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ORIGINAL ARTICLE

Treatment patterns in essential tremor: Real-world evidence from a United Kingdom and France primary care database

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Abstract

Background and purpose: Essential tremor (ET) is one of the most common neurological disorders, but information on treatment pattern is still scant. The aim of this study was to describe the demographic and clinical characteristics, treatment patterns, and determinants of drug use in patients with newly diagnosed ET in France and the United Kingdom.

Methods: Incident cases of ET diagnosed between January 1, 2015 and December 31, 2018 with 2 years of follow-up were identified by using The Health Improvement Network (THIN®) general practice database. During the follow-up, we assessed the daily prevalence of use and potential switches from first-line to second-line treatment or other lines of treatment. Logistic regression models were conducted to assess the effect of demographic and clinical characteristics on the likelihood of receiving ET treatment.

Results: A total of 2957 and 3249 patients were selected in the United Kingdom and France, respectively. Among ET patients, drug use increased from 12 months to 1 month prior the date of index diagnosis (ID). After ID, nearly 40% of patients received at least one ET treatment, but during follow-up drug use decreased and at the end of the follow-up approximately 20% of patients were still on treatment. Among treated patients, ≤10% maintained the same treatment throughout the entire follow-up, nearly 20% switched, and 40%–75% interrupted any treatment. Results from the multivariate analysis revealed that, both in France and the United Kingdom, patients receiving multiple concomitant therapies and affected by psychiatric conditions were more likely to receive an ET medication.

Conclusion: This study shows that ET is an undertreated disease with a lower-than-expected number of patients receiving and maintaining pharmacological treatment. Misclassification of ET diagnosis should be acknowledged; thus, results require cautious interpretation.

KEYWORDS
essential tremor, France, THIN database, treatment, United Kingdom

INTRODUCTION

Essential tremor (ET), primarily characterized by an uncontrolled rhythmic oscillation of agonist and antagonist muscle groups, is one of the most common neurological disorders. ET is characterized by isolated bilateral upper-limb tremor, with or without tremor in other body locations such as the head, larynx, and lower limbs, with a variable frequency inversely related to age [1, 2]. Studies on ET prevalence have indicated marked heterogeneity in their estimates, largely due to variations in the investigated sample (such as age, sex, and ethnicity), case definition, and diagnostic approaches [3]. However, if we limit the observation to the most recent meta-analyses [4, 5], estimated global prevalence ranges from 0.32% to 1.33%, showing a significant increase with advancing age, while mixed evidence exists on potential sex differences.

While traditionally regarded as a benign disorder, ET is actually recognized as a chronic, progressive disease [6]. Generally, in the first phase of the disease, patients may experience mild symptoms characterized by rhythmic shaking, predominantly affecting the upper limb, that do not necessarily require treatment. However, over time, tremor progression may spread to other body segments to severely impair basic daily activities such as eating, writing, personal care, and driving [1, 2, 6]. In this regard, a recent longitudinal study evaluated the temporal progression of ET severity and reported an annual worsening ranging between 3.1% and 12% [7].

Several factors may influence the decision to treat patients with ET, including the severity of symptoms, functional limitations, comorbidities, polytherapy, and patient preferences. However, available medications are few and the number has not grown much over the last decades [8–10]. Furthermore, existing drugs for ET are suboptimal, as many patients do not respond to them, and even those who respond may not experience significant improvements in their daily life [11, 12].

Among the available medications, propranolol and primidone, two front-line interventions, led to symptom relief in up to 50% of treated patients, whereas other drugs such as gabapentin, benzodiazepines and topiramate showed lower efficacy [13–18]. Non-pharmacological treatments, such as thalamotomy and deep brain stimulation, have demonstrated high effectiveness in reducing limb tremor magnitude. However, these interventions are invasive procedures associated with significant risks of side effects [19, 20]; therefore, only 3% of patients with ET whose tremors are refractory to pharmacotherapy choose to undergo deep brain stimulation [21].

Despite its limited efficacy, pharmacological therapy remains the main therapeutic approach for treating patients with ET. However, information regarding the overall treatment patterns of ET patients is still scarce, is generally focused on US data, and is limited to small samples [8, 22–25]. We therefore conducted a retrospective cohort study aimed at describing the demographic and clinical characteristics of patients with ET, treatment patterns, and potential variables affecting the use of ET medications in two large cohorts of patients from France and the United Kingdom.

METHODS

Data source

The Health Improvement Network (THIN®) is a large standardized European network of databases of fully anonymized electronic medical records collected from general practices that agreed to participate in the network. The database consists of coded information on patient characteristics, drug prescriptions, diagnoses, consultations, diagnostic test results, and referrals to secondary care [26]. Specifically, symptoms and diagnoses are coded according to Read codes in the United Kingdom and according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) in France, whereas drug prescriptions are classified using the Anatomical Therapeutic Chemical (ATC) classification in both countries.

The UK data were collected from approximately 400 general practices, representing approximately 6% of the UK population. Several published reports have demonstrated the representativeness of the collected information in terms of patient demographics, prevalence of chronic conditions, and mortality rates [26, 27]. The French data were retrieved from a pool of approximately 2000 general practitioners (GPs) and were representative of the French population in terms of age, gender, and living area [28].

For each patient, we had access to all diagnoses recorded by GPs, regardless of whether they were the main reason for a visit or were the justification for a therapeutic-diagnostic intervention. The study was approved by the THIN® Scientific Research Committee (SRC) on July 6, 2021 (SRC reference 21–014).

Study population and cohort selection

All patients actively registered in the list of participating GPs both in the United Kingdom and France between January 1, 2015 and December 31, 2018 were considered. Access to a GP is regulated differently in the two countries: in the United Kingdom, GPs take charge of a list of patients and act as gatekeepers for their access to all healthcare services [29], whereas in France patients can choose different GPs as required. Therefore, a subgroup of GPs was identified by the THIN® network as representative of the French population. Based on these considerations, we included all patients recruited in the UK database and only those patients referred to representative GPs in France.

