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REVIEW

Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian Movement Disorders Association

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Abstract Essential tremor (ET) is one of the most common movement disorders of adults, characterized by postural and kinetic tremor. It often causes embarrassment and more rarely serious disability, requiring treatment. To assess the current state of knowledge on ET therapy and produce recommendations based on the analysis of evidence the authors reviewed the literature regarding pharmacologic and surgical therapies, providing a quality assessment of the studies and the strength of recommendations for each treatment. A committee of experts selected clinical-based questions to guide the search. A systematic literature review was performed to identify all the studies conducted on patients with ET published until September 2010. Articles were classified according to GRADE evidence profile, a system for grading the quality of evidence and the strength of recommendation based on the quality of the studies. The quality of evidence was often rated as "low" or "very low" for the studies analyzed. Propranolol, long-acting propranolol, primidone, and topiramate are recommended as first-line therapy, with restrictions for their side effects. Arotinolol, sotalol, ICI 118.551 and LI 32.468 (experimental drugs), zonisamide, gabapentin, alprazolam, clozapine, and olanzapine are recommended as a second-line treatment. Botulinum toxin type A and thalamic deep-brain stimulation are recommended for refractory ET. The results highlight the need of well-designed direct comparison trials aimed at evaluating relative effectiveness and safety of the drugs currently used in clinical practice. Furthermore, additional controlled clinical trials are required to define other possible treatment strategies for ameliorating the management of ET.

Keywords Essential tremor · Treatment · Systematic review · Recommendations

On behalf of the Italian Movement Disorders Association (DISMOV-SIN) Essential Tremor Committee.

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Introduction

Essential tremor (ET) is the most common movement disorder with a widely estimated prevalence of 0.4–3.9 % [1] and higher (4.6 %) among people over 65 years of age [2]. It is characterized by a 4–12-Hz postural and kinetic tremor involving the arms and less commonly the head, lower limbs, and voice, frequently accompanied by a family history of a similar tremor. However, ET is a heterogeneous disorder and there is little agreement among specialists regarding both clinical definition and diagnostic criteria [3]. Although benign in term of its effect on life expectancy, it often causes embarrassment and, in a small percentage of patients, also serious disability [4, 5].

Moreover, symptoms are typically progressive and potentially disabling, often forcing patients to change jobs or seek early retirement [6].

The treatment is based primarily on pharmacological agents, although surgical intervention may be an option in the most disabling cases. Pharmacotherapy may be used to improve function or reduce the embarrassment associated with ET, but the management of ET should be tailored to the patient's level of disability. Although primidone and propranolol are well-established treatments in the clinical practice of ET [7], the numerous studies present in literature show weak evidence. Moreover, propranolol and primidone tend to lose efficacy over time and are limited by adverse events (AEs) particularly in elderly persons, often for the interactions with medications commonly used in these patients [8]. Though additional agents may be useful in reducing tremor as anticonvulsants, neuroleptics, antidepressants, and botulinum toxin, to date, these drugs constitute second-line therapies in non-responders [7]. Interestingly, surgical approaches by lesion or deep-brain stimulation in the ventral intermediate nucleus of the thalamus have been reported to be efficacious even in the most severe cases [2, 9]. Nevertheless, the latter alternative is neither widely available nor devoid of AEs.

Despite the elevate frequency of this disorder, there are no published guidelines establishing and regulating its treatment. In 2005, the American Academy of Neurology published the Practice Parameter for Essential Tremor [7], basing the recommendations on an arbitrary four-tiered level of evidence scheme, and concluding that propranolol and primidone should be used as first-line therapy. In a recent update of this guideline, the conclusions on these two treatments appeared unchanged while for other treatments the evidence was considered insufficient to make recommendations [10]. In 2011, another review, based on a newly developed algorithm to compare the magnitude of effect of available treatments, produced similar results [11].

The objective of the present work was the assessment of the current state of knowledge on ET therapy, to evaluate the efficacy of the different treatments and to produce specific recommendations based on analysis of evidence. The work was committed, funded, and coordinated by the Italian Movement Disorders Association affiliated to Italian Neurological Society (DISMOV-SIN).

The committee of experts selected the following key questions to guide the review of the literature: (1) Which are the efficacy and the safety of the different agents? (2) Which treatment could be recommended as first-line therapy? (3) Which as second-line therapy? (4) Which is the best management for each agent (doses, duration of therapy, follow-up)?

Methods

Panel selection

In an attempt to provide a useful guide for neurologists and physicians using a standardized and reliable method, we categorized the studies found into quality categories according to the GRADE evidence profile (http://www.gradeworkinggroup.org/news.htm), a systematic and explicit system for grading the quality of evidence and the strength of recommendation based firstly on the global judgment of the quality of each study.

The neurologists involved in the study underwent a training course on systematic reviews and on the utilization of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) software. Literature reviews of the different pharmacological classes have been performed by five study groups consisting of at least one senior neurologist expert in movement disorders and two or more junior neurologists of different Italian neurological departments. Two meetings, chaired by a clinical epidemiologist with experience in systematic reviews, were held in order to discuss the results and to clarify all the doubts. Further, a revision committee, composed by senior neurologists expert in movement disorders and not involved in the previous phases, reviewed the final manuscript.

Literature search

A systematic search without language restrictions was conducted to identify all published and unpublished articles relevant to each key question. The electronic searches were conducted on: The Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library), MEDLINE (January 1966–September 2010), EMBASE (January 1988–September 2010), NICE (1999–September 2010). The search strategies for each database were based on the strategy developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules (Appendix 1).

We conducted the following additional searches: screening of reference lists of all available review articles and primary studies found; hand-searching of the references quoted in the recent abstract books of movement disorder society (MDS), European Federation of Neurological Societies (EFNS), European Neurological Society (ENS), American Academy of Neurology (AAN) and American Neurological Association (ANA); contact with corresponding authors of relevant trials or reviewers; contact and inquiry of drug manufactures.

Study selection

All the articles and abstracts fulfilling the following eligibility criteria were included.

Population

Patients with a clinical diagnosis of ET according to the diagnostic criteria proposed by the Tremor Investigation Group in the Consensus Statement of the Movement Disorder Society on Tremor [12] or according to other accepted criteria were included [13–15]. Studies including patients with other forms of tremor such as tremor in other neurological conditions (parkinsonian disorders, dystonia, etc.), or thyroid diseases were excluded.

Drugs

We included the following pharmacological and surgical treatments: acetazolamide, amantadine anticholinergics, anticonvulsants, antidepressants, benzodiazepines, beta-blockers, botulinum toxin, calcium channel blockers (CCBs), Catechol-O-methyltransferase inhibitors (COMT-Is), deep-brain stimulation (DBS), dopamine agonists, gamma-knife radiosurgery, isoniazide, levodopa, monoamine oxidase inhibitors (MAO-Is), neuroleptics, and thalamotomy.

