SLEEPJ, 2020, 1–11

doi: 10.1093/sleep/zsaa039
Advance Access Publication Date: 12 March 2020
Review

REVIEW

Sleep disorders in essential tremor: systematic review and meta-analysis

Félix Javier Jiménez-Jiménez[1,*], Hortensia Alonso-Navarro[1], Elena García-Martín[2] and José A. G. Agúndez[2]

[1]Section of Neurology, Hospital Universitario del Sureste, Madrid, Spain and [2]University Institute of Molecular Pathology Biomarkers, UNEx. ARADyAL Instituto de Salud Carlos III, Cáceres, Spain

*Corresponding author. Félix Javier Jiménez-Jiménez, C/ Marroquina 14, 3º B, E-28030 Madrid, Spain. Email: fjavier.jimenez@salud.madrid.org; felix.jimenez@sen.es.

Abstract

Sleep disorders are frequent in patients diagnosed with essential tremor (ET). The present review focuses on sleep disorders and the results of polysomnographic studies performed in patients with ET. For this purpose we performed a systematic review crossing the search term "essential tremor" with "sleep," "sleep disorders," "sleep disturbances" and "polysomnography," and with specific sleep disorders, according to the International Classification of the Sleep Disorders—Third Edition, using the PubMed, EMBASE, MEDLINE, and Web of Science Databases. The most frequent sleep problems reported by patients with ET were the bad quality of sleep and excessive daytime somnolence (the latter could be related to drugs commonly used for the treatment of ET). Probable rapid eye movement sleep behavior disorder, coexistent restless legs syndrome, insomnia, and nocturia were not infrequent complaints, while the presence of other sleep disorders in patients with ET was restricted to anecdotal reports or not described. Meta-analyses of previous reports showed that patients with ET (according to the PRISMA and MOOSE guidelines) showed higher scores in the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale than controls and lower scores than those of patients diagnosed with Parkinson's disease. Studies using polysomnography in patients with ET are scarce and do not permit to establish valid conclusions regarding polysomnographic features in this disorder.

Statement of Significance

Reports addressing sleep disorders in essential tremor (ET) are scarce. This review, based on the current literature available, shows that sleep disorders are not infrequent in this disorder, especially poor sleep quality and excessive daytime sleepiness (confirmed by a meta-analysis of previous reports), although the causes have not been established. The coexistence of ET with probable rapid eye movement sleep behavior disorder or restless legs syndrome is not infrequent.

Key words: essential tremor; sleep disorders; insomnia; hypersomnia; restless legs syndrome

Submitted: 2 January, 2020; **Revised:** 19 February, 2020

Introduction

Essential tremor (ET), one of the most prevalent movement disorders, is mainly characterized by the presence of postural and/or kinetic tremor at a frequency of 4–12 Hz that affects predominantly upper limbs, but it can also affect, in a variable number of patients, head, voice, tongue, legs, and trunk [1, 2]. Tremor usually disappears during sleep. Several studies have shown that patients diagnosed with ET show impairment in certain motor tasks suggesting the presence of bradykinesia [3–8]. Recent reports described, besides tremor and motor impairment, the presence of non-motor symptoms in patients with ET, including cognitive impairment, anxiety, depression, fatigue [9–16], personality changes [10, 11, 13, 15], olfactory dysfunction [9–11, 13–15], hearing impairment [10, 11, 13–15], upper airway dysfunction [17], and sleep disturbances [9, 10, 15].

Over the last few years, there has been an increasing interest in the issue of non-motor symptoms in general, and the presence of sleep disturbances in particular, in patients with ET. As Louis [13] stated, the possible role of locus coeruleus in sleep regulation and the description of brainstem Lewy bodies in postmortem studies in patients with ET with a higher frequency than in control brains could be related with the development of sleep disturbances in this disease. Surprisingly, despite the increasing evidence for the presence of sleep disturbances in ET, the most used scales to assess ET severity, such as the Fahn-Tolosa-Marín Tremor Rating Scale, the Bain and Findley Clinical Tremor Rating Scale, and the Washington Heights-Inwood Genetics Study of ET Rating Scale, do not include any score related with sleep [18]. This review focuses on the results of studies addressing sleep features in patients diagnosed with ET, the possible association of specific sleep disorders with ET, and the results of polysomnographic studies performed in patients with this disease.

Methods

Search strategy and criteria for eligibility of studies

We performed a literature search, without language restrictions, using the PubMed, EMBASE, MEDLINE, and Web of Science (main collection) Databases from 1966 to February 11, 2020. The search strategy used, which is summarized in Table 1, retrieved a total of 147 references. These references were examined manually one by one, and those strictly related to the issue of sleep and ET were then selected for this systematic review. Abstracts, duplicates, or overlapping articles were removed. Criteria for eligibility of studies are summarized in Table 1.

Selection of studies and methodology for the meta-analyses

After analyzing the eligible studies for this review, we performed a meta-analysis of those observational studies assessing the quality of sleep or the presence of excessive daytime sleepiness in patients with ET compared with controls and/or with patients having Parkinson's disease (PD). Data extracted for the studies included in the meta-analysis were first author, year of publication, country, study design, and quantitative measures.

Studies assessing the quality of sleep were included if they gave results on the mean ± *SD* scores in the Pittsburgh Sleep Quality Index (PSQI) [20], the frequency of participants with PSQI scores at least 5 (indicating poor quality sleep), or both, in patients with ET compared with those of controls, patients with PD or both groups. Inclusion of studies assessing excessive daytime somnolence required the results of the mean ± *SD* scores in the Epworth Sleepiness Scale (ESS) [21], the frequency of participants with ESS scores at least 10, or both, in patients with ET compared with those of controls, patients with PD or both groups. The risk of bias of included studies was analyzed with

Table 1. Search Strategy and Criteria for Eligibility of Studies for the Review of Sleep Disorders in Patients With Essential Tremor