In these two cohorts, all individuals who reported at least one of the following diagnosis codes during the study period were identified: ET (ICD10/France: G25.0); ET and other specified forms of tremor (Read code/UK: F131.00); benign ET (Read code/United Kingdom: F131.00); essential and other specified forms of tremor not otherwise specified (Read code/United Kingdom: F131z00).

In accordance with a previous study [30], to ensure the selection of incident cases, individuals were included only if they had at least 3 years of database history prior to the date of the first coded ET diagnosis (index date [ID]), as well as ≥2 years of follow-up. With this

approach we limited the possibility of including prevalent cases that were diagnosed before the patient joined a practice participating in THIN® because the current ET definition requires the symptoms to persist for at least 3 years before diagnosis. Additionally, ending the observation period by December 31, 2020 at the latest allowed us to mitigate the impact of the COVID-19 pandemic on the diagnostic-therapeutic management of newly diagnosed individuals with ET. Finally, patients with dystonia, ataxia, Parkinson's disease, or parkinsonism diagnosed at any time before the ID were excluded from the selected cohorts.

Covariates

For each selected individual, demographic characteristics such as sex and age were extracted at the date of ET diagnosis (i.e., ID), whereas the presence of comorbidities was investigated prior to the ID. Finally, concomitant drug use, GPs' requests for neurological visits, and lifestyle variables were investigated in the year prior to the ID.

The following clinical domains and corresponding comorbidities were identified: (i) neurological comorbidities (stroke/transient ischemic attack, hearing loss, epilepsy, polyneuropathy, restless leg syndrome); (ii) psychiatric comorbidities (anxiety disorders, depression, schizophrenia, and other psychotic disorders); and (iii) other comorbidities (diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cancer, hyperthyroidism, hyperparathyroidism, chronic kidney disease, liver disease). The Charlson Comorbidity Index value for each patient at the ID was calculated to determine a synthetic score of disability/mortality risk [31–33].

Treatment exposure and outcome assessment

The use of the following therapies was observed between 1 year prior the ID and during follow-up (2 years after ID): propranolol, primidone and topiramate (i.e., first line); gabapentin, alprazolam, zonisamide, olanzapine and clozapine (i.e., second line); clonazepam and nimodipine (i.e., other line of treatment) [11, 12].

The duration of each treatment was calculated by dividing the total quantity of active substance prescribed by the relevant defined daily dose [34, 35]. Then, the exposure to ET treatments was assessed during the observation period, and the daily prevalence of use was estimated. Specifically, the daily prevalence of use was calculated by dividing the number of patients under treatment by the number of patients with ET. The analysis was conducted overall and stratified by line of treatment.

For each patient, treatment patterns were assessed during follow-up at 6, 12, 18, and 24 months after ID. Therefore, at each time point patients were classified as: (i) treated with first-line, second-line or other-line treatment; (ii) poly-treated (i.e., patient treated with multiple lines of treatment); (iii) untreated (i.e., patient with ET diagnosis and with no treatment); and (iv) discontinued (i.e., patient who discontinued/interrupted the treatment). At each time point, the prevalence of patients classified into the four mutually exclusive statuses was estimated.

Statistical analysis

The daily prevalence of ET treatment was reported as a percentage of treated individuals with associated 95% confidence interval (CI). Differences in prevalence of ET drug use between the United Kingdom and France were assessed using Pearson's chi-squared or Fisher's exact tests. Then, treatment patterns were assessed, and Sankey plots were used to illustrate the patient flow during the study period.

Thereafter, demographic and clinical characteristics of treated versus untreated patients were described with means (±SD) or median (interquartile range) for continuous variables, and frequencies (%) for categorical variables. Differences between the groups were assessed using Student's *t*-test, the Mann–Whitney *U*-test, or the Kruskal–Wallis test for continuous variables, and Pearson's chi-squared or Fisher's exact test for categorical variables. Univariable and multivariable logistic regression models were used to assess the effect of study year, and patients' demographic and clinical characteristics on the likelihood of receiving an ET treatment. In the multivariable model, age and sex were included as fixed variables. Additionally, in the model only the variables that showed significant results in the univariable analysis (p value ≤0.05) were included. Results were expressed as odds ratios (ORs) with 95% 95% CIs.

All statistical analyses were performed using R version 4.0.5 (the R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute).

RESULTS

In the United Kingdom, of a total of 3230 patients with ET, 2957 with at least 2 years of follow-up were selected. Similarly, in France, from the initial cohort of 3277 ET patients, 3249 had at least 2 years of follow-up and were included in the final cohort.

Figure 1 shows the prevalence of drug use before and after ET diagnosis. In the pre-diagnosis period, the use of ET-related medications slightly increased as the timeline approached the ET diagnosis, both in the United Kingdom (from 5.72% to 12.68% in the 12 months and 1 month prior the ID, respectively) and France (from 4.74% to 12.74% in 12 months and 1 month prior to the ID, respectively), with no statistically significant differences observed between the countries.