Data collection and analysis

We reviewed all randomized controlled trials (RCTs), observational studies, and case series about pharmacological and surgical treatments for ET. Single case reports were excluded from the research; all the other studies were included. Two reviewers independently assessed the eligibility of trials and possible articles of interest by reading the titles and abstracts of all reports identified by the electronic or hand-searching. The full copies of studies were obtained and were independently examined in order to evaluate the possibility to be included. Disagreements between reviewers were solved by consensus.

The following data extracted by the reviewers were recorded in an ad hoc-created collecting form according to methods set out in the Cochrane reviewer's handbook [16]: methods (study design, total study duration, allocation concealment, blinding); participants (number, setting, diagnostic criteria, age, and sex); interventions (number, doses, duration of treatment, length of follow-up); outcome measures; results (summary data, lost to follow-up, AEs).

Each group independently judged trial quality according to GRADE evidence profile [17].

Outcomes

To assess efficacy and safety, we classified the outcome measures into three different levels, according to GRADE evidence profile: critical, important but not critical and not important. The principal parameter considered as critical was the patient motor dysfunction due to tremor severity measured by validated clinical scales. The most widely used standardized scales are: the Fahn-Tolosa-Marin Tremor rating scale (TRS) [18]; the Unified Tremor Rating Scale (UTRA) [19]; the ADL scale devised by Bain and coworkers [20]; the scale developed by Louis et al. [21]; the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) Rating Scale [22]. Other critical outcome measures were: number of withdrawals and discontinuation of the therapy due to AEs associated with interventions; efficacy measured by quality-of-life validated scales or questionnaires. Outcome measures classified as important but not critical were: frequency of any AE or reactions associated with interventions. Even though GRADE system recommends to consider as surrogate outcome measures the evaluation of intrinsic tremor parameter such as tremor amplitude measured by neurophysiological methods, we have considered these measures of efficacy as important but not critical, referring to the well-known relationship between tremor amplitude and clinical tremor ratings reported in literature [11, 23].

Quality assessment and strength of recommendations

The studies were categorized into four quality categories (high, moderate, low, very low, respectively indicated as A, B, C, and D) according to GRADE evidence profile. The GRADE approach assigns initial ratings of low score to observational studies and high score to RCTs. The very low quality level includes, but is not limited to, studies with critical problems and unsystematic clinical observations such as case reports and case series. This rating may be modified by the sequential judgment of limitations, inconsistency of the results, indirectness of the evidence, imprecise data and presence of publication bias (for a complete description of GRADE methodology see GRADE guideline [17]. We then categorized the strength of recommendations into two levels—strong and weak (respectively indicated as 1 and 2)—considering quality of evidence and balance between desirable an undesirable effects [24]. Notation indicating strength of recommendations and quality of evidence was adapted from a previous study [25] and is reported in Table 1.

Table 1 Grading the strength of recommendations and quality of evidences according to the GRADE system

Notation[a]	Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable effects	Quality of supporting evidence	Implications
1A	Strong recommendation High-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or unbiased observational studies	Recommendations can apply to most patients in most circumstances Further research is unlikely to change our confidence in the estimate effect
1B	Strong recommendation Moderate quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations or strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances Further research is likely to have an important impact on our confidence in the estimate effect and may change it
1C	Strong recommendation Low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least one critical outcome from RCTs with serious flaws, observational studies, or indirect evidence	Recommendation may change when higher-quality evidence becomes available Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change it
1D	Strong recommendation Very low quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least one critical outcome from unsystematic clinical observation or very indirect evidence	Recommendation may change when higher-quality evidence becomes available Any estimate of the effect is very uncertain
2A	Weak recommendation High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or unbiased observational studies	The best action may differ depending on circumstances or patients' or societal views Further research is unlikely to change our confidence in the estimate effect
2B	Weak recommendation Moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations or from unbiased observational studies	Alternative approach likely to be better for some patients under some circumstances Further research is likely to have an important impact on our confidence in the estimate effect and may change it
2C	Weak recommendation Low-quality evidence	Uncertainty in the estimates of desirable and undesirable effects; desirable effects may be closely balanced with undesirable effects	Evidence for at least one critical outcome from RCTs with serious flaws, observational studies, or indirect evidence	Other alternatives may be equally reasonable Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change it
2D	Weak recommendation Very low quality evidence	Major uncertainty in the estimates of desirable and undesirable effects; desirable effects may be closely balanced with undesirable effects	Evidence for at least one critical outcome from unsystematic clinical observation or very indirect evidence	Other alternatives may be equally reasonable Any estimate of the effect is very uncertain

[a] Notation is not a part of GRADE system (adapted from Costa et al. [25])

1 strong recommendation, *2* weak recommendation

A, *B*, *C*, *D* indicate the quality of evidences (respectively high, moderate, low, very low)

Results

We found studies evaluating the following treatments: amantadine, anticonvulsants and benzodiazepines, beta-blockers, botulinum toxin type A (BTXA), neuroleptics, thalamic and subthalamic DBS, thalamotomy. No eligible studies were found for acetazolamide, anticholinergics, antidepressants, CCBs, COMT-Is, dopaminoagonists, gamma-knife, isoniazide, levodopa, MAO-Is.

In the evaluated studies, ET was defined according to different diagnostic criteria, and a large part of them did not specify any diagnostic criteria.

Our systematic review highlighted several issues that made it difficult to draw firm conclusions from the available evidence. In particular, the following methodological limitations were often noted: diagnostic criteria not specified; small sample size; random sequence generation and allocation sequence concealment not reported in the RCTs; blinding methods not specified or absent; lack of baseline characteristics description; drug regimen (dose and frequency) variable between different trials; a carry-over effect underestimated and only first-period data available for the cross-over studies; shortness of follow-up period; absence of absolute data reporting.

Considering surgical treatment, the difficulty of realizing randomized placebo-controlled studies for obvious ethical reasons limited the quality of the studies found.

Furthermore, quality of life, considered as a critical outcome, was usually not assessed.

Thus, according to GRADE quality rating, we rated the evidence for most treatments as low or very low quality.

Beta-blockers

Included studies

Table 2 summarizes the main evidence found. A total of 46 studies were examined (many of them considering more than one beta-blocker). Of these, only five were RCTs, comparing propranolol (PRP) versus placebo [26, 27], metoprolol [28] or clonidine [29] and a long-acting formulation of propranolol (PRP-LA) versus primidone [30]. Considering the other studies analyzed, four were case series [31–34] and the others were cross-over (randomized or not randomized) designs. Evidence from the above-mentioned studies are summarized in Appendix 2.

The majority of these latter studies compared PRP versus placebo [26, 27, 31] or versus different beta-adrenoreceptor antagonists, such as pindolol [35, 36], bufetolol, indenolol, oxprenolol [36], atenolol and sotalol [37, 38], timolol [38], metoprolol [39, 40], LI 32-468 [41], ICI-118.551 [42, 43], arotinolol [44], and PRP-LA [45, 46]. Accelerometer and clinical rating scales were the most frequent outcome measures utilized. Considering PRP, the dosage was 120–240 mg daily divided into three oral administrations, and the most frequent follow-up period ranged from 2 weeks to 1 month.