Identification of the references for this review was done using the PubMed, EMBASE, MEDLINE, and Web of Science (main collection) Databases from 1966 to February 11, 2020. We crossed the search term "essential tremor" with the following search terms (the total number of items found in PubMed, EMBASE, MEDLINE, and Web of Science, respectively, are mentioned in parenthesis): "sleep" (96, 136, 89, and 123 items), "sleep disorders" (81, 22, 65, and 83 items), "sleep disturbances" (51, 39, 21, and 25 items), and "polysomnography" (7, 4, 7, and 1 items), and with each of the specific sleep disorders according to the International Classification of the Sleep Disorders—Third Edition: [19] "insomnia" (8, 7, 10, and 8 items), "sleep breathing disorders" (0, 0, 0, and 1 items), "sleep apnea" (3, 7, 3, and 7 items), "snoring" (0, 0, 0, and 0 items), "hypersomnia" (0, 2, 0, and 1 2 items), "narcolepsy" (3, 4, 2, and 3 items), "Kleine-Levin syndrome" (0, 0, 0, and 0 items), "excessive daytime somnolence" (5, 11, 1, and 1 items), "circadian rhythm sleep disorders" (0, 0, 0, and 0 items), "parasomnia" (27, 2, 1, and 0 items), "somnambulism" (2, 2, 2, and 2 items), "sleepwalking" (2, 1, 1, and 0 items), "sleeptalking" (0, 0, 0, and 0 items), "REM sleep behavior disorder" (15, 23, 14, and 23 items), "isolated sleep paralysis" (0, 0, 0, and 0 items), "nightmare disorder" (0, 0, 1, and 1 items), "sleep enuresis" (0, 0, 0, and 0 items), "restless legs syndrome" (41, 50, 38, and 71items), "periodic limb movements during sleep" (3, 1, 1, and 2 items), "sleep induced bruxism" (0, 0, 0, and 0 items), and "sleep induced myoclonus" (0, 0, 0, and 1 items). We applied the following criteria for eligibility:

Studies assessing the quality of sleep in patients with ET compared with controls, with patients diagnosed with PD, or both (nine studies).

Studies addressing the influence of sleep quality on the risk for ET (one study).

Studies assessing the influence of cognitive status on the quality of sleep of patients with ET (one study).

Studies assessing the presence of excessive daytime sleepiness in patients with ET compared with controls, with patients diagnosed with PD, or both (10 studies).

Studies assessing the influence of cognitive status in the presence of excessive daytime sleepiness in patients with ET (one study).

Studies assessing the frequency of REM sleep behavior disorder (RBD) in patients with ET (12 studies).

Studies comparing the clinical features of patients with ET regarding the presence or absence of RBD (two studies).

Studies assessing the presence of RLS in patients with ET or exploring the relationship between these two disorders (eight studies).

Studies assessing the presence of other sleep disorders associated with ET, which included insomnia (three studies), vivid dreams (three studies), nocturia (three studies), and sleepwalking (one report).

Studies reporting results of polysomnography in patients with ET (three studies).

the Newcastle–Ottawa Scale (all selected studies showed good or fair quality) [22] and the Begg–Mazumdar test [23].

The meta-analyses were carried out with the software Comprehensive Meta-Analysis [24]. We used the Mantel-Haenszel method [25] or the DerSimonian–Laird method [26], depending on the absence or presence of heterogeneity between studies (which was assessed with the Q-statistic and the I^2 metric), and Random Effects [24] to calculate the odds ratios (ORs). Publication bias was assessed by using Duval and Tweedie's trim and fill and Begg and Mazumdar rank correlation as calculated with the software Comprehensive Meta-Analysis [24]. We also calculated statistical power for the pooled samples. For these meta-analyses, we followed the PRISMA (Supplementary Table S1) [27] and MOOSE guidelines (Supplementary Table S2) [28].

Results

Studies assessing the quality of sleep in patients with ET

Nine studies assessed the quality of sleep, using the PSQI, in patients diagnosed with ET compared with controls, with patients having PD, or both [9, 12, 16, 29–34]. Supplementary Figure S1 shows the flowchart for the study selection for the meta-analysis of studies assessing PSQI. Table 2 summarizes the mean ± *SD* scores of these studies. Six of them showed significantly higher scores, therefore a poorer quality of sleep, in patients with ET compared with controls [9, 12, 16, 30, 31, 33], while the other two showed no significant differences [29, 35]. Patients with ET showed significantly lower scores than patients with PD in four studies [29, 30, 32, 35] and similar scores in another one

Table 2. Mean ± *SD* Scores in the PSQI in Patients With ET, PD, RLS, and Controls

Authors, year [reference]	Country	ET patients *N*; Mean ± *SD* (95% CI) PSQI score	Controls *N*; Mean ± *SD* (95% CI) PSQI score	PD patients *N*; Mean ± *SD* (95% CI) PSQI score	ET patients vs controls, OR (95% CI), *p*	ET vs PD patients, OR (95% CI), *p*	Treatment of patients with ET
Chandran et al., 2012 [9]	India	50; 5.9 ± 4.6 (4.62–7.18)	50; 2.6 ± 2.3 (1.96–3.24)	—	5.18 (2.46–10.94), <0.001	—	14 propranolol, 5 benzodiazepines, 1 topiramate, 2 primidone
Gerbin et al., 2012 [35]	United States of America	120; 8.0 ± 3.3 (7.41–8.59)	120; 7.8 ± 2.8(7.3–8.3)	40; 9.9 ± 3.9 (8.69–11.1)	1.13 (0.71–1.78), 0.613	0.37 (0.19–0.71), 0.003	Not specified, but patients with PD had "a higher medication with sleep effects score" than patients with ET and controls
Sengul et al., 2015 [12]	Turkey	45; 6.31 ± 3.30 (5.35–7.27)	35; 3.60 ± 2.04 (2.92–4.28)		5.71 (2.45–13.30), <0.001	—	None of the participants were taking beta-blocking, antiepileptic, antipsychotic, or antidepressant drugs
Lee et al., 2015 [29]*	Korea	60; 5.93 ± 3.99 (4.92–6.94)	22; 5.41 ± 3.45 (3.97–6.85)	30; 6.43 ± 4.26 (4.91–7.95)	1.28 (0.53–3.10), 0.589	0.80 (0.36–1.77), 0.584	Not specified
Barut et al. 2015 [30]†	Turkey	16; 5.87 ± 1.03 (5.37–6.38)	14; 3.78 ± 0.66 (3.43–4.13)	21; 8.86 ± 1.10 (8.39–9.33)	75.07 (13.73–410.52), <0.001	0.01 (0.00–0.03), <0.001	4 beta-blockers plus primidone, 3 beta-blockers, 7 primidone
Chen et al., 2015 [31]	China	62; 6.0 ± 4.0 (5.0–7.0)	60; 4.7 ± 2.5 (4.07–5.33)	62; 7.4 ± 3.7 (6.48–8.32)	2.02 (1.06–3.88), 0.034	0.52 (0.27–0.99), 0.045	Not specified
Louis et al. 2016 [32]‡	United States of America	109; 8.3 ± 5.0 (7.36–9.24)	—	35; 11.0 ± 6.8 (8.75–13.3)	—	0.41 (0.20–0.82), 0.012	Not specified, but patients with ET took nonsignificantly lower number of prescription medications than patients with PD and ET ± PD
Acar and Acar, 2019 [33]	Turkey	40; 6.2 ± 1.9 (5.61–6.79)	38; 2.7 ± 1.7 (2.16–3.24)	—	33.66 (12.68–89.34), <0.001	—	None were taking antiepileptic, antidepressant, or neuroleptic drugs
Shalash et al., 2019 [16]	Egypt	30; 6.1 ± 2.9 (5.06 ± 7.14)	30; 4.4 ± 2.5 (3.51 ± 5.29)	—	3.12 (1.22–8.00), <0.001	—	Not specified
Total series					4.73 (2.02–11.09), <0.001	0.27 (0.11–0.69), 0.006	