After ET diagnosis, nearly 40% of patients received pharmacological treatment. Specifically, in the United Kingdom, 37.57% received first-line, 5.51% second-line, and 1.08% other lines of treatment. France showed similar patterns, with no statistically significant

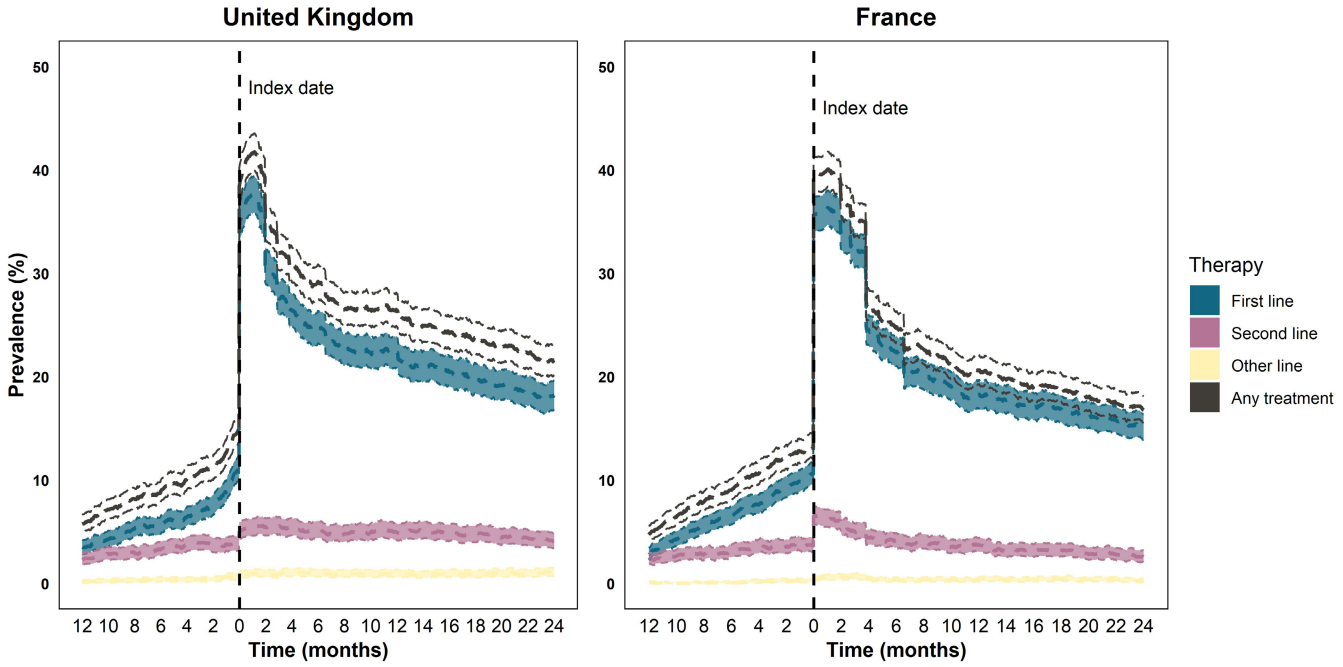

FIGURE 1 Prevalence of treatment lines use in the United Kingdom and France.

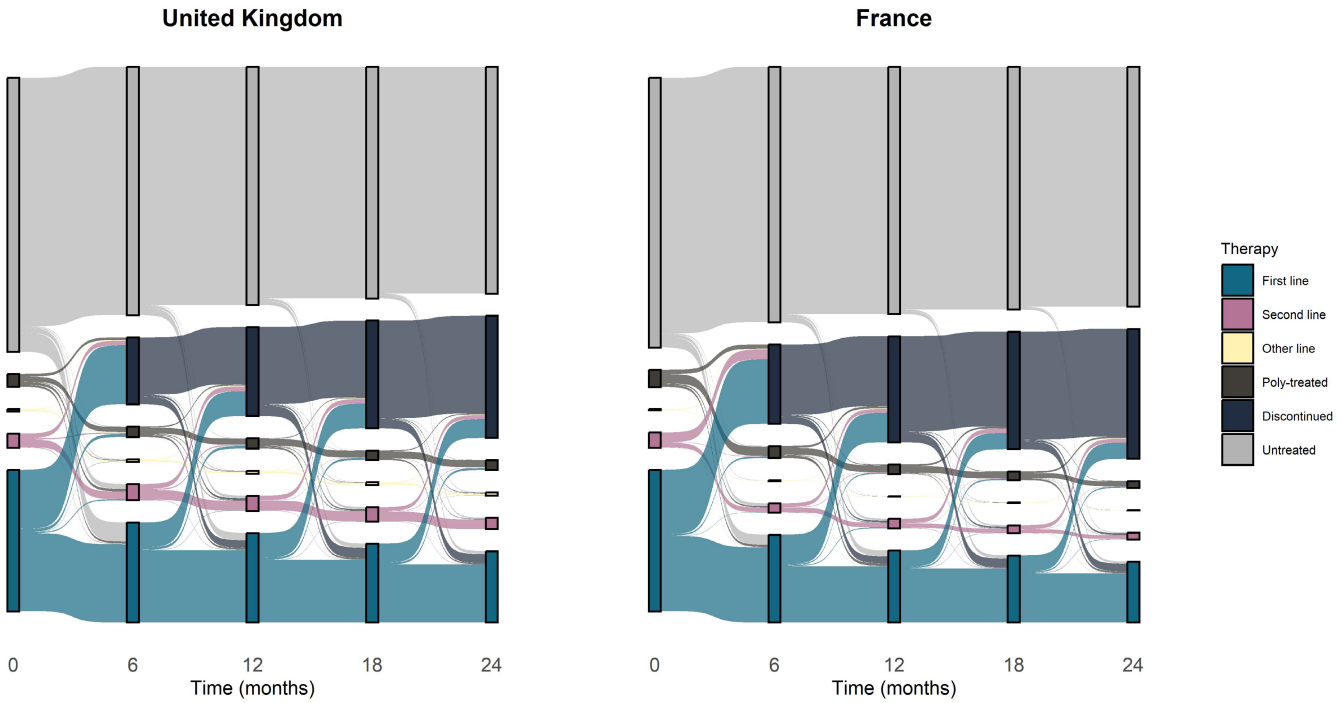

FIGURE 2 Drug utilization patterns among essential tremor patients.

differences being reported: 36.32% were treated with a first-line, 6.49% with a second-line, and 0.62% with other treatments. During follow-up, ET treatment decreased, and after 2 years of follow-up a significantly higher proportion of patients in the United Kingdom were on treatment compared to France (21% vs. 16.81%; p value <0.001). In the United Kingdom, the most prescribed drug was propranolol, followed by primidone and gabapentin, whereas in France, propranolol, alprazolam, and primidone were the most prescribed drugs (Figure A1).