Efficacy

In the majority of studies, baseline tremor magnitude, amplitude, and clinical scores decreased significantly after treatment with PRP as compared to placebo. However, the size of the clinical response was variable. Even if the comparative data about various beta-blockers are not univocal, they all found that PRP had the most potent antitremor effect. PRP-LA provided similar and in some cases greater improvement than divided doses [45, 46]. Only one cross-over study [44] reported a higher efficacy of arotinolol compared to PRP. Sotalol, ICI 118.551 and LI 32.468 showed an efficacy comparable to PRP [26–28], while a weaker effect was observed for atenolol, metoprolol, timolol, and other beta-blockers (bufetol, indenolol, oxprenolol) [36, 37, 39]. Pindolol showed no efficacy [35].

Considering head and voice tremor, PRP was ineffective on both head [47] and voice tremor [48], while another study showed a good response after a single dose, but not during chronic treatment [49].

Safety

A very low discontinuation rate was observed during PRP treatment. The most common AEs during PRP were hypotension, bradycardia, limb extremities coldness, depression, apathy, dizziness, sleepiness, fatigue, and dryness of mouth. The highest rate of AEs was observed during the long-term PRP-LA therapy. Cases of severe bradycardia and syncope and discontinuation due to a severe skin eruption were observed with PRP-LA [30, 46]. Minor AEs such as vertigo, nausea, tiredness, and loss of concentration, were described during atenolol, metoprolol, timolol, arotinolol, and ICI 118.551. No discontinuations due to severe AEs were reported during treatment with atenolol, metoprolol, sotalol, pindolol, timolol, ICI 118.551, LI 32–468, bufetolol, indenolol, oxprenolol, and nadolol.

Regarding blood pressure, heart and respiratory rate, PRP caused a statistically significant reduction of blood pressure and heart rate (considering in particular standing tachycardia) compared to placebo [26, 37–43, 46, 49–55].

Table 2 Beta-blockers: qualitative evaluation based on the results of the analyzed studies

Drug	Number of studies	Efficacy	Side-effects	Recommendation/evidence
PRP	37			1 C
	4 RCTs [26–29]	+++	↑	
	31 Cross-over [35–55, 81, 87, 157–164]	+++	↑	
	2 Case series [31, 34]	+++	↑	
PRP-LA	4			1 D
	1 RCT [30]	+	↑↑	
	2 Cross-over [45, 46]	+	↑	
	1 Case series [33]	+	↑	
Metoprolol	5			2 D
	1 RCT [28]	++	↔	
	4 Cross-over [39, 40, 165, 166]	+/−	↑	
Atenolol	5			2 D
	5 Cross-over [37–39, 165, 167]	++	↑	
Sotalol	4			2 D
	4 Cross-over [37, 38, 165, 166]	++	↔	
Arotinolol	3			2 D
	2 Cross-over [44, 85]	+++	↑↑	
	1 Case Series [32]	+++	↑	
Pindolol	2			1 D
	2 Cross-over [35, 36]	–	↔	
Timolol	2			2 D
	2 Cross-over [38, 167]	++	↑	
ICI 118.551	2			2 D
	2 Cross-over [42, 43]	+++	↑	
LI 32-468	1			2 D
	1 Cross-over [41]	+++	↔	
Bufetolol	1			2 D
	1 Cross-over [36]	++	↔	
Oxprenolol	1			2 D
	1 Cross-over [36]	++	↔	
Indenolol	1			2 D
	1 Cross-over [36]	++	↔	
Nadolol	1			2 D
	1 Cross-over [168]	++	↔	

PRP propranolol, *PRP-LA* propranolol long-acting, *RCT* randomized controlled trial

+++ Good degree of symptom control

++ Moderate degree of symptom control

+ Limited degree of symptom control

– No symptom control

↑↑↑ Severe side-effects/high discontinuation rate

↑↑ Moderate side-effects/low discontinuation rate

↑ Mild side-effects/very low discontinuation rate

↔ No side-effects

Conclusions and recommendations

In patients with definite ET, clinicians should administer PRP 120–240 mg divided into three doses daily (strong recommendation low quality of evidence, 1C) or, to improve compliance, PRP-LA (strong recommendation very low quality of evidence, 1D). The other beta-blockers should be used as second-line treatments for the very low

Table 3 Anticonvulsants and benzodiazepines: qualitative evaluation based on the results of the analyzed studies

Drug	Number of studies	Efficacy	Side-effects	Recommendation/evidence
Primidone	14			1 C
	3 RCTs [30, 56, 57]	+++	↑↑	
	9 Cross-over [54, 55, 77–83]	+++	↑↑	
	2 Case series [65, 75]	+++	↑	
Topiramate	5			1 B
	1 RCT [58]	+++	↑↑	
	2 Cross-over [76, 84]	+++	↑↑	
	2 Case series [66, 67]	+	↑	
Levetiracetam	6			2 C
	1 RCT [59]	+	↔	
	2 Cross-over [169, 170]	–	↑	
	3 Case series [68–70]	++	Not reported	
Zonisamide	6			2 C
	1 RCT [60]	++	↑↑	
	2 Cross-over [47, 85]	+++	Not reported	
	3 Case series [71–73]	+++	↑	
Gabapentin	4			2 D
	3 Cross-over [164, 171, 172]	++	↑	
	1 Case series [74]	++	Not reported	
Phenobarbital	3			2 D
	3 Cross-over [52, 82, 173]	+	↑↑	
Alprazolam	2			2 D
	1 RCT [61]	Not reported	↔	
	1 Cross-over [83]	+++	↑	
Clonazepam	2			2 D
	1 RCT [62]	+	↑↑↑	
	1 Cross-over [160]	++	Not reported	
Barbiturate T2000	1			2 D
	1 RCT [64]	+	↑↑	
Pregabalin	2			2 D
	1 RCT [63]	–	↑↑	
	1 Cross-over [174]	–	↑↑	
Progabide	2			2 D
	2 Cross-over [175, 176]	–	↔	

RCT randomized controlled trial

+++ Good degree of symptom control

++ Moderate degree of symptom control

+ Limited degree of symptom control

– No symptom control

↑↑↑ Severe side-effects/high discontinuation rate

↑↑ Moderate side-effects/low discontinuation rate

↑ Mild side-effects/very low discontinuation rate

↔ No side-effects

quality of evidence assigned to all the studies (weak recommendation very low quality of evidence, 2D) and considering arotinolol and sotalol the most effective agents. ICI 118.551 and LI 32.468 are experimental drugs that could be used for ET (weak recommendation very low quality of evidence, 2D). Pindolol should not be used considering the lack of efficacy (strong recommendation very low quality of evidence, 1D).

