications, 31 (19.0%) had taken ≥5 medications, and 3 (1.8%) had taken ≥10 medications. Eleven (4.2%) patients had undergone ET surgery; among these, the mean number of medications they had had to try was 6.0±2.8 (median 5, range 3–12). Thirteen (5.0%) of 260 patients had been treated with botulinum toxin injections.

Approximately one-half (124/223 [55.6%]) had taken primidone at some point (Table 1), yet nearly two-thirds of these (79/124 [63.7%]) had discontinued it. Reasons for discontinuing primidone were: side effects (41/79 [51.9%]), lack of efficacy (15 [19.0%]), both (16 [20.3%]), unknown (7 [8.9%]). A similar number of patients (119/223 [53.4%]) had taken propranolol at some point (Table 1), of whom 65 (54.6% of 119) had discontinued it. Reasons for discontinuing propranolol were: lack of efficacy (29/65 [44.6%]), side effects (16 [24.6%]), both (9 [13.9%]), unknown (11 [16.9%]).

Nearly three-quarters of patients (158 [70.9%]) had taken either primidone or propranolol at some point, yet 89/158 (56.3%) were taking neither of these two front-line agents anymore, 10 (6.3%) were taking both, and the remaining 59 (37.3%) were taking one or the other. Use of other ET medications is shown (Table 1). A small proportion of patients had taken anti-parkinsonian medications for a resting tremor component to their severe ET.

Patients Cared for By General Neurologists

During their lifetime, patients had had seen 1.3±1.0 (range 1–7) neurologists for their tremor and had visited our center 3.9±4.9 times (range 1–24 times). The mean age at their most recent visit to our center was 58.0±19.3 years and the mean age at which they first noticed tremor was 49.3±18.7 years. On average, they had been under neurological care for 1.1±2.0 years (i.e., 1.1 years had elapsed between their first neurological visit to any neurologist and their most recent visit to our center). This value was 3.1±2.4 years if we excluded those patients who had had only a single visit to a neurologist. Seventeen patients (45.9%) had visited our general neurology center only once.

Fourteen (37.8%) patients had taken one or more medications for ET; this proportion was lower than the proportion (73.1%) among patients cared for by movement disorder neurologists (chi-square = 18.15, $p<0.001$). Twenty three (62.2%) patients had never taken medications for ET. The mean number of medications taken for ET was 0.5±0.7 (median 0, range 0–2), which was lower than that number (2.2±2.2) for patients cared for by movement disorder neurologists ($p<0.001$). Among the 14 patients who had taken one or more medications, the mean number

was 1.2±0.4 (median 1, range 1–2). None of the patients had undergone surgery for ET and none had received botulinum toxin injections. General neurologists prescribed fewer front-line medications than movement disorder neurologists (Table 1) as well as fewer of many of the second-line medications (Table 1).

Seven (18.9%) of 37 patients had taken primidone at some point (Table 1), yet 3 (42.9%) of 7 had discontinued it. A similar number of patients (8/37 [21.6%]) had taken propranolol at some point (Table 1), of whom 4/8 (50.0%) had discontinued it.

One-third of patients (14 [37.8%-) had taken either primidone or propranolol at some point, yet 6 (42.9%) of these 14 were taking neither propranolol nor primidone anymore, 0 (0.0%) were taking both, and the remaining 8 (57.1%) were taking one or the other. Use of other ET medications is shown (Table 1).

Combined Sample

Discontinuation of ET medications was high (range 44.3–80.0%, median 62.5%) (Table 2). The total number of medications correlated with age ($r = 0.22$, $p<0.001$), duration of follow-up at our center ($r = 0.32$, $p<0.001$), severity of tremor on spiral drawing at initial visit ($r = 0.12$, $p=0.06$), presence of head tremor on examination (the mean ± standard deviation [median] number of medications for patients with head tremor = 2.6±2.4 [2] vs. 1.8±2.0 [1] for patients without head tremor, $p = 0.01$) and presence of voice tremor on examination (number of medications for patients with voice tremor = 2.7±2.4 [2] vs. 1.8±2.0 [1] for patients without voice tremor, $p = 0.003$). Total number of medications did not differ by age at first symptom, age at diagnosis, education or gender.

Discussion

We examined basic medication usage patterns across a large group of ET patients followed at our center. Patients cared for by general neurologists and those cared for by movement disorder neurologists provided contrasting data on treatment patterns. Among the latter, approximately three-quarters had taken at least one medication for ET and nearly one-third of these had had to test ≥4 medications in their attempt to obtain relief. For the patients who eventually underwent ET surgery, the mean number of attempted medications had been six. Among the ET patients under the care of general neurologists, one-third had taken medications and none had taken more than two medications. Overall, greater number of treatment trials was associated with older age, longer duration of follow-up, greater tremor severity, presence of head tremor and voice tremor, and having been under the care of a movement disorder neurologist.