*Three with "pure ET," 25 with "cerebellar ET," 12 with ET ± PD.

†This group used the Turkish version of PSQI scale.

‡Patients with ET ± PD (*n* = 27; 8.6 ± 4.5); OR (95% CI), *p* compared with patients having ET = 1.17 (0.52–2.40), 0.776.

[29]. Four of these studies assessed the frequency of PSQI scores at least 5 (indicating poor quality sleep) in patients with ET compared with controls (three of them showed a significantly higher frequency in ET group [9, 12, 33], while another did not reach statistical significance [31]), and one in patients with ET compared with patients having PD (PD patient group showed a nonsignificant trend toward a higher frequency) [31] (Table 3).

We performed a meta-analysis of the eight eligible studies reporting mean ± *SD* PSQI scores in patients with ET (n = 393) compared to controls (n = 339), and of the five studies reporting mean ± *SD* PSQI scores in patients having ET (n = 367) compared with patients having PD (n = 188) (Table 2 and Figure 1, A and B). We also performed a meta-analysis of the four eligible case–control studies reporting frequency or PSQI scores at least 5 in patients with ET (n = 197) and controls (n = 183) (Table 3, Figure 2). The meta-analyses showed that patients with ET had a significantly higher mean ± *SD* PSQI score than that of controls (Table 2, Figure 1, A), while this value was significantly lower than that of patients with PD (Table 2, Figure 1, B). Regarding bias analyses, Supplementary Figure S2, A and B shows the funnel plots for the data shown in Figure 1, A and B, respectively. For Figure 1, A, under the random-effects model, the point estimate (95% confidence intervals [95% CIs]) for the combined studies is 4.73 (2.02 to 11.09), whereas using Trim and Fill the imputed point estimate is 1.82 (0.65 to 5.11). The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.536, p-value (one-tailed) 0.032, p-value (two-tailed) 0.063. This suggests that publication bias might exist. For Figure 1, B, under the random-effects model, the point estimate (95% CI) for the combined studies is 0.271 (0.11–0.69), whereas using Trim and Fill the imputed point estimate does not change. The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ –0.100, p-value (one-tailed) 0.403, p-value (two-tailed) 0.807, thus suggesting the absence of publication bias.

In addition, patients with ET showed a significantly higher frequency of scores in the PSQI at least 5 than controls (Table 3, Figure 2). Supplementary Figure S3 shows the funnel plot for the data shown in Figure 2. Under the random-effects model, the point estimate (95% CI) for the combined studies is 6.79 (2.36 to 19.53), whereas using Trim and Fill the imputed point estimate is 3.29 (1.14 to 9.47). The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.50, p-value (one-tailed) 0.154, p-value (two-tailed) 0.308, thus suggesting the absence of publication bias.

In summary, patients with ET showed a poorer quality of sleep than control individuals, but a better quality of sleep than that of patients with PD.

Benito-León et al. [34] analyzed the influence of the average total sleep duration on the risk for ET in a prospective population-based study of a cohort of 3,303 individuals aged younger than 65 years, followed up during 3.3 years, with 76 incident ET cases. They found an increased risk of developing ET in the subgroup of "short sleepers" (participants sleeping ≤5 h daily) compared with the reference group (participants sleeping 6–8 h daily), with an OR [95% CI] = 2.25 [1.21 to 4.16] (1.95 [1.03 to 3.70] after adjustment for potential confounders), while "long sleepers" (participants sleeping ≥9 h daily) showed a nonsignificant trend toward a decreased risk, with an OR [95% CI] = 0.74 [0.41 to 4.16]. These data suggest a relationship between the poor quality of sleep and the risk for ET. Finally, Rohl et al. [34] showed similar mean ± *SD* PSQI scores and a similar percentage of participants with PSQI scores greater than 5 between patients experiencing ET with normal cognition (n = 65), mild cognitive impairment (n = 16), and dementia (n = 13).

Studies assessing excessive daytime somnolence in patients with ET

Eight studies assessed the presence of excessive daytime somnolence, using the mean ± *SD* ESS scores, in patients diagnosed with ET compared with controls, patients with PD, or both [9, 12, 29–32, 35, 36] (Table 4). The flowchart for the selection of studies is shown in Supplementary Figure S4. In one of these studies, the results were also compared with those of patients with restless legs syndrome (RLS) [36]. The mean ± *SD* ESS scores were significantly higher in patients with ET than in controls in four of these studies [9, 29, 33, 35], while they did not differ significantly between these two groups in other

Table 3. Frequency of Poor Sleep Quality (Scores of PSQI ≥5) in Patients With ET, PD, RLS, and Controls