Anticonvulsants and benzodiazepines

Included studies

Table 3 summarizes the main evidence found. Ten of the analyzed studies were RCTs. Three RCTs compared primidone versus PRP-LA [30] or different doses of primidone in the initial phase and in the long-term follow-up [56, 57]. The other studies examined the efficacy versus placebo of topiramate [58], levetiracetam [59], zonisamide [60], alprazolam [61], clonazepam [62], pregabalin [63], and barbiturate T2000 [64]. Considering the other articles analyzed, 11 were case series [65–75] and 26 were cross-over (randomized and non-randomized) trials. Evidence from these studies is summarized in Appendix 3.

Accelerometer and clinical rating scales were the most frequent outcome measures utilized. Considering primidone, the dosage was 250–750 mg daily and the most frequent follow-up period lasted 4–5 weeks. Topiramate was administered at a dosage of 25–400 mg daily and the follow-up periods lasted from 6 [76] to 24 weeks [58].

Efficacy

Considering primidone, in the cross-over studies [54, 55, 77–83] tremor magnitude and amplitude decreased after treatment. One RCT [57] found that primidone at low doses (250 mg) was more effective than primidone at high doses (750 mg) at 1-year follow-up, while no significant difference between the two doses was found at shorter follow-up. A direct comparison [30] of primidone (up to 250 mg/die) with PRP-LA (up to 160 mg/die) did not show any significant difference between the two treatments after 1 year. Considering topiramate, in the RCT and in the cross-over study conducted on the same population, the overall TRS total score and subscales (motor tasks function and functional disabilities) presented a reduction from baseline, with a percentage improvement in overall TRS score of 29–31 % [58, 84].

One cross-over study [76] did not report absolute data and the author just underlined that "no outcome measures improved significantly in the active treatment period as compared with the placebo-control period".

A weak effect was observed for zonisamide, gabapentin, phenobarbital, alprazolam, clonazepam, and barbiturate T2000, while no effect was observed for levetiracetam, progabide, and pregabalin.

Regarding the effect of anticonvulsants on tremor of head or voice, primidone showed a good efficacy on reducing tremor of the head in two studies [79, 81], topiramate showed no improvement on head and voice tremor in a case-series [66], while zonisamide caused a better improvement compared to both PRP [47] and arotinolol [85] in two cross-over studies.

Safety

A high proportion of patients (50 %) reported AEs during primidone treatment with a very high discontinuation mainly due to sedation [56]. AEs seem to be linked to higher doses of primidone [57], especially sedation and drowsiness. No difference was reported in the occurrence of AEs at short-term follow-up (3 weeks) between individuals who received primidone at a low initial dose with gradual titration schedule in suspension formulation and those who received tablets at an higher dosage [56]. Also, the cross-over studies reported a high incidence of AEs, often leading to discontinuation from therapy, ranging from 10 to 50 %. Usually, AEs were more important during the initiation of the therapy (acute AEs: somnolence, confusion, vertigo, nausea, vomiting, ataxia), and subsided thereafter [65, 81].

Considering topiramate, a higher proportion of patients reported AEs during treatment compared with placebo exposure. Discontinuation for AEs ranged from 24 [84] to 31.9 % [58] after topiramate and from 9.5 [58] to 10 % after placebo [84]. The most common AEs were paresthesia, weight loss, taste perversion, upper respiratory tract infection, fatigue, nausea, appetite decrease, memory difficulty, dizziness, somnolence, diarrhea, and headache. Other anticonvulsants showed similar AEs.

Conclusions and recommendations

In patients with definite ET, clinicians should use topiramate at doses of 25–400 mg daily in two administrations (strong recommendation moderate quality of evidence, 1B) or, in alternative, primidone 250–750 mg daily (strong recommendation low quality of evidence, 1C), depending on concurrent medical conditions and potential AEs. Zonisamide (weak recommendation low quality of evidence, 2C) gabapentin and alprazolam (weak recommendation very low quality of evidence, 2D) should be considered as second-line treatments. Phenobarbital and clonazepam should not be used considering that AEs outweigh benefits (weak recommendation very low quality of evidence, 2D). The use of levetiracetam and barbiturate T2000 is not recommended because of the low efficacy (weak recommendation very low quality of evidence, 2D), while pregabalin and progabide are probably ineffective and should not be used (weak recommendation very low quality of evidence, 2D).

Table 4 Neuroleptics: qualitative evaluation based on the results of the analyzed studies

Drug	Number of studies	Efficacy	Side-effects	Recommendation/evidence
Clozapine	2			2 C
	1 Cross-over [86]	+++	↑	
	1 Case series [88]	+++	↑	
Olanzapine	2			2 C
	1 Cross-over [87]	++	↑	
	1 Case series [89]	+	↑	
Quetiapine	1	–		2 D
	1 Case series [90]	–	↑	

+++ Good degree of symptom control

++ Moderate degree of symptom control

+ Limited degree of symptom control

– No symptom control

↑ Mild side-effects/very low discontinuation rate

Neuroleptics

Included studies

Table 4 summarizes the main evidence found. Typical neuroleptics could induce tremor and extrapyramidal signs, so they are not used in the treatment of ET, whereas atypical neuroleptics give less extrapyramidal effects and, on these grounds, five articles examined the efficacy of atypical neuroleptics for the treatment of ET. One randomized, placebo-controlled, double-blind cross-over study examined the short-term efficacy and safety of clozapine for ET, while the long-term effects were examined in an open-label extension of the trial [86]. One cross-over study analyzed the efficacy and safety of olanzapine versus PRP [87]. Three case series examined the efficacy of clozapine [88], olanzapine [89], and quetiapine [90]. Evidence from these studies are summarized in Appendix 4.

The studies used different efficacy outcome measures. Clinical rating scales were the most frequent measures used [86, 87, 89, 90], but self-assessment [87, 89] and accelerometer [88] measures were also reported.

Efficacy

Acute administration of 12.5 mg of clozapine induced a significant improvement (more than 50 %) of tremor compared to baseline measures in 13/15 patients. This improvement was maintained in all 13 patients who entered the extension phase of the trial for a mean duration of 15.8 ± 7.7 months [86]. The case series about clozapine demonstrated approximately a 45 % reduction in tremor amplitude [88]. In the case series about olanzapine, the median tremor score decreased significantly after 2 months of treatment [89], while the cross-over trial examining olanzapine versus PRP showed that both treatments significantly improved all evaluation measures [87]. The only study examining quetiapine (mean dosage 60 ± 21 mg) found no differences in pre- and post-treatment conditions [90].

Safety

Sedation was the only AE reported during the acute administration of clozapine. Nevertheless, it decreased markedly in 6–7 weeks in all patients but one withdrew from the study [86]. No cases of agranulocytosis due to clozapine were reported [86, 88]. Patients treated with olanzapine complained of sedation, weight gain, fatigue, and nausea [87, 89]. Quetiapine frequently caused serious AEs, such as anguish and hallucinations/delusions, and somnolence [90].