There are two front-line medications for ET and approximately two-thirds of our combined sample had tried one or both of them. More than one-half on propranolol had discontinued it and nearly two thirds on primidone had discontinued it. Similar high rates of discontinuation (44.3- 80.0%) were observed for other (second-line) medications used in ET treatment, indicating that ET patients seemed equally likely to stop taking front- and second-line medications.

Overall, these data point to a considerable number of patients trying medication and, among those cared for my movement disorder specialists, the necessity of having to try several different agents. These data also point to the overall failure of the two front-line medications. Indeed, few patients (6.3% cared for by movement disorder specialists and 0% cared for by general neurologists) remained on combination therapy with both primidone and propranolol. Approximately one-half (56.3% in movement disorder sample and 42.9% in general

neurologist sample) who had taken either primidone or propranolol were no longer on either medication. These data further quantify the inadequacy of front-line pharmacotherapy for ET.

Patients had mainly stopped primidone due to side effects, whereas for propranolol, it was because of inefficacy. These data are in agreement with prior studies, which have shown that nausea and vertigo are common side effects with primidone use, necessitating drug discontinuation in a considerable number of patients (e.g., 13.6% [6], 22.7% [7] 30.0% [8]). Sedation and drowsiness occur in patients as well, often resulting in dosage adjustments [9].

Movement disorder neurologists and general neurologists differed in several respects. As expected, movement disorder neurologists prescribed medication to a larger proportion of their cases. Interestingly, they not only prescribed more second-line medications but also more front-line medications to their patients.

In a previously-published study of ET cases ascertained from a variety of sources (population, brain donors, clinical-epidemiological study)[11], we found that 105/353 (29.8%) cases who had been prescribed medication for their tremor had stopped taking ET medication, yet in that study we did not attempt to quantify the number of medications patients had taken nor did we have access to data on duration of neurological care or whether patients were seeing general neurologists or movement disorder specialists or data on reasons for discontinuation as reported here. An older study of 678 ET patients, comprised of a mixture of cases who had been under the care of a movement disorder specialist and those who were ascertained from a National Database, indicated that 37.0% of patients reported greater than 50% tremor reduction with propranolol and 42.6% reported greater than 50% tremor reduction with primidone [12].

ET is a chronic medical condition and it is similar to other chronic conditions in that effective medical management can be elusive and challenging. In a study of 3,272 migraine patients in a primary care setting, 58% were dissatisfied with their current pharmacotherapy and, in 65.1%, treatment was changed during a three month study period [13]. Indeed, refractory migraine, which is defined in part based on the failure to respond to at least two pharmacotherapeutic agents, is an entity that occurs not-uncommonly in the migraine population.

Although patients were followed longitudinally, a limitation of this study was the retrospective abstraction of data from clinical charts. As is often the case with such retrospective abstraction, missing data can occur and it may be difficult to precisely reconstruct why medications were discontinued. Second, if at the time of their visit, patients are reporting on past events, they may not recall all of the medications they had tried and their responses to these medications. Third, it can be difficult to disentangle the independent effects of lack of efficacy and side effects on the decision to discontinue medications and, furthermore, other considerations (inconvenience of taking pills every day and costs) may enter in to the decision to discontinue medications. Fourth, although our sample was large, patients were followed at a single tertiary medical center in northern Manhattan and it would be useful to compare these results with those obtained in future studies in other centers. Despite this limitation, our data were not limited to the largely referred group of patients seen by movement disorder specialists, but also included a group of largely non-referred patients seen by primary care neurologists. Finally, the general neurologists we sampled were practicing at a tertiary urban center and it is possible that general neurologists in other settings (e.g., rural) would have different treatment patterns. Strengths of the study included its large sample size and use of data from different types of neurological practitioners.

A substantial proportion of ET patients failed treatment with both of the front-line medications. Among patients seeing movement disorder specialists, the number of medications they had had to try was sizable. These data demonstrate in a quantitative manner the limitations of current pharmacological options for ET.

Acknowledgments

Full financial disclosure for the previous 12 months

Dr. Louis has received research support from the NIH [NINDS #R01 NS42859 (principal investigator), NINDS #R01 NS39422 (principal investigator), NINDS #R56 NS042859 (principal investigator), NINDS #T32 NS07153-24 (principal investigator), NIA #2P01 AG0027232-16 (principal investigator), and NINDS #R01 NS36630 (co-Investigator)], the Parkinson's Disease Foundation (principal investigator), the Arlene Bronstein Essential Tremor Research Fund (Columbia University) and the Claire O'Neil Essential Tremor Research Fund (Columbia University). Nancy Diaz has not received any support.