Authors, year [reference]	Country	ET patients with PSQI ≥5/total ET group (%; 95% CI)	Controls with PSQI ≥5/total control group (%; 95% CI)	PD patients with PSQI ≥5 /total PD group (%; 95% CI)	ET patients vs controls, OR (95% CI), p	ET patients vs PD patients OR (95% CI), p	Treatment of patients with ET
Chandran et al., 2012 [9]	India	23/50 (46; 32.2–59.8)	4/50 (8; 0.5–15.5)	—	9.80 (3.06–31.35), <0.001	—	14 propranolol, 5 benzodiazepines, 1 topiramate, 2 primidone
Sengul et al., 2015 [12]	Turkey	28/45 (62.2; 48.1–76.4)	6/35 (17.1; 4.7–29.6)	—	7.96 (2.74–23.11), <0.001	—	None of the participants were taking beta-blocking, antiepileptic, antipsychotic, or antidepressant drugs
Chen et al., 2015 [31]	China	34/62 (54.8; 42.5–67.2)	23/60 (38.3; 26.0–50.6)	40/62 (64,5; 52.6–76.4)	1.95 (0.95–4.02), 0.069	0.67 (0.32–1.37), 0.273	Not specified
Acar and Acar, 2019 [33]	Turkey	32/40 (80; 67.6–92.4)	7/38 (18.4; 6.1–30.7)	—	17.71 (5.73–54.74), <0.001	—	None were taking antiepileptic, antidepressant, or neuroleptic drugs
Total series				40/62 (64,5; 52.6–76.4)	6.97 (2.36–19.53), <0.001	0.67 (0.32–1.37), 0.273	

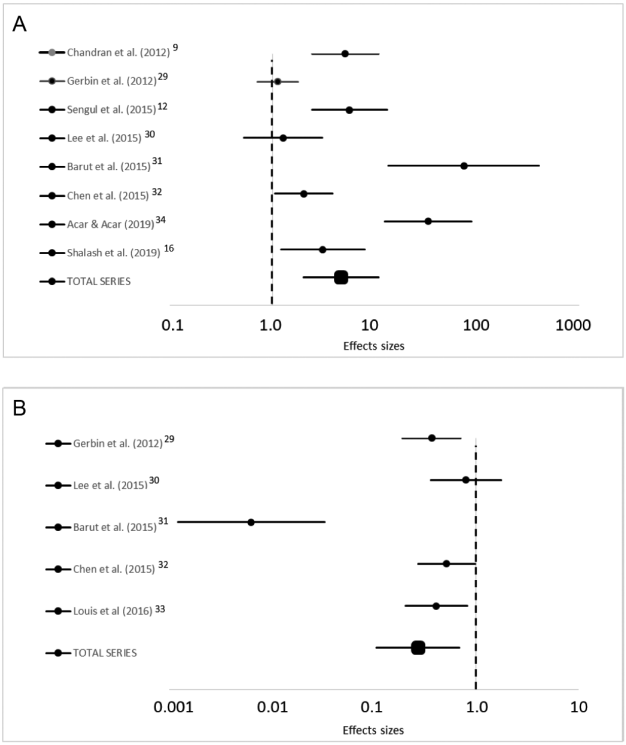

Figure 1. Results of the meta-analysis of studies assessing mean ± *SD* PSQI scores in patients with ET compared to healthy controls (A) and to patients with PD (B).

five studies [12, 30, 36] (Table 4). When compared with patients having PD, patients with ET showed significantly lower mean ± *SD* ESS scores in four studies [30–32, 36], while there were nonsignificant differences in the other two [29, 35] (Table 4). The mean ± *SD* ESS scores were nonsignificantly higher in patients with RLS compared with patients having ET in a single study [36].

Seven studies assessed the frequency of ESS scores at least 10 (indicating excessive daytime sleepiness) in patients with ET compared with controls and/or with patients having PD (Table 5). Two of six studies showed a significantly higher frequency of patients with ET than controls with ESS scores at least 10 (suggesting the presence of excessive daytime somnolence) [31, 35], while the other four did not find significant differences between these two groups [9, 30, 36, 37] (Table 5). When compared with patients having PD, a significantly lower frequency of patients with ET showed ESS scores at least 10 in one study [36], while the other three did not find significant differences [31, 35, 38] (Table 5). The frequency of patients with ET with ESS scores at least 10 was significantly lower than that of patients with RLS in a single study [36].

We performed a meta-analysis of the seven studies comparing mean ± *SD* ESS scores in patients with ET (n = 446) and controls (n = 597) (Table 4, Figure 3, A), and the six studies assessing the mean ± *SD* ESS scores in patients with ET (n = 460) and in patients with PD (n = 248) (Table 4, Figure 3, B). Supplementary Figure S5, A and B shows the funnel plots for the data shown in Figure 3, A and B, respectively. For Figure 3, A, under the random-effects model, the point estimate (95% CI)

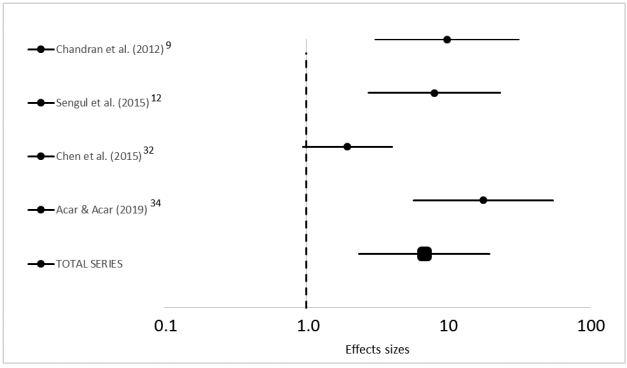

Figure 2. Results of the meta-analysis of studies assessing the frequency of participants with PSQI scores at least 5 in patients with ET compared to healthy controls.

for the combined studies is 3.06 (1.37 to 6.81), whereas using Trim and Fill the imputed point estimate is 1.47 (0.61 to 3.59). The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.48, p-value (one-tailed) 0.066, p-value (two-tailed) 0.133. For Figure 3, B, under the random-effects model, the point estimate (95% CI) for the combined studies is 0.26 (0.12 to 0.58), whereas using Trim and Fill the imputed point estimate and 95% CI are identical. The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.00, p-value (one-tailed) 0.500, p-value (two-tailed) 1.000, thus suggesting the absence of publication bias in Figure 3, A and B.