Conclusions and recommendations

In patients with defined ET, clozapine should be used as second-line treatment (weak recommendation low quality of evidence, 2C) due to the well-known risk of important AEs (such as agranulocytosis), even if the analyzed studies reported only mild AEs. Olanzapine probably reduces tremor (weak recommendation low quality of evidence, 2C), while quetiapine is probably ineffective and should not be used (weak recommendation very low quality of evidence, 2D).

Amantadine

Included studies

Table 5 summarizes the main evidence found. We found only three studies examining the efficacy and safety of

Table 5 Amantadine: qualitative evaluation based on the results of the analyzed studies

Number of studies	Efficacy	Side-effects	Recommendation/ evidence
3			1 D
1 Cross-over [91]	–	↑	
2 Case series [92, 93]	–	↔	

– No symptom control

↑ Mild side-effects/very low discontinuation rate

↔ No side-effects

amantadine in ET: a cross-over [91] with a double-blind placebo-controlled design and two case series [92, 93]. Evidence from these studies is summarized in Appendix 5.

The cross-over study [91] considered as outcome measures the tremor clinical rating scale (TCRS) score, a slightly modified version of the TRS scale [18], and the score assessed by a self-reported disability scale.

Efficacy

The cross-over study [91] found no significant improvement in any outcome measures for amantadine (100–200 mg daily) compared to placebo after 2 weeks of treatment.

Furthermore, when patients were asked about the treatment course they preferred, none of them chose amantadine.

Safety

Anxiety, nervousness, and an increase in postural tremor were reported by six patients while on amantadine, causing discontinuation. Four patients reported insomnia, two dry mouth, and one blurred vision while on amantadine. No patients reported AEs while on placebo.

Conclusions and recommendations

Amantadine is not recommended for ET treatment (strong recommendation very low quality of evidence, 1D).

Botulinum toxin type A

Included studies

An overall number of nine studies examined the efficacy of botulinum toxin type A (BTXA) for the treatment of ET (Table 6); given the local administration of this drug, they can be divided into studies addressing BTXA treatment for

Table 6 Botulinum toxin type A: qualitative evaluation based on the results of the analyzed studies

Number of studies	Efficacy	Side-effects	Recommendation/ evidence
9			1 C
2 RCT [94, 95]	++	↑↑	
1 Cross-over [96]	++	↑↑	
6 Case series [97–102]	++	↑↑	

RCT randomized controlled trial

++ Moderate degree of symptom control

↑↑ Moderate side-effects/low discontinuation rate

ET of the hand [94, 95], ET of the head [96], and ET of the voice [97]. Two studies were placebo-controlled trials [94, 95], one [96] a cross-over placebo-controlled study, and six were open-label studies [97–102], of which one [97] with a cross-over design. The cross-over open-label study [97] compared bilateral versus unilateral BTXA injections into the vocalis muscles in patients with voice tremor. Evidence from these studies is summarized in Appendix 6.

The studies used different efficacy outcome measures. Clinical tremor severity rating scales were the most frequent measures utilized [94, 96–99, 101], but accelerometer measures [98, 99, 101] and functional/disability scales or motor task scores [94, 95, 100, 102] were also reported. The follow-up period was different between studies, from a minimum of 6 weeks [101] to a maximum of 5 months [98].

Efficacy

ET of the hand RCTs [94, 95] reported a mild improvement of postural tremor, compared to placebo (infusion of normal control saline), which was not statistically different between low- and high-dose experimental arms [95]; the improvement on kinetic tremor was smaller. Motor task scores were measured using the UTRA scale. The results were slightly discrepant across the two RCTs, which, overall, found significant effects of BTXA on several motor tasks, although these outcome data were not sufficiently detailed in either of the two studies. The same criticism concerning outcome data presentation raised for motor tasks applies also to the report of changes on functional activities sub-scores. Overall, there was an improvement at the lower tested dose of BTXA of a few functional activities, which was however consistent across the two RCTs only for feeding. The comparison between different doses [95] showed that a larger number of activities could be improved by a higher dose of BTXA, and that such improvement, for some activities, could last

longer (up to 16 weeks for drinking, writing, and fine movements). In the open-label studies [98–101], magnitude and amplitude of hands tremor decreased from baseline after treatment with BTXA until mean of 9 weeks duration of follow-up.

ET of the head subjective and objective assessment of treatment response yield a judgment of mild-to-moderate improvement in the BTXA group in the only one cross-over RCT [96]. Similar findings were documented in an open-label study on head ET [99].

ET of the voice in the first of two open-label studies on voice ET [102], subjective evaluations indicated a beneficial effect in 67 % of the patients; perceptual evaluations showed a significant decrease in voice tremor during connected speech; acoustic analysis showed a nearly significant decrease in the fundamental frequency variations and a significant decrease in fundamental frequency during sustained vowel phonation. The results of perceptual evaluation coincide most closely with the subjective judgments. The authors concluded that the treatment was successful in 50–65 % of the patients, depending on the method of evaluation. The second cross-over open-label study [97] compared efficacy of BTXA as either a bilateral 2.5-U or a unilateral 15-U electromyography-guided injection, followed by the alternative injection 16–18 weeks later. A reduction in vocal effort appeared to be coincident with reduction in laryngeal airway resistance after BTXA injection. Using objective acoustic measures, only a small proportion of patients achieved benefit from BTXA injection for ET.

Safety

In the RCTs [94, 95], weakness of the injected muscles was a common AE of BTXA, but not of the placebo. In the two studies on hand ET [94, 95], hand weakness ranged between 30 % on the low BTXA dose, and 70 % on the high-dose. Other AEs (pain at injection site, stiffness, cramping, rash, hematoma, and paresthesias) were overall slightly more frequent in patients treated with BTXA (at any dose) than in placebo-treated patients [95], but none of these was significantly different in frequency between treatment arms. Other AEs were overall more frequent in BTXA-treated patients also in the cross-over study [96]. A similar range of frequency of muscle weakness was documented in open-label studies on hand and head ET.

Conclusion and recommendations

Available results provide evidence of mild-to-moderate efficacy of low-dose BTXA injection in the forearm muscles of patients with hand ET, whereas the presence of methodological limitations in the only cross-over RCT on head ET limits the clinical relevance of the observed mild-to-moderate treatment response. Muscle weakness is observed in 30–70 % of treated patients, but the exact impact of this AE on patient global functioning needs further investigation. Therefore, BTXA should be used as secondary treatment in patients with defined limb or head ET refractory to medical therapies (strong recommendation low quality of evidence, 1C), and for voice ET (weak recommendation very low quality of evidence, 2D).