A graphic illustration of treatment flows across the different therapeutic options is provided in Figure 2. In the United Kingdom, the median time from primary diagnosis to the initiation of an ET treatment was 76.6 days. Only 8.89% of patients were continuously treated throughout the entire follow-up, whereas 19.75% showed at least one switch from the initial therapy. On 1136 patients who started treatment (38.4% on total ET), the proportion of patients discontinuing treatment at 6, 12, 18, and

TABLE 1 Demographic and clinical characteristics of selected individuals by treatment status.

	UK		France	
Patient characteristics	**Never treated *N* = 1320**	**Treated *N* = 1637**	**Never treated *N* = 1628**	**Treated *N* = 1621**
Demographic				
Gender: Female, *n* (%)	607 (46.0)	843 (51.5)*	860 (52.8)	892 (55.0)
Age, mean (SD) years	60.5 (20.3)	61 (18.2)	59.8 (21.4)	61.4 (18.8)
Age group, *n* (%)				
0–39 years	224 (17.0)	249 (15.2)*	321 (19.7)	233 (14.4)*
40–65 years	393 (29.8)	557 (34.0)*	464 (28.5)	537 (33.1)*
65+ years	703 (53.3)	831 (50.8)*	843 (51.8)	851 (52.5)*
Calendar year of onset, *n* (%)				
2015	369 (28.0)	446 (27.2)	361 (22.2)	309 (19.1)
2016	354 (26.8)	419 (25.6)	377 (23.2)	395 (24.4)
2017	336 (25.5)	428 (26.1)	446 (27.4)	472 (29.1)
2018	261 (19.8)	344 (21)	444 (27.3)	445 (27.5)
Comorbidities, *n* (%)				
Neurological comorbidities				
Stroke/TIA	35 (2.7)	49 (3.0)	92 (5.7)	95 (5.9)
Hearing loss	180 (13.6)	198 (12.1)	36 (2.2)	49 (3.0)
Epilepsy	30 (2.3)	56 (3.4)	17 (1.0)	33 (2.0)*
Polyneuropathy	37 (2.8)	63 (3.8)	24 (1.5)	38 (2.3)
Restless leg syndrome	25 (1.9)	40 (2.4)	0 (0.0)	0 (0.0)
Psychiatric comorbidities				
Anxiety disorders	216 (16.4)	353 (21.6)*	275 (16.9)	346 (21.3)*
Depression	327 (24.8)	489 (29.9)*	222 (13.6)	343 (21.2)*
Schizophrenia and other psychotic disorders	6 (0.5)	13 (0.8)	1 (0.1%)	2 (0.1)
Other comorbidities				
Diabetes mellitus	197 (14.9)	266 (16.2)	121 (7.4)	130 (8.0)
CVD (MI, HF, PAD)	129 (9.8)	145 (8.9)	154 (9.5)	166 (10.2)
Cancer	96 (7.3)	123 (7.5)	274 (16.8)	316 (19.5)
Hyperthyroidism	13 (1.0)	22 (1.3)	33 (2.0)	31 (1.9)
Hyperparathyroidism	5 (0.4)	8 (0.5)	8 (0.5)	7 (0.4)
Chronic kidney disease	206 (15.6)	284 (17.3)	30 (1.8)	21 (1.3)
Liver disease	12 (0.9)	18 (1.1)	23 (1.4)	22 (1.4)
Charlson Comorbidity				
No disease	567 (43.0)	723 (44.2)	1162 (71.4)	1092 (67.4)*
Mild	485 (36.7)	593 (36.2)	373 (22.9)	448 (27.6)*
Moderate and Severe	268 (20.3)	321 (19.6)	93 (5.7)	81 (5.0)*
Lifestyle and body parameters, *n* (%)				
BMI				
≤24.9 kg/m^2 (Normal range)	375 (32.1)	467 (31.0)	363 (53.2)	296 (42.0)*
25–29.9 kg/m^2 (Overweight)	426 (36.4)	545 (36.2)	200 (29.3)	244 (34.7)*
≥30 kg/m^2 (Obese)	369 (31.5)	493 (32.8)	119 (17.4)	164 (23.3)*
Missing	150 (11.4)	132 (8.1)	945 (58.0)	917 (56.6)

(Continues)

TABLE 1 (Continued)

Patient characteristics	UK		France	
	Never treated $N = 1320$	Treated $N = 1637$	Never treated $N = 1628$	Treated $N = 1621$
Number of concomitant therapies, *n* (%)				
0–4	551 (41.7)	503 (30.7)*	781 (48.0)	398 (24.6)*
5–9	361 (27.3)	475 (29.0)*	373 (22.9)	443 (27.3)*
≥10	408 (30.9)	659 (40.3)*	474 (29.1)	780 (48.1)*
Specialist neurological visits (1 year prior to the index date), *n* (%)	68 (5.2)	89 (5.4)		

Abbreviations: CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

*p value ≤0.05.

24 months was 39.26%, 51.85%, 63.03%, and 71.48%, respectively (Figure 2).

Similar patterns of treatment were observed in France. The median time from diagnosis to treatment was 54.1 days. Moreover, adherence to treatment was similar to that observed in the United Kingdom. In particular, 8.03% were continuously treated within the 2 years of follow-up, and 14.53% had at least one switch of therapy. Furthermore, 45.38% to 74.26% discontinued the treatment during follow-up (Figure 2).