We also performed a meta-analysis of the six eligible studies reporting the frequency of ESS scores at least 10 in patients with ET (n = 428) and controls (n = 682) (Table 5, Figure 4, A) and of four reporting the frequency of ESS scores at least 10 in patients with ET (n = 297) and patients with PD (n = 193) (Table 5, Figure 4, B). Supplementary Figure S6, A and B shows the funnel plots for the data shown in Figure 4, A and B, respectively. For Figure 4, A, under the random-effects model the point estimate (95% CI) for the combined studies is 1.96 (1.29 to 2.98), whereas using Trim and Fill the imputed point estimate is 1.85 (1.24 to 2.76). The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.00, p-value (one-tailed) 0.500, p-value (two-tailed) 1.000. For Figure 4, B, under the random-effects model, the point estimate (95% CI) for the combined studies is 0.61 (0.22 to 1.64), whereas using Trim and Fill the imputed point estimate and 95% CI are 0.46 (0.17 to 1.19). The Begg and Mazumdar rank correlation (Kendall's tau) with continuity correction is as follows: τ 0.50, p-value (one-tailed) 0.154, p-value (two-tailed) 0.308, thus suggesting the absence of publication bias in Figure 3, A and B.

Patients with ET showed a significantly higher mean ± *SD* ESS scores than those of controls, while significantly lower mean ± *SD* ESS scores than those of patients with PD. The frequency of patients with ET with ESS scores at least 10 was significantly higher than that of controls, while it did not differ significantly from that of patients with PD.

Rohl et al. [39] showed a significantly higher mean ± *SD* ESS scores and a significantly higher frequency ESS scores at least 10 in participants with ET and mild cognitive impairment (n = 16) than in patients with ET and normal cognition (n = 65) and with patients with ET and dementia (n = 13).

Table 4. Mean ± *SD* Scores in the ESS in Patients With ET, PD, RLS, and Controls

Authors, year [reference]	Country	ET patients, *N*; mean ± *SD* (95% CI) ESS score	Controls, *N*; mean ± *SD* (95% CI) ESS score	PD patients, *N*; mean ± *SD* (95% CI) ESS score	ET patients vs controls OR (95% CI), *p*	ET vs PD patients OR (95% CI), *p*	Treatment of patients with ET
Adler et al., 2011 [36]*	United States of America	93; 5.6 ± 3.7 (4.85–6.35)	296; 5.2 ± 3.7 (4.78–5.62)	60; 10.2 ± 5.6 (8.78–11.6)	1.22 (0.80–1.86), 0.363	0.16 (0.09–0.30), <0.001	Not specified
Chandran et al., 2012 [9]	India	50; 4.5 ± 0.6 (4.33–4.67)	50; 3.4 ± 0.5 (3.26–3.54)	—	37.07 (15.53–88.44), <0.001	—	14 propranolol, 5 benzodiazepines, 1 topiramate, 2 primidone
Gerbin et al., 2012 [35]	United States of America	120; 6.8 ± 4.6 (5.98–7.62)	120; 5.7 ± 3.7 (5.04–6.36)	40; 7.8 ± 4.9 (6.28–9.32)	1.61 (1.02–2.56), 0.042	0.68 (0.35–1.30), 0.242	Not specified, but patients with PD had "a higher medication with sleep effects score" than patients with ET and controls
Sengul et al., 2015 [12]	Turkey	45; 5.08 ± 4.44 (3.78–6.38)	35; 5.05 ± 3.22 (5.04–6.36)	—	1.01 (0.46–2.26), 0.973	—	None of the participants were taking beta-blocking, antiepileptic, antipsychotic, or antidepressant drugs
Lee et al., 2015 [29]†	Korea	60; 5.75 ± 3.39 (4.89–6.61)	22; 2.68 ± 2.57 (1.61–3.75)	30; 6.93 ± 5.88 (4.83–9.03)	5.71 (2.27–14.41), <0.001	0.61 (0.28–1.36), 0.229	Not specified
Barut et al., 2015 [30]	Turkey	16; 5.25 ± 1.18 (4.67–5.83)	14; 4.57 ± 0.88 (4.11–5.03)	21; 9.19 ± 1.63 (8.49–9.89)	1.01 (0.46–2.26), 0.973	0.01 (0.00–0.04), <0.001	4 beta-blockers plus primidone, 3 beta-blockers, 7 primidone
Chen et al., 2015 [31]	China	62; 6.3 ± 4.8 (5.11–7.49)	60; 4.4 ± 2.5 (3.77–5.03)	62; 8.2 ± 4.2 (7.15–9.25)	2.45 (1.28–4.71), 0.007	0.47 (0.24–0.89), 0.020	Not specified
Louis et al., 2016 [32] ‡	United States of America	109; 6.5 ± 4.0 (5.75–7.25)	—	35; 8.8 ± 4.9 (7.18–10.4)	—	0.37 (0.19–0.75), 0.006	Not specified, but patients with ET took nonsignificantly lower number of prescription medications than patients with PD and ET + PD
Total series					3.06 (1.37–6.81), 0.006	0.26 (0.12–0.58), 0.001	

*Mean ± *SD*; 95% CI ESS score of patients with RLS (6.96 ± 4.7; 5.48–8.44; *n* = 39) did not differ significantly from that of patients with ET (5.6 ± 3.7; 4.85–6.35; *n* = 93); OR (95% CI) 0.54 (0.27–1.07), *p* = 0.078.

†Three with "pure ET," 25 with "cerebellar ET," 12 with ET + PD.

‡Patients with ET + PD (*n* = 27; 9.7 ± 6.4); OR (95% CI), *p* compared with patients having ET: 3.57 (1.64–7.77), 0.001.

Studies assessing the frequency of probable rapid eye movement sleep behavior disorder in patients with ET

The first reference in the literature regarding the possible association between rapid eye movement (REM) behavior disorder and ET was a study by Adler et al. [36], using the Mayo Sleep Questionnaire, in 307 participants enrolled in a longitudinal clinicopathological study (175 healthy controls, 49 patients with PD, 30 with RLS, and 53 with ET). They assessed the presence of REM sleep behavior disorder (RBD) in the four study groups based on the response to the question: "Have you ever been told that you act out your dreams?", which showed greater than 98% of sensitivity and at least 78% of specificity for confirmed RBD by polysomnography. The frequency of RBD in patients with ET applying this criterion was 13%, which was similar to that of patients with RLS and controls, but significantly lower than that of patients diagnosed with PD (69%). Drugs used for the treatment of ET, PD, and RLS were not specified.