Thalamotomy

Included studies

Stereotaxic operations to produce a localized coagulative lesion within the physiologically identified ventralis intermedius (VIM) nucleus of the thalamus is a procedure used for the treatment of various kinds of tremor. Eleven studies, which examined the efficacy of thalamotomy for the treatment of drug-resistant ET, were included and the main evidence is shown in Table 7. Only one study is a RCT [103], in which thalamotomy was compared with thalamic deep-brain stimulation (DBS). Results of this trial after 5 years' follow-up were also available [104]. Ten observational studies (with at least ten patients treated) were also included [105–114]. Of these, one was a case control series that compared thalamotomy versus thalamic-DBS [105] and nine were uncontrolled studies (clinical series or retrospective cohorts). Gamma-knife thalamotomy was performed in three studies [112–114]. The studies used different efficacy outcome measures: disability scales [103, 104], TRS, and subscores of severity and disability [105]. Evidence from these studies is summarized in Appendix 7.

Efficacy

The RCT [103] reported that thalamic DBS and thalamotomy were equally effective for the suppression of

Table 7 Thalamotomy: qualitative evaluation based on the results of the analyzed studies

Number of studies	Efficacy	Side-effects	Recommendation/ evidence
11			1 C
1 RCT [103, 104]	+++	↑↑↑	
10 Case series [105–114]	+++	↑↑↑	

RCT randomized controlled trial

+++ Good degree of symptom control

↑↑↑ Severe side-effects/high discontinuation rate

drug-resistant ET, but thalamic stimulation results in a greater improvement in function (assessed by Frenchay activity index) 6 months after treatment. After 5 years' follow-up a diminished effect of stimulation was observed in half of the ET patients. Subjective outcome-assessment by the patients was more favorable in the stimulation group [104].

In the case control study [105], no significant differences were found between any efficacy outcome variables (TRS and subscores of severity and disability) comparing thalamotomy to thalamic-DBS at baseline or at follow-up visits. All the uncontrolled studies [105–114] reported improvement of tremor in the majority of patients.

Safety

Thalamotomy had more AEs than thalamic-DBS in the available RCT [103, 104]. In the case control study [105], the immediate surgical complications were reported and they were higher in the thalamotomy group. The authors concluded that DBS of the thalamus should be the procedure of choice for the surgical treatment of ET in most cases [105]. In two uncontrolled studies [110, 113], data on AEs were not available. In the other seven studies [106–109, 111, 112, 114], AEs were reported in the 24.4 % of patients and determined permanent disorders in 5.6 % of patients.

Conclusion and recommendations

In patients with limb ET refractory to medical therapies, unilateral VIM-thalamotomy should not be used considering that the risk of AEs outweighs benefits (strong recommendation low quality of evidence, 1C).

Deep-brain stimulation

Included studies

Thirty-seven studies analyzing thalamic DBS were considered. Only the RCT [103, 104] with direct comparison of thalamotomy with DBS was available. The other 36 studies were case series [105, 115–150]. Two studies written in German [151, 152] were not considered in this review.

Two studies considering subthalamic nucleus (STN) stimulation were included [153, 154], in which DBS comparison between thalamic and STN was made at short- and long-term follow-up. The main evidence found is summarized in Table 8.

The RCT compared thalamic-DBS and thalamotomy efficacy at short, medium, and long-term follow-up. Some of the case series studies used each patient as his own control comparing the 'on' and 'off' status with baseline status before surgery; one study [117] used a cross-over procedure (switch to on–off) after 6–7 years of follow-up. Almost all studies were single-blind (the evaluator), and two studies [117, 124] were double-blind. Almost all studies examined unilateral placement, but two [116, 119], which compared unilateral and bilateral electrode placement. The follow-up period varied from a minimum of 3 months to a maximum of 7 years. In some studies [116, 118, 121, 123, 124], an open phase followed blinded assessment of outcome.

Considering the 'open' observational studies, the majority of them were retrospective. Two studies [127, 137] compared on–off stimulation with baseline; another study [105] compared thalamotomy and thalamic-DBS in an open-label study. The follow-up varied from 1 month to 7 years. Evidence from these studies is reported in Appendix 8.

Table 8 Deep-brain stimulation: qualitative evaluation based on the results of the analyzed studies

	Number of studies	Efficacy	Side-effects	Recommendation/evidence
Thalamic DBS	37			1 C
	1 RCT [103, 104]	+++	↑↑↑	
	36 Case series [105, 115–150]	+++	↑↑	
Subthalamic nucleus DBS	2			2 D
	2 Case series [153, 154]	+++	↔	

RCT randomized controlled trial, *DBS* deep-brain stimulation

+++ Good degree of symptom control

↑↑↑ Severe side-effects/high discontinuation rate

↑↑ Moderate side-effects/low discontinuation rate

↔ No side-effects

As a primary outcome, the majority of the studies reported TRS (total score and subscales) and ADL, while only the RCT reported the Frenchay activity index [103].

Efficacy

One RCT [103, 104] reported that thalamic-DBS and thalamotomy significantly improved disability after 6 months, with superiority of thalamic-DBS. Considering thalamic-DBS, others studies [116, 124] also reported significant disability reduction in the 'on state', with a tremor reduction after bilateral implant compared with unilateral implant [105]. Another study [118] reported significant tremor reduction on contralateral side as respect to the side of surgery, while no change in voice, head, and ipsilateral tremor was noted. Otherwise, it has been reported [119] mild ipsilateral reduction of tremor and also reduction of head tremor after one side implant, with additional significant appendicular (blinded evaluation) and head tremor reduction (only in open label) after second implant at 3-month evaluation. The effects were long-lasting with reported significant tremor reduction at 2 and 6–7 years of follow-up [117]. Considering tremor of hand, a significant reduction was observed at a short [124] and long-term [123] follow-up, while considering head tremor a significant reduction was reported at 3, 6, and 12 months [121]. Also, the unblinded studies reported a significant tremor reduction on contralateral upper limb, with effect reduction over 7 years of follow-up [137].

Regarding STN-DBS, one case series [154] reported that STN-DBS was more effective than thalamic-DBS in controlling tremor in the long-term treatment of ET (up to 9 years of follow-up). According to this study, STN-DBS was associated with important AEs in patients above the age of 70 years. The efficacy of STN-DBS was also confirmed in another small uncontrolled study [153].

Safety

In the RCT study [103] immediately after surgery, 27.5 % of patients reported paresthesias, 18.5 % reported gait or balance disorder, 11 % dysarthria, and 10.6 % died, but the authors considered all patients together (ET patients and Parkinson's disease patients) and did not consider death as a consequence of surgery, and the cause of death was not clearly explained. Thalamic-DBS had fewer AEs than thalamotomy [105]. Bilateral placement increased AEs, especially dysarthria [119, 132]. Few data were available on the safety of STN-DBS in patients with ET. In the largest study, STN-DBS was associated with important AEs in patients above the age of 70 years. For these patients, the VIM was a preferable target.

Conclusions and recommendations

The difficulty of realizing placebo-controlled studies for obvious ethical reasons limits the quality of studies.

In patients with medically refractory limb ET, unilateral thalamic-DBS is effective for treating contralateral limb tremor (strong recommendation, low quality of evidence, 1C). There are no sufficient data regarding the superiority of bilateral stimulation on reducing tremor. Placement of the second lead is associated with mild midline (head and voice) tremor improvement but, due to lack of controlled studies and serious AEs with bilateral stimulation, bilateral thalamic-DBS should not be used (strong recommendation, low quality of evidence, 1C).