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Table 1

Characteristics and medication usage of 260 ET patients

	ET Patients Followed by Movement Disorder Neurologists (N = 223)	ET Patients Followed by General Neurologists (N = 37)	All ET Patients (N = 260)
Characteristics			
Women	107 (48.0)	16 (43.2)	123 (47.3)
Men	116 (52.0)	21 (56.8)	137 (52.7)
Education			
Primary or secondary	4 (1.7)	1 (2.7)	5 (1.9)
Completed high school	60 (26.9)	8 (21.6)	68 (26.2)
Completed college	58 (26.0)	21 (56.8)	79 (30.3)
Completed graduate school	64 (28.7)	2 (5.4)	66 (25.4)
Unknown	37 (16.6)	5 (13.5)	42 (16.2)
Family History of ET			
None	81 (36.3)	22 (59.4)	103 (39.6)
1st degree relative	119 (63.3)	9 (24.3)	128 (49.2)
2nd degree relative	20 (9.0)	1 (2.7)	21 (8.1)
Unknown	3 (1.3)	5 (13.5)	8 (3.1)
Age when first noticed tremor (y)	44.0 ± 21.6	49.3 ± 18.7	44.5 ± 21.4
Age at first visit to any neurologist (y)	56.3 ± 18.8	53.2 ± 18.2	55.8 ± 18.7
Age at ET diagnosis (y)	57.1 ± 18.6	56.5 ± 18.9	57.0 ± 18.6
Age at first visit to our center (y)	62.1 ± 17.1	56.7 ± 18.4	61.3 ± 17.4
Age at most recent visit to our center (y)	64.3 ± 17.5	58.0 ± 19.3	63.4 ± 17.9
Age when ET medications first started (y)*	56.5 ± 18.6	48.5 ± 23.1	55.7 ± 19.2
Total number of neurologist seen for ET	2.2 ± 1.1	1.3 ± 1.0	2.1 ± 1.1
Head tremor on examination	90 (40.4)	7 (18.9)	97 (37.3)
Voice tremor on examination	80 (35.9)	1 (2.7)	81 (31.2)
Medication Usage			
Primidone**	124 (55.6)	7 (18.9)	131 (50.4)
Propranolol**	119 (53.4)	8 (21.6)	127 (48.9)
Benzodiazepines**	67(30.0)	0 (0.0)	67 (25.8)
Beta blockers other than propranolol	53 (23.8)	8 (21.6)	61 (23.5)
Gabapentin	49 (22.0)	6 (16.2)	55 (21.2)

	ET Patients Followed by Movement Disorder Neurologists (N = 223)	ET Patients Followed by General Neurologists (N = 37)	All ET Patients (N = 260)
Topiramate**	49 (22.0)	1 (2.7)	50 (19.2)
Carbonic anhydrase inhibitors	19 (8.5)	0 (0.0)	19 (7.3)
Sodium oxybate	15 (6.7)	1 (2.7)	16 (6.2)
Levetiracetam	15 (6.7)	1 (2.7)	16 (6.2)
Levodopa-carbidopa	13 (5.8)	0 (0.0)	13 (5.0)
Mirtazapine	9 (4.0)	0 (0.0)	9 (3.5)
Pregabalin	8 (3.6)	0 (0.0)	8 (3.1)
Amantadine	7 (3.1)	1 (2.7)	8 (3.1)
Calcium channel blockers	6 (2.7)	1 (2.7)	7 (2.7)
Trihexyphenidyl	7 (3.1)	0 (0.0)	7 (2.7)
Other anticholinergic agents	6 (2.7)	0 (0.0)	6 (2.3)
Zonisamide	6 (2.7)	0 (0.0)	6 (2.3)
Dopamine agonists	4 (1.8)	1 (2.7)	5 (1.9)

Values are mean ± SD or proportion (percentage)

Y = years

*Among the ET cases who had taken medication.

** $p < 0.05$ comparing 223 ET patients seen by a movement disorder neurologist to 37 ET patients seen by a general neurologist.

Table 2

Medication use in all 260 ET patients

Medication	Proportion of 260 ET patients who had taken the medication	Proportion of ET patients who had taken the medication and then discontinued it
Primidone	131 (50.4)	82 (62.6)
Propranolol	127 (48.8)	69 (54.3)
Benzodiazepines	67(25.8)	37 (55.2)
Beta blockers other than propranolol	61 (23.5)	27 (44.3)
Gabapentin	55 (21.2)	44 (80.0)
Topiramate	50 (19.2)	29 (58.0)
Carbonic anhydrase inhibitors	19 (7.3)	15 (78.9)
Sodium oxybate	16 (6.2)	8 (50.0)
Levetiracetam	16 (6.2)	11 (68.7)
Levodopa-carbidopa	13 (5.0)	11 (84.6)
Mirtazapine	9 (3.5)	7 (77.8)
Pregabalin	8 (3.1)	5 (62.5)
Amantadine	8 (3.1)	5 (62.5)
Calcium channel blockers	7 (2.7)	4 (57.1)
Trihexyphenidyl	7 (2.7)	5 (71.4)
Other anticholinergic agents	6 (2.3)	3 (50.0)
Zonisamide	6 (2.3)	2 (33.3)
Dopamine agonists	5 (1.9)	4 (80.0)

Values are proportions (percentages).