Giorelli et al. [38, 40] reported the "acting out during dreams" (suggesting RBD) in 6 of 22 patients with ET (27.3%) and 18 of 31 patients with PD (58.1%) at baseline, and 3 of 21 patients with ET (14.3%) and 15 of 31 patients with PD (48.4%) after 1 year of follow-up. Barut et al. [30] reported that 0 of 16 patients with ET and 0 of 16 controls (10 years younger) showed RBD by history or had a current diagnosis with RBD, while 8 of 28 patients with PD (28.6%) had RBD by history and 5 of 28 (17.9%) had a current diagnosis with RBD. The frequency of RBD-like symptoms has been reported to be significantly lower in patients with ET than in patients with ET who developed PD (10% vs 51.9%) [41], in patients with ET than in PD-tremor dominant patients (15% vs 47.8%) [42], and in patients with ET who developed PD than in patients diagnosed with idiopathic PD (28% vs 53.2%) [43]. Drugs used for the treatment of ET in these six studies were not specified.

Several recent studies have used the RBD screening questionnaire (RBDSQ) [44] to assess the frequency of RBD in patients with ET. Lacerte et al. [45] described a frequency of 43.5% of RBD in 46 patients with ET, which was significantly higher than the frequency described in the general population (19.4%). In contrast, in a population-based door-to-door screening followed

Table 5. Frequency of Excessive Daytime Somnolence (Scores of ESS ≥10) in Patients With ET, PD, RLS, and Controls

Authors, year [reference]	Country	ET patients with ESS ≥10/ total ET group (%; 95% CI)	Controls with ESS ≥10/total control group (%; 95% CI)	PD patients with ESS ≥10/ total PD group (%; 95% CI)	ET patients vs controls, OR (95% CI), *p*	ET vs PD patients, OR (95% CI), *p*	Treatment of patients with ET
Adler et al.,2011 [36]	United States of America	12/93 (12.9; 6.1–19.7)	34/296 (11.5; 7.9–15.1)	29/60 (48.3; 35.7–61.0)	1.14 (0.57–2.31), 0.712	0.16 (0.072–3.49), <0.001	Not specified
Chandran* et al., 2012 [9]	India	6/50 (12; 3.0–21.0)	5/50 (10; 1.7–18.3)	—	1.23 (0.35–4.32), 0.750	—	14 propranolol, 5 benzodiazepines, 1 topiramate, 2 primidone
Gerbin et al., 2012 [35]	United States of America	27/120 (22.5; 15.0–30.0)	11/120 (9.2; 4.0–14.3)	10/40 (25; 11.6–38.4)	2.88 (1.35–6.11), 0.006	0.87 (0.38–2.01), 0.745	Not specified, but patients with PD had "a higher medication with sleep effects score" than patients with ET and controls
Giorelli et al., 2014 [38]	Italy	4/22 (18.2; 2.1–34.3)	—	3/31 (9.7; –0.7 to 20.1)	—	2.07 (0.42–10.37), 0.374	Not specified
Sengul et al., 2015 [12]	Turkey	6/45 (13.3; 3.4–23.3)	3/35 (8.6; –0.7 to 1.78)	—	1.64 (0.38–7.09), 0.507	—	None of the participants were taking beta-blocking, antiepileptic, antipsychotic, or antidepressant drugs
Chen et al., 2015 [31]	China	16/62 (25.8; 14.9–36.7)	6/60 (10; 2.4–17.6)	20/62 (32.3; 20.6–43.9)	3.13 (1.13–8.66), 0.028	0.73 (0.34–1.59), 0.429	Not specified
Wu et al., 2016 [37]	China	5/58 (8.6; 1.4–5.8)	3/121 (2.5; –0.3 to 5.2)	—	3.71 (0.86–16.1), 0.08	—	Not specified
Total series					1.96 (1.29–2.98), 0.002	0.61 (0.22–1.64), 0.324	

*The frequency of patients having RLS with ESS at least 10 of patients with RLS (12/39; 30.8%; 95% CI = 16.3%–45.3%) was significantly higher than that of patients with ET (12/93: 12.9%; 6.1%–19.7%); OR (95% CI) = 0.33 (0.13–0.83), *p* = 0.018.

by a face-to-face interview to establish the prevalence of ET in Shangai rural area, 1 of 60 patients with ET (1.7%) and 0 of 123 controls showed RBDSQ scores suggesting RBD [37]. Drugs used for the treatment of ET in these two studies were not specified.

Barbosa et al. [46] found RBDSQ score greater than 5 (suggesting RBD) in 14 of 53 patients diagnosed with ET (26.4%). Compared with patients with ET with RBDSQ score not greater than 5, those with RBD greater than 5 showed nonsignificant differences in age, age at onset of ET, duration of ET, positive family history of tremor, and symmetric versus asymmetric onset of tremor. However, patients with RBD showed higher total and thermoregulatory scores in the Scales for Outcomes in Parkinson's Disease—Autonomic questionnaire. A total of 77.4% of patients with ET included in this study were treated with at least one drug (53.6% used primidone, 36.5% propranolol, 14.6% topiramate, 4% gabapentine, and 1% alprazolam and trihexyphenydil).

Finally, Salsone et al. [47] using the RBD Single Question (RBD1Q) [48] reported RBD in 10 of 55 patients with ET (18.2%), which was confirmed by polysomnography. This group also described that compared with patients having ET without RBD, patients with both ET and RBD showed significantly reduced scores in several memory domain tests, while there were no significant differences in tests assessing executive function, attention, language, and visuospatial function. Drugs used for the treatment of ET in this study were not specified.

Studies assessing the frequency of RLS in patients with ET and the relationship between these conditions

The relationship between ET and RLS has been the matter of a recent review [49]. Together with some anecdotal reports of association between ET and RLS, and the coexistence of ET, RLS, and PD in many individuals of a large family, a cross-sectional study found a prevalence of 33% of RLS in patients with ET [50], and a population-based study described RLS symptoms as a part of a non-motor symptoms questionnaire in 16.7% of patients with ET, a frequency that was significantly higher than that found in matched healthy controls [37].