STN-DBS could be a target for long-term treatment of ET even if there is very low quality of evidence to support this treatment (weak recommendation very low quality of evidence, 2D). Moreover, for patients above the age of 70 years, VIM seems to be a preferable target (weak recommendation very low quality of evidence, 2D).

Discussion

The aim of this systematic review of the evidence about treatment of ET was to provide practical answers to the most common clinical questions on the management of ET that physicians can meet during their everyday activity.

We based our work on the use of GRADE system, a method for grading the quality of evidence and the strength of recommendations, created in 2000 by the Grading of Recommendations Assessment, Development and Evaluation Working Group [155]. This method allows a critical appraisal to clinical questions, producing standard judgments that facilitate the comparison of results obtained by different study groups. One of the main advantages of the GRADE system is the possibility to modify the level of evidence assigned to a study considering factors going beyond the study design alone. These factors are represented by standardized judgment formulated on the presence of risk of bias, inconsistency, indirectness, imprecision, and publication bias. This is the main difference between GRADE system and other methods, such as that proposed by the Guideline Standards Scientific Subcommittee of the EFNS [156] and the similar four-tiered classification scheme used by the Quality Standards Subcommittee of the AAN [7] in which only some of these parameters are considered for the assessment of the level of evidence.

Using the above-mentioned system, we often rated the quality of evidence of the studies analyzed as ''low'' or ''very low''. This could have been caused by the inclusion of numerous trials performed in the 1970s and 1980s, when trial design was in its infancy. In fact, in the majority of the studies examined, clinical outcomes were measured by different non-validated or poorly described scales, producing a large heterogeneity in the quantification of tremor and in the assessment of the results; furthermore, the low accuracy of the current diagnostic criteria in the identification of ET cases should be recognized, and thus the consequent inclusion of others forms of tremors rather than ET in numerous studies; finally, critical outcomes such as AEs and quality of life were often poorly or inadequately assessed, making judgments on these aspects difficult.

It was therefore difficult to furnish a clear response to all the clinical questions formulated, making necessary to recur to the judgment of our commission of senior neurologists.

Moreover, this systematic review of the literature had also highlighted a paucity of studies conducted in recent years, aimed at analyzing additional safe and well-tolerated treatment options. For instance, only ten studies [47, 60, 63, 64, 70–73, 84, 170] on pharmacological treatment of ET have been published from 2007 and only seven studies [104, 114, 115, 137–139, 154] have been produced in the same period on surgical treatment. Despite the management of ET is still poorly satisfactory for many patients, the effort of the scientific community and of pharmaceutical companies to promote researches on new treatment options seems to have lowered over the years due to the scarce interest to develop new drugs and to perform expensive clinical trials with adequate methodology on old drugs. On this field, our work has contributed to analyze the presence of very low evidence on which is based the conventional clinical practice.

Which treatment could be recommended as first-line therapy? Which is the best management for each agent (doses, duration of therapy, follow-up)?

As first-line therapies we recommend PRP (120–240 mg), PRP-LA (up to 160 mg), primidone (250–750 mg; strong recommendation low quality of evidence, 1C) and topiramate (25–400 mg; strong recommendation moderate quality of evidence, 1B).

Which are the efficacy and the safety of the different agents?

Primidone and PRP cannot be recommended to some classes of individuals (respectively, young and old people) where they could lead to important AEs (sedation and cardiovascular effects). Considering the limitations in the administration of such agents and that the studies on topiramate presented an adequate methodology (moderate quality of evidence), we should point out a potential role of topiramate in ET treatment, which should deeper investigated. On these grounds, we underline the need of further trials analyzing the efficacy and safety of topiramate compared to PRP and primidone.

Which treatments could be recommended as a second-line therapy?

Even if arotinolol and sotalol showed an efficacy comparable to PRP, they should be considered as a second-line therapy for the low quality of evidence provided. ICI 118.551 and LI 32.468 are experimental drugs demonstrating a good efficacy so that could be recommended as second-line treatments. We also recommend as second-line therapy zonisamide, gabapentin, alprazolam, and clozapine, being aware of the risk of agranulocytosis and olanzapine.

The other pharmacological treatments considered in our review are not recommended in the ET therapy because the weak effect observed and/or the very low quality of evidence assessed.

In patients with definite limb or head ET refractory to medical therapies, BTXA could be considered as secondary treatment. Further trials with a parallel group design (BTXA versus placebo), an adequate sample size and sufficient duration of follow-up are required to better assess the efficacy of BTXA on voice ET.

Considering surgical treatment, a single randomized study with low quality of evidence [103, 104] showed that unilateral thalamic-DBS is more efficacious than thalamotomy with less serious AEs. Thalamic-DBS should therefore be considered for treating contralateral limb tremor in medically refractory limb ET (strong recommendation low quality of evidence, 1C). STN-DBS [154] may be better target for long-term treatment of ET (weak recommendation very low quality of evidence, 2D), but studies are needed for further clarifications.

In conclusion, taken together, all these results highlight the need of well-designed research aimed at obtaining reliable and comparable data on efficacy and safety of the drugs currently used in clinical practice. Furthermore, additional controlled clinical trials are required to define other possible treatment strategies for ameliorating the management of ET.

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Conflicts of interest The authors declare that they have no conflicts of interest.

Appendix 1

See Table 9.

Table 9 MEDLINE search strategy

1. "Clinical trials as topic" (MH)
"Clinical trial, phase IV" (publication type)
"Clinical trial, phase III" (publication type)
"Clinical trial, phase II" (publication type)
"Clinical trial, phase I" (publication type)
"Controlled clinical trial" (publication type)
"Randomized controlled trial" (publication type)
"Clinical trial" (publication type)
"Multicenter studies as topic" (MH)
"Meta-analysis as topic" (MH)
"Clinical trials, phase I as topic" (MH)
"Cross-over studies" (MH)
2. "Trial" (tw)
3. 1 OR 2
4. "Essential tremor" (MH)
5. "Essential tremor" (tw)
6. 4 OR 5
7. 3 OR 6
8. Generic and proprietary names all as MeSH headings and as text words

Appendix 2

See Table 10.