The demographic and clinical characteristics of treated and untreated ET patients are reported in Table 1. We observed a significantly higher proportion of drug use among females, patients with concurrent psychiatric conditions, such as anxiety and depression, and those with multiple concomitant drug treatments (Table 1). This result was confirmed in the multivariable analysis. Specifically, in the United Kingdom, the concomitant use of 5–9 different medicines (1.52; 1.25–1.85) or ≥10 (1.88; 1.55; 2.28) was associated with ET drug use. In France, the presence of depression (1.31; 1.06–1.62), being overweight (1.31; 1.02–1.70) or obese (1.41; 1.05–1.89), and the concomitant use of 5–9 different medicines (2.34; 1.94–2.82) or ≥10 (3.19; 2.66–3.83) were associated with increased probability of receiving an ET prescription (Table 2).

DISCUSSION

This population-based study explored the treatment patterns and the potential variables affecting the use of ET medications in two cohorts of patients with ET in France and the United Kingdom. Our findings indicate that such patients were substantially undertreated at the time of diagnosis and afterwards during follow-up. Additionally, a relevant proportion of patients receiving pharmacological treatment in the first month after diagnosis, mainly based on primidone and propranolol, interrupted this treatment during 2 years of follow-up.

These findings are consistent with previous studies conducted in the United States, which showed that nearly 27% to 44% of ET patients did not receive any specific treatment after diagnosis [22–24]. ET presentation is extremely variable in terms of clinical characteristics, tremor characteristics, and associated signs. Tremor frequency is typically moderate to high (6 to 12 Hz), although there is considerable variability. The type of tremor in ET may vary from a low-amplitude, high-frequency postural tremor of the hands to a much larger amplitude that may be associated with functional disability and other neurological signs [1, 2, 6]. We believe that such heterogeneity in the clinical presentation and severity of ET patients may partially explain our results. In fact, many patients may report symptoms of tremor as mild and opt to delay intervention. Patients might seek medical intervention only when symptoms interfere with activities of daily living or with quality of life.

Among patients starting ET medications after diagnosis, more than 50% discontinued the treatment after 1 year of follow-up and 70% after 2 years. This evidence is in line with two other studies [8, 36] that reported treatment interruption or poor response to treatment in 30% and 50% of cases, respectively, and confirms that a relevant proportion of ET patients initiating first-line therapies (propranolol, primidone) may develop pharmacoresistance when using these drugs in the long term [11–17]. In addition, chronic treatment, especially with propranolol, may lead to the occurrence of adverse events, such as bradycardia, hypotension and breathlessness and it may prompt patients to discontinue or switch to alternative therapeutic options where available [9, 10, 20, 37–40].

It should be also acknowledged, however, that relying on diagnostic codes from GP databases to select incident ET cases might lead to an incorrect diagnosis in approximately 35% to 50% of ET cases, as reported in previous studies [7, 41–44]. This, in turn, might overestimate our results either in terms of undertreatment or in terms of proportion of true ET patients discontinuing the treatment. Individuals diagnosed with ET that are not truly ET patients are in fact less likely to respond to ET medications and more likely to discontinue them.

Study results also indicate that a higher number of concomitant therapies and the presence of psychiatric conditions among ET patients were associated with an increased likelihood of receiving

TABLE 2 Univariable and multivariable model to investigate the association between demographic and clinical characteristics and the probability of being treated in the United Kingdom and France.

	United Kingdom		France	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Demographic				
Gender (Female)	**1.25 (1.08–1.44)**	1.13 (0.97–1.31)	1.09 (0.95–1.25)	1.05 (0.91–1.21)
Age (Mean [SD])				
Age classes				
0–39 yeras	Reference	Reference	Reference	Reference
40–65 years	**1.28 (1.02–1.59)**	1.02 (0.81–1.29)	**1.59 (1.29–1.97)**	1.23 (0.99–1.55)
65+ years	1.06 (0.86–1.31)	0.76 (0.60–0.95)	**1.39 (1.15–1.69)**	0.94 (0.76–1.17)
Calendar year of onset				
2015	Reference	Reference	Reference	Reference
2016	0.98 (0.80–1.19)	0.96 (0.79–1.17)	**1.22 (1.00–1.51)**	1.14 (0.92–1.42)
2017	1.05 (0.86–1.29)	1.04 (0.85–1.27)	**1.24 (1.01–1.51)**	1.18 (0.96–1.45)
2018	1.09 (0.88–1.35)	1.09 (0.88–1.36)	1.17 (0.96–1.43)	1.10 (0.89–1.35)
Comorbidities				
Neurological comorbidities				
Stroke/TIA	1.13 (0.73–1.77)		1.04 (0.77–1.40)	
Hearing loss	0.87 (0.70–1.08)		1.38 (0.89–2.14)	
Epilepsy	1.52 (0.98–2.42)		**1.97 (1.11–3.63)**	1.76 (0.97–3.31)
Polyneuropathy	1.39 (0.92–2.11)		1.60 (0.96–2.72)	
Restless leg syndrome	1.30 (0.79–2.18)			
Psychiatric comorbidities				
Anxiety disorders	**1.41 (1.17–1.70)**	1.21 (0.98–1.49)	**1.34 (1.12–1.59)**	0.88 (0.71–1.08)
Depression	**1.29 (1.10–1.52)**	1.02 (0.84–1.23)	**1.70 (1.41–2.05)**	**1.31 (1.06–1.62)**
Schizophrenia and other psychotic disorders	1.75 (0.69–5.00)		2.01 (0.19–43.28)	
Other comorbidities				
Diabetes mellitus	1.11 (0.91–1.35)		1.09 (0.84–1.41)	
CVD (MI, HF, PAD)	0.90 (0.70–1.15)		1.09 (0.87–1.38)	
Cancer	1.04 (0.79–1.37)		**1.20 (1.00–1.43)**	0.95 (0.78–1.15)
Hyperthyroidism	1.37 (0.70–2.80)		0.94 (0.57–1.55)	
Hyperparathyroidism	1.29 (0.43–4.28)		0.88 (0.31–2.45)	
Chronic kidney disease	1.14 (0.93–1.38)		0.70 (0.39–1.22)	
Liver disease	1.21 (0.59–2.59)		0.96 (0.53–1.73)	
Charlson Comorbidity				
No disease	Reference		Reference	
Mild	0.96 (0.81–1.13)		**1.28 (1.09–1.50)**	
Moderate and Severe	0.94 (0.77–1.14)		0.93 (0.68–1.26)	
Lifestyle and body parameters				
BMI				
≤24.9 kg/m^2 (Normal range)	Reference		Reference	Reference
25–29.9 kg/m^2 (Overweight)	1.03 (0.85–1.24)		**1.50 (1.18–1.91)**	**1.31 (1.02–1.70)**
≥30 kg/m^2 (Obese)	1.07 (0.89–1.30)		**1.69 (1.28–2.24)**	**1.41 (1.05–1.89)**
Missing				