Giorelli et al. [38, 40] described a prevalence of 36.3% of RLS symptoms in 22 patients with ET, which was significantly higher than that found in 31 patients with PD (29.0%), but the differences disappeared after 1 year of follow-up. Ghika et al. [41] reported a frequency of 34.8% of RLS in 121 patients with "pure" ET, which was significantly higher than that found in 54 patients with ET who developed PD (3.7%). In contrast, Kwon et al. [42] described RLS symptoms in 0 of 19 patients with ET and in 4 patients with ET + PD. Barut et al. [30] described the presence of periodic limb movements during sleep in 5 of 16 patients with ET (34.8%) and a similar frequency in 7 of 21 patients with PD (33.3%).

An interesting recent case–control association study involving 200 patients diagnosed with ET and 201 controls found

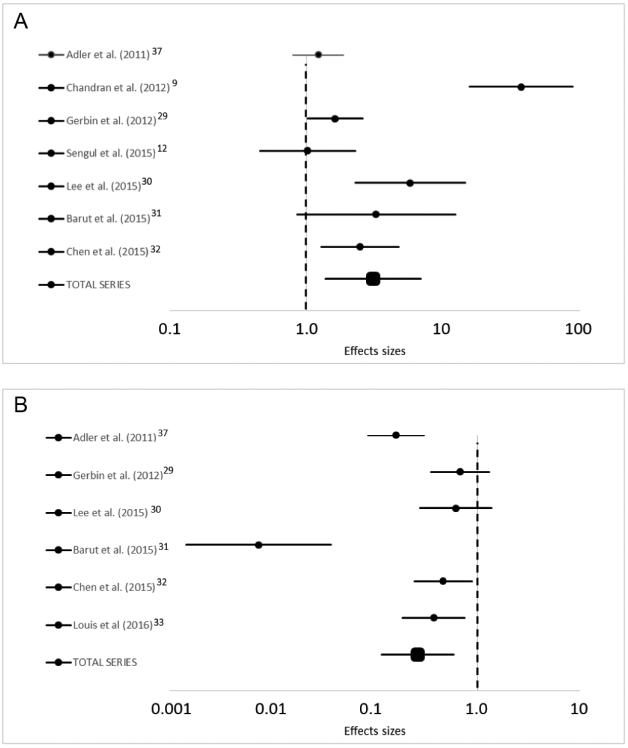

Figure 3. Results of the meta-analysis of studies assessing mean ± *SD* ESS scores in patients with ET compared to healthy controls (A) and to patients with PD (B).

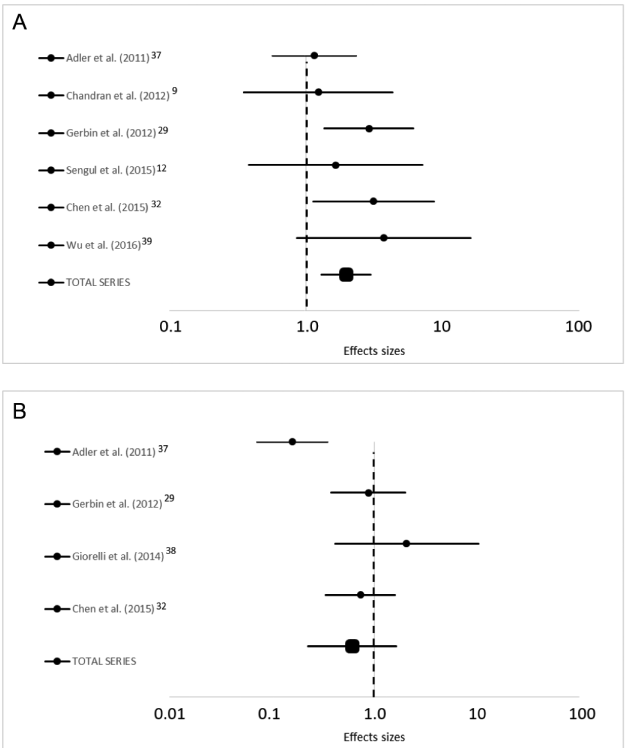

Figure 4. Results of the meta-analysis of studies assessing the frequency of participants with ESS scores at least 10 in patients with ET compared to healthy controls (A) and to patients with PD (B).

an association between a haplotype consisting of five variants in the *MAP2K5/SKOR1* gene (related with the risk for RLS) and the risk for ET [51].

Studies describing other sleep disorders associated with ET

The prevalence of *insomnia* reported in patients diagnosed with ET ranges from 12.5% to 56.6% [30, 37, 38, 40, 42]. Miller et al. [52] described insomnia in 56.6% of 53 patients diagnosed with ET, considering as such the response to a specific item in the Beck Depression Inventory, and being this frequency similar to that reported by patients with PD or primary dystonia. In other series, the frequency of insomnia in patients with ET was not significantly different from that of patients with PD [30, 38, 40, 52], patients with PD-tremor dominant [42], and controls [37].

Giorelli et al. [38, 40] reported *vivid dreams* in 4.5% to 4.8% of patients with ET, while they reported this symptom in 29.0% to 32.2% in patients with PD. Wu et al. [37] reported this sleep symptom in 38.3% patients with ET and 39.8% controls in a door-to-door population (no significant differences); and Kwon et al. [42] reported in 35% of patients with ET and in 60.9% of patients with PD-tremor dominant (however, this difference did not reach statistical significance).

Giorelli et al. [38, 40] reported *nocturia* in 33.3%–50.0% and *urinary urgency* in 38%–54.5% of patients with ET, a frequency that was similar to that found in patients with PD. Kwon et al. [42] reported nocturia in 29.6% of patients with ET and in 34.8% of patients with PD-tremor dominant. Finally, *sleepwalking* has been described as an anecdotal report in a patient with the combination of ET, initial signs of PD, and RBD [53].

Polysomnographic studies in patients with ET

Studies addressing polysomnographic features of patients with ET are scarce. Two studies have used polysomnography to assess the presence of RBD in patients with ET, and both of them confirmed this diagnosis in patients selected by using a single specific question suggesting RBD from the clinical point of view [36, 47].