(Continues)

TABLE 2 (Continued)

	United Kingdom		France	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Number of concomitant therapies				
0–4	Reference	Reference	Reference	Reference
5–9	**1.44 (1.20–1.73)**	**1.52 (1.25–1.85)**	**2.33 (1.94–2.80)**	**2.34 (1.94–2.82)**
≥10	**1.77 (1.49–2.10)**	**1.87 (1.54–2.28)**	**3.23 (2.74–3.82)**	**3.19 (2.66–3.83)**
Specialist neurological visits (1 year prior to the index date)	1.06 (0.77–1.47)			

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; TIA, transient ischemic attack.

The bold values indicate significance level is 0.05.

treatments. Patients receiving multiple concomitant medications are in fact likely to be affected by different diseases, which in turn demands a great commitment of healthcare services, including diagnostics, hospital services, and physician visits [45]. It is well known that patients' expectations as well as patient pressure might result in unnecessary prescriptions, referrals, and investigations [46]. Therefore, it is possible to speculate that ET patient pressure might result in medical prescription even when there are doubts about the benefit–risk ratio of these medications.

In addition, it is well known that neurological disorders often result in increased disability and decreased quality of life that might make patients more prone to develop psychiatric conditions and consequently to seek formal medical care for both ET and psychiatric symptom management [47–50]. In this context, the onset of new ET symptoms might encourage patients to receive a new therapy for its management. It is also possible that clinicians may prescribe certain therapies (olanzapine, clozapine, and clonazepam) to manage psychiatric symptoms resulting from the ET, rather than treating ET-specific symptoms.

Strengths of this study include the presence of representative samples of the UK and French populations, making the results generalizable to these whole countries. Furthermore, THIN databases encompass fully anonymous electronic medical records registered from the GPs that have joined the network [26]. This makes the databases a suitable source from which to collect prospectively clinical information on patients attending general practices. Second, THIN databases capture the long-term use of medications and potential confounders, thus preventing exposure misclassification.

Nevertheless, some limitations of this study should be considered. First, as previously mentioned, we used a set of diagnostic codes from GP databases to select incident ET cases rather than employing a population-based design. This approach, on the one hand, might underestimate the true disease burden [7], but on the other hand, might lead to an incorrect diagnosis of ET [7, 41–44]. To avoid these biases, we applied very strict criteria to exclude tremor-related diseases, such as dystonia, ataxia, Parkinson's disease, or parkinsonism. However, even recognizing that data from GP databases are continuously refined to reflect new patient symptoms, clinical information, and specialists' evaluations, as opposed to administrative databases [51], the misdiagnosis of a complex condition such as ET is unlikely to be properly mitigated.

Second, THIN contains medication records based on prescriptions, but it is not known whether the prescribed medications were taken by patients. Nonetheless, a validation study has confirmed that THIN data are effective in producing reliable results in drug patterns, particularly for chronic treatments [52]. Finally, potential differences in case selection might have occurred due to different coding vocabulary used by GPs in the United Kingdom (read code) and those in France (ICD-10). Moreover, differences in the type of registered records as well as the codes used for diagnosis coding might have had an impact on comorbidity prevalence estimates. However, similarities in demographic and clinical characteristics among the study cohorts have been observed, thus supporting the validity and generalizability of our results.

In conclusion, our findings revealed a significant undertreatment of patients with ET, with a substantial proportion of patients either never treated or discontinuing treatment during follow-up. These results require cautious interpretation because of the likelihood of incorrect ET diagnosis. However, they are in line with clinical trials data indicating for first-line therapies, such as propranolol and primidone, a mean efficacy of approximately 50% in terms of tremor reduction. This is particularly concerning because, in patients who do not have an adequate response to pharmacotherapy, ET may significantly impact their quality of life, including difficulties with daily activities and decreased social and occupational functioning. A new generation of pharmacological agents specifically targeted for ET are under investigation. Our results emphasize the need to complete ongoing clinical trials [53, 54] to develop tailored ET treatment and improve patient engagement for better management of this condition.

AUTHOR CONTRIBUTIONS

Ippazio Cosimo Antonazzo, Dennis Valentine, Sara Conti, Carla Fornari, Paolo Angelo Cortesi, Lorenzo Giovanni Mantovani and Giampiero Mazzaglia: study concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis. Davide Rozza, Sara Conti and Carla Fornari: statistical analysis. Caroline Eteve-Pitsaer, Claire Paris, Laurène Gantzer, Dennis Valentine: data extraction. All authors: critical revision of the manuscript for

important intellectual content. The corresponding author attests that all listed authors meet the authorship criteria that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

Ippazio Cosimo Antonazzo, Sara Conti, Davide Rozza, Carla Fornari, Paolo Angelo Cortesi, Caroline Eteve-Pitsaer, Claire Paris, Laurène Gantzer, Dennis Valentine and Giampiero Mazzaglia have no conflicts or financial to disclose. Lorenzo Giovanni Mantovani has no conflict of interest related to the research of this article; Lorenzo Giovanni Mantovani has received grants and personal fees from Bayer AG, Boehringer Ingelheim, Pfizer and Daiichi-Sankyo for advisory board and consultancies.

DATA AVAILABILITY STATEMENT

The data used in the preparation of this article are available from the Cegedim company upon reasonable request (info@the-health-improvement-network.co.uk).

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REFERENCES

1. Reich SG. Essential Tremor. *Med Clin North Am*. 2019;103(2):351-356. doi:10.1016/j.mcna.2018.10.016
2. Haubenberger D, Hallett M. Essential Tremor. *N Engl J Med*. 2018;378(19):1802-1810. doi:10.1056/NEJMcp1707928
3. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord*. 2010;25(5):534-541. doi:10.1002/mds.22838
4. Song P, Zhang Y, Zha M, et al. The global prevalence of essential tremor, with emphasis on age and sex: a meta-analysis. *J Glob Health*. 2021;11:4028. doi:10.7189/jogh.11.04028
5. Louis ED, McCreary M. How common is Essential tremor? Update on the worldwide prevalence of Essential tremor. *Tremor Other Hyperkinet Mov (N Y)*. 2021;9(11):28. doi:10.5334/tohm.632
6. Bhatia KP, Bain P, Bajaj N, et al. Consensus statement on the classification of tremors. from the task force on tremor of the international parkinson and movement disorder society. *Mov Disord*. 2018;33(1):75-87. doi:10.1002/mds.27121
7. Angelini L, Paparella G, De Biase A, et al. Longitudinal study of clinical and neurophysiological features in essential tremor. *Eur J Neurol*. 2023;30(3):631-640. doi:10.1111/ene.15650
8. Louis ED, Rios E, Henchcliffe C. How are we doing with the treatment of essential tremor (ET)?: persistence of patients with ET on medication: data from 528 patients in three settings. *Eur J Neurol*. 2010;17(6):882-884. doi:10.1111/j.1468-1331.2009.02926.x
9. Ferreira JJ, Mestre TA, Lyons KE, et al. MDS evidence-based review of treatments for essential tremor. *Mov Disord*. 2019 Jul;34(7):950-958. doi:10.1002/mds.27700
10. Shanker V. Essential tremor: diagnosis and management. *BMJ*. 2019 Aug;5(366):l4485. doi:10.1136/bmj.l4485
11. Sharma S, Pandey S. Treatment of essential tremor: current status. *Postgrad Med J*. 2020 Feb;96(1132):84-93. doi:10.1136/postgradmedj-2019-136647
12. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol*. 2011;10(2):148-161. doi:10.1016/S1474-4422(10)70322-7
13. Gironell A, Kulisevsky J, Barbanoj M, López-Villegas D, Hernández G, Pascual-Sedano B. A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol*. 1999 Apr;56(4):475-480. doi:10.1001/archneur.56.4.475
14. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology*. 1986 Jan;36(1):121-124. doi:10.1212/wnl.36.1.121
15. Sullivan KL, Hauser RA, Zesiewicz TA. Essential tremor. Epidemiology, diagnosis, and treatment. *Neurologist*. 2004;10(5):250-258. doi:10.1097/01.nrl.0000138736.07840.b2
16. Zappia M, Albanese A, Bruno E, et al. Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian movement disorders association. *J Neurol*. 2013;260(3):714-740. doi:10.1007/s00415-012-6628-x
17. Benito-León J, Louis ED. Clinical update: diagnosis and treatment of essential tremor. *Lancet*. 2007;369(9568):1152-1154. doi:10.1016/S0140-6736(07)60544-3 Erratum in: Lancet 2007 Aug 18;370(9587):566.
18. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology*. 1989;39(12):1587-1588. doi:10.1212/wnl.39.12.1587
19. Zesiewicz TA, Chari A, Jahan I, Miller AM, Sullivan KL. Overview of essential tremor. *Neuropsychiatr Dis Treat*. 2010;6:401-408. doi:10.2147/ndt.s4795
20. Dai D, Samiian A, Fernandes J, Coetzer H. Multiple comorbidities, psychiatric disorders, healthcare resource utilization and costs among adults with Essential tremor: a retrospective observational study in a large US commercially insured and Medicare advantage population. *J Health Econ Outcomes Res*. 2022;9(2):37-46. doi:10.36469/001c.37307
21. Kestenbaum M, Ford B, Louis ED. Estimating the proportion of Essential tremor and Parkinson's disease patients undergoing deep brain stimulation surgery: five-year data from Columbia University medical center (2009-2014). *Mov Disord Clin Pract*. 2015;2(4):384-387. doi:10.1002/mdc3.12185
22. Diaz NL, Louis ED. Survey of medication usage patterns among essential tremor patients: movement disorder specialists vs. general neurologists. *Parkinsonism Relat Disord*. 2010;16(9):604-607. doi:10.1016/j.parkreldis.2010.07.011
23. Shah C, Jackson GR, Sarwar AI, Mandava P, Jamal F. Treatment patterns in Essential tremor: a retrospective analysis. *Tremor Other Hyperkinet Mov (N Y)*. 2022;12:10. doi:10.5334/tohm.682
24. Delgado N, Berry DS, Hernandez DI, Louis ED. Prospective, longitudinal analysis of medication use in a cohort of elderly essential tremor cases. *J Neurol Sci*. 2022;15(442):120387. doi:10.1016/j.jns.2022.120387
25. Gupta HV, Pahwa R, Dowell P, Khosla S, Lyons KE. Exploring essential tremor: results from a large online survey. *Clin Park Relat Disord*. 2021;25(5):100101. doi:10.1016/j.prdoa.2021.100101
26. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the health improvement network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011;19(4):251-255. doi:10.14236/jhi.v19i4.820
27. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol*. 2015;14(1):57-64. doi:10.1016/S1474-4422(14)70287-X
28. Iordache L, Strazzulla A, Lekens B, Bergmann J, Diamantis S. Évaluation du suivi des recommandations de prise en charge des infections urinaires en médecine de ville en France. *Med Malad Infect*. 2018;48:S101-S102.
29. Greenfield G, Foley K, Majeed A. Rethinking primary care's gatekeeper role. *BMJ*. 2016;23(354):i4803. doi:10.1136/bmj.i4803