Barut et al. [30] performed polysomnography in 16 patients with ET and compared the sleep parameters with those of 21 patients with PD and 16 controls. The majority of polysomnographic parameters did not differ significantly between the three groups, although patients with PD showed a trend toward spend a longer time in stage I and to report wake after sleep onset than controls, which disappeared after adjustment for age; and patients with ET showed a significantly lower mean SpO2 than patients with PD. The presence of subclinical RBD (or REM without atonia) confirmed by polysomnography was more frequent in patients with PD than in patients with ET, although the statistical significance disappeared after excluding patients taking serotoninergic antidepressants. This finding was interpreted by the authors because an association between the use of serotoninergic antidepressants and RBD was previously described [54], and more patients with PD than patients with ET of their series were receiving these drugs.

Conclusions

Patients diagnosed with ET show impairment in quality sleep in comparison with control participants, although this is less marked than that found in patients with PD. This finding is supported by the previously described meta-analysis of studies comparing PSQI scores of patients with ET with those of controls and with patients having PD and by the results of a population-based study that showed an increased risk for ET in "short sleepers" [34]. The presence of cognitive impairment showed a lack of influence in sleep quality in patients with ET [36]. However, in many of these studies, the medications used in patients with ET were not specified, and in others, an important part of patients with ET was taking medications commonly used for the treatment of ET, such as beta-blockers, primidone, antiepileptics, or benzodiazepines [55] (Tables 2 and 3). This fact could have any influence on the quality of sleep. It is of note than in the study by Barut et al. [30], the quality of sleep assessed with the PSQI scale was significantly impaired in patients with ET and PD in comparison with controls, while the sleep efficiency index assessed by polysomnography did not differ significantly between the three groups.

Excessive daytime somnolence is a frequent complaint of patients diagnosed with ET as well, although, according to the results of the meta-analysis described in a previous section, it is more marked than in control participants and less marked than that of patients with PD. Differences in excessive daytime somnolence between patients with ET and RLS have been only addressed in the study by Adler et al. [36], who reported a nonsignificant trend toward higher mean ± *SD* ESS scores and a significantly higher frequency of participants with ESS scores at least 10 in patients with RLS than in patients with ET. In this work, the treatment used by patients with ET and RLS was not specified. The causes of this sleep disturbance remain to be determined, although hypothetically it could be related to impairment in the quality of sleep and the high frequency of insomnia and RLS symptoms. In addition, many of the drugs used commonly by patients with ET (Table 1), PD, and RLS (especially dopamine agonists) can induce somnolence, and this fact could influence the results of several of these studies.

The results of studies assessing the frequency of RBD or "RBD-like symptoms" have been widely variable, ranging from 0% to 43.5% [30, 36–38, 40, 43–46]. These differences could be related to the study setting and the inclusion criteria used. When compared with control populations, only one study showed a higher frequency of RBD in patients with ET [44], while the other two did not find significant differences [30, 36]. However, when compared with patients having PD, patients with ET have shown a significantly lower frequency of RBD [30, 36, 38, 40, 42]. In addition, one study showed a higher frequency of RBD in patients with ET who developed PD later [41], while the prevalence of RBD was higher in patients diagnosed with idiopathic PD than in those with ET who later developed PD in another study [43]. The possible coexistence of RBD with ET is difficult to explain from a pathophysiological point of view, since RBD should be likely related with degeneration of glutamatergic neurons from the sublaterodorsal tegmental nucleus glutamatergic neurons and GABAergic or glycinergic from several ventral medullary nuclei [56], and there is not current evidence of affectation of these brain areas in ET [57]. Specific studies performed in patients with coexistent ET and RBD compared with those with "pure" ET should be useful to clarify this question.

The coexistence of RLS with ET has been the matter of only a few studies. In general, there was a trend toward a higher frequency of RLS symptoms in patients with ET than in the general population, and a similar frequency than that found in patients with PD [49]. Similarly to that commented on RBD, the pathophysiological explanation of the coexistence of RLS and ET is difficult. The main pathogenetic hypothesis of RLS is brain iron regional deficiencies (this should be likely the initial event), and dopaminergic dysfunction, with a likely contribution of a hyperglutamatergic state, hypoadenosinergic state, and a deficit in GABA inhibition [58, 59]. The most consistent neurochemical data of ET affect GABAergic and glutamatergic systems, with a lesser contribution of adenosinergic, dopaminergic, and adrenergic systems [57]. Interestingly, both in RLS and in ET have been described alterations in thalamic glutamate: while in RLS patients it has been described an increase the glutamate + glutamine/creatinine concentrations ratio in the right thalamus, that was correlated with several polysomnographic features [59], in ET patients this value it has been reported to be increased in the ventral intermediate nuclei of thalami [57].

Information regarding polysomnographic studies in patients with ET is restricted to a single study with a low sample size [30] and is not enough to reach valid conclusions. To our knowledge, there are no reports published on multiple sleep latency or maintenance of wakefulness tests in patients with ET.

The results of this review have several limitations, such as (1) the relatively small sample size, (2) the low number of studies addressing sleep disorders in patients with ET, (3) the differences in diagnostic criteria for ET used in these studies, (4) the fact that many of the patients included were under specific therapies for ET or PD, (5) the fact that most of these studies were cross-sectional, and probably included patients with ET and PD in different stages of severity, and this could influence the results, and (6) the diagnostic tools used in these studies to investigate sleep quality (PSQI) and excessive daytime sleepiness (ESS) are commonly used but are not specific.

The development in a future of multicentre studies involving an important number of untreated patients diagnosed with ET and healthy age- and sex-matched controls using a protocol which should include an exhaustive questionnaire regarding sleep complaints, and performance of polysomnographic studies when appropriate, should be useful in an attempt to establish the frequency and the aetiology or sleep disorders in ET.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Acknowledgments

We recognize the effort of the personnel of the Library of Hospital Universitario "Príncipe de Asturias," Alcalá de Henares (Madrid, Spain), who retrieved an important number of papers for us.

Funding

The work at the authors' laboratory is supported in part by grants PI15/00303, PI18/00540, and RETICS RD16/0006/0004 from Fondo de Investigación Sanitaria, Instituto de Salud Carlos III,

Spain; and IB16170 and GR18145 from Junta de Extremadura, Spain. Financed in part with Fondo Europeo de Desarrollo Regional (FEDER) from the European Union.

Financial disclosure statement: None of the authors declared any financial conflict of interest.

Nonfinancial disclosure statement. None of the authors declared any nonfinancial conflict of interest.

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