30. Antonazzo IC, Conti S, Rozza D, et al. Time trends in the incidence of essential tremor: Evidences from UK and France primary care data. *Front Neurol*. 2022;20(13):987618. doi:10.3389/fneur.2022.987618
31. Metcalfe D, Masters J, Delmestri A, et al. Coding algorithms for defining Charlson and Elixhauser co-morbidities in read-coded databases. *BMC Med Res Methodol*. 2019 Jun 6;19(1):115. doi:10.1186/s12874-019-0753-5
32. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson index for read/OXMIS coded databases. *BMC Fam Pract*. 2010 Jan;5(11):1. doi:10.1186/1471-2296-11-1
33. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson comorbidity index: ICD-9 update and ICD-10 translation. *Am Health Drug Benefits*. 2019 Jun-Jul;12(4):188-197.
34. Pazzagli L, Brandt L, Linder M, et al. Methods for constructing treatment episodes and impact on exposure-outcome associations. *Eur J Clin Pharmacol*. 2020;76(2):267-275. doi:10.1007/s00228-019-02780-4
35. Merlo J, Wessling A, Melander A. Comparison of dose standard units for drug utilisation studies. *Eur J Clin Pharmacol*. 1996;50(1–2):27-30. doi:10.1007/s002280050064
36. Lolekha P, Dharmasaroja P, Uransilp N, Sukphulloprat P, Muengtaweepongsa S, Kulkantrakorn K. The differences in clinical characteristics and natural history between essential tremor and essential tremor plus. *Sci Rep*. 2022;12(1):7669. doi:10.1038/s41598-022-11775-8
37. Pasina L, Brucato AL, Falcone C, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging*. 2014;31(4):283-289. doi:10.1007/s40266-014-0163-7
38. Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med*. 2012;28(2):287-300. doi:10.1016/j.cger.2012.01.008
39. Vetterick C, Lyons KE, Matthews LG, Pendal R, Ravina B. The hidden burden of disease and treatment experiences of patients with Essential tremor: a retrospective claims data analysis. *Adv Ther*. 2022;39(12):5546-5567. doi:10.1007/s12325-022-02318-8
40. Huang H, Yang X, Zhao Q, et al. Prevalence and risk factors of depression and anxiety in Essential tremor patients: a cross-sectional study in Southwest China. *Front Neurol*. 2019;10:1194. doi:10.3389/fneur.2019.01194
41. Louis ED. Commentary: time trends in the incidence of essential tremor: Evidences from UK and France primary care data. *Front Neurol*. 2023;14:1136150. doi:10.3389/fneur.2023.1136150
42. Amlang CJ, Trujillo Diaz D, Louis ED. Essential tremor as a "waste basket" diagnosis: diagnosing Essential tremor remains a challenge. *Front Neurol*. 2020;25(11):172. doi:10.3389/fneur.2020.00172
43. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? *Arch Neurol*. 2006;63(8):1100-1104. doi:10.1001/archneur.63.8.1100
44. Louis ED, Applegate LM, Rios E. ICD-9 CM code 333.1 as an identifier of patients with essential tremor: a study of the positive predictive value of this code. *Neuroepidemiology*. 2007;28(3):181-185. doi:10.1159/000104096
45. Buja A, Elvini S, Caberlotto R, et al. Healthcare service usage and costs for elderly patients with obstructive lung disease. *Int J Chron Obstruct Pulmon Dis*. 2020;18(15):3357-3366. doi:10.2147/COPD.S275687
46. Little P, Dorward M, Warner G, Stephens K, Senior J, Moore M. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. *BMJ*. 2004;328(7437):444. doi:10.1136/bmj.38013.644086.7C
47. Gandy M, Karin E, Fogliati VJ, et al. Emotional and cognitive difficulties, help-seeking, and barriers to treatment in neurological disorders. *Rehabil Psychol*. 2018;63(4):563-574. doi:10.1037/rep0000241
48. Fortin M, Bravo G, Hudon C, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res*. 2006;15(1):83-91. doi:10.1007/s11136-005-8661-z
49. Shalash AS, Mohamed H, Mansour AH, et al. Clinical profile of non-motor symptoms in patients with Essential tremor: impact on quality of life and age-related differences. *Tremor Other Hyperkinet Mov (N Y)*. 2019;9. doi:10.7916/tohm.v0.736
50. Lee S, Chung SJ, Shin HW. Neuropsychiatric symptoms and quality of life in patients with adult-onset idiopathic focal dystonia and Essential tremor. *Front Neurol*. 2020;11:1030. doi:10.3389/fneur.2020.01030
51. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: a systematic review. *Br J Gen Pract*. 2010;60(572):e128-e136. doi:10.3399/bjgp10X483562
52. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf*. 2007;16(4):393-401. doi:10.1002/pds.1335
53. Shetty N. Essential tremor-do we have better therapeutics? A review of recent advances and future directions. *Curr Neurol Neurosci Rep*. 2022;22(3):197-208. doi:10.1007/s11910-022-01185-8
54. Louis ED. The pharmacotherapeutic landscape for Essential tremor: quantifying the level of unmet need from a patient and epidemiologic perspective. *Clin Neuropharmacol*. 2022;45(4):99-104. doi:10.1097/WNF.0000000000000509

SUPPORTING INFORMATION

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