Table 10 Beta-blockers: characteristics of included studies

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
PRP	RCT [26–29]	4	136	More efficacious than placebo in single oral doses (120 mg) [27, 28] and in both medium [26] and long-term [29] follow-up. No differences between PRP and metoprolol [28] or PRP and clonidine [29]	No serious adverse events reported. Pulse rate average decrease: 15 beats per minute [26, 29]. Moderate decrease of blood pressure values. No discontinuation due to side-effects	Low [29] Very low [26–28]
	Cross-over [35–55, 81, 87, 157–164]	31	610	Tremor magnitude reduction of 59.7 % [54] and amplitude up to 72 % [160]. Decrease of tremor assessed by clinical rating scale up to 67 % [158] and improvement of patient's self-assessment [40, 51, 158]. Improvement (92.2 %) of ET assessed by a volumetric method [163]	Bradycardia, malaise, fatigue, nausea, depression, sleepiness. Decrease of pulse rate, standing tachycardia, blood pressure. Low discontinuation rate due to adverse events (usually bradycardia or malaise)	Very low
	Case series [31, 34]	2	30	Clinical and self-assessed tremor improvement was noted after 10 days with excellent improvement in six cases and good improvement in the other six. An increase in daily dosage was required after 3-6 months in order to maintain adequate tremor control [34]	No serious side-effects observed One case of mild nausea and two of vague sense of malaise	Very low
PRP-LA	RCT [30]	1	25	10/25 patients had benefit after 1 year of treatment, 30 % of patients had no improvement. Only 14 % of patients lost effectiveness over a 1-year period	24 % of patients with serious adverse events Acute side-effects in two cases (two discontinuations) Chronic side-effects: fatigue, impotency, bradycardia (four discontinuations)	Very low
	Cross-over [45, 46]	2	41	No significant differences between PRP and PRP-LA. PRP-LA preferred by 87 % of patients for ease of administration and by 67 % for tremor control [45]	A case of discontinuation due to a severe skin eruption [46] Mild adverse events reported (breathless, tiredness, diarrhea, headache, dizziness, depression)	Very low
	Case series [33]	1	40	Clinical tremor improvement after 1 month in most cases (82.5 %) with excellent improvement in 52.5 %	Not reported	Very low
Metoprolol	RCT [28]	1	23	Average decrease of tremor magnitude of 47 % after metoprolol	No adverse events reported Reduction of standing tachycardia similar to that observed after PRP	Very low
	Cross-over [39, 40, 165, 166]	4	81	Weak effect [39, 166] or no significant differences [40, 165] with placebo	No discontinuations. Most common undesirable effects: tiredness, loss of concentration, breathlessness, sedation, depression, blurred vision, sexual difficulty	Very low
Atenolol	Cross-over [37–39, 165, 167]	5	80	Reduction of tremor magnitude inferior to PRP, sotalol and timolol but superior (or equal) to metoprolol	No discontinuations. Vertigo, tiredness	Very low

Table 10 continued

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Sotalol	Cross-over [37, 38, 165, 166]	4	55	More potent than placebo, considering both the response to a single intravenous administration [38] and after a short-term follow-up [37, 165, 166]. As efficacious as PRP [37] and more efficacious than atenolol and metoprolol [37, 165, 166]	No discontinuations No adverse events	Very low
Arotinolol	Cross-over [44, 85]	2	103	Better than PRP with 20 or 30 mg daily dosage for 6 weeks	Moderate discontinuation rate Gastroenteric adverse events, bradycardia, headache	Very low
	Case series [32]	1	15	Subjective and objective improvement in all cases after 2 weeks (90 mg daily) Average reduction in amplitude of postural tremor 43 %	One discontinuation because of asymptomatic bradycardia No neurological side-effects	Very low
Pindolol	Cross-over [35, 36]	2	44	No efficacy compared to placebo [35]; the least efficacious compared to PRP, bufetolol, indenolol, oxprenolol [36]	No adverse events reported	Very low
Timolol	Cross-over [38, 167]	2	25	Effective in reducing ET after 1 week of treatment (5 mg/die). Patients with moderate tremor showed the most uniform and useful effect [167]. A single intravenous timolol dose had an efficacy on ET similar to sotalol, and less than PRP [38]	Vertigo, nausea, weakness [167] Decrease of pulse rate, standing tachycardia, blood pressure No discontinuation reported	Very low
ICI 118.551	Cross-over [42, 43]	2	28	Improvement of tremor intensity up to 40 %. Similar antitremor potency than PRP; more effective than placebo	Mild headache, insomnia, dizziness No significant effect on blood pressure; small but not significant reduction of standing tachycardia [42] and of exercise-induced tachycardia [43]. No discontinuations	Very low
LI 32.468	Cross-over [41]	1	12	Decreased tremor amplitude more than placebo in all dosages but only the effect of the lower dose (2 mg) differed statistically significantly from that of placebo	No discontinuations No adverse events	Very low
Bufetolol	Cross-over [36]	1	20	PRP showed the strongest effect, followed by bufetolol, indenolol, oxprenolol, pindolol	No discontinuations No adverse events	Very low
Indenolol	Cross-over [36]	1	20	PRP showed the strongest effect, followed by bufetolol, indenolol, oxprenolol, pindolol	No discontinuations No adverse events	Very low
Oxprenolol	Cross-over [36]	1	20	PRP showed the strongest effect, followed by bufetolol, indenolol, oxprenolol, pindolol	No discontinuations No adverse events	Very low
Nadolol	Cross-over [168]	1	10	Significant reduction of tremor assessed by a four-rate clinical scale and by accelerometer	No discontinuations No adverse events	Very low

ET essential tremor, *PRP* propranolol, *PRP-LA* propranolol long-acting, *RCT* randomized controlled trial

Appendix 3

See Table 11.

Table 11 Anticonvulsants and benzodiazepines

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Primidone	RCT [30, 56, 57]	3	203	No significant difference in long-term follow-up (1 year) between primidone (up to 250 mg/die) and PRP-LA (up to 160 mg/die) [30] High doses (750 mg/die) no more effective than low doses (250 mg/die) [65]	50 % of patients reported side effects (sedation, drowsiness), mainly with higher doses. Gradual titration do not improve tolerability [56] Discontinuation in 25 % of patients at low doses and in 50 % at high doses [57]	Low [56, 57] Very low [30]
	Cross-over [54, 55, 77–83]	9	150	Reduction of magnitude from baseline from 20 % [80] to 55.9 % [78] and of amplitude of 35 % [79] Tremorgrams reduction of 75.6 % [54]. Decrease of tremor assessed by clinical rating scale [78, 82] up to 35 % [83] and improvement of patient's self-assessment [78, 83]	50 % sedation, 40 % drowsiness fatigability or asthenia, 30 % mental confusion, 30 % headache, 10 % nausea, 7 % vomiting, 6 % ataxia	Very low
	Case series [65, 75]	2	31	Reduction of tremor magnitude (accelerometric measures) of 45 ± 41 % at 4 weeks, 44 ± 36 % at 3 months, 44 ± 39 % at 6 months, 41 ± 34 % at 12 months. Good clinical response [75]	Acute intolerance (malaise, headache dizziness, drowsiness, nausea, and vomiting) that subsides within a few days. Sedation tended to decrease during long-term treatment	Very low
Topiramate	RCT [58]	1	225	Overall TRS score at study end was 27.9 (SD 13.2) after topiramate and 31.5 (SD 13.4) after placebo, representing a reduction from baseline of 10.8 (SD 9.5) and 5.8 (SD 7.5) in placebo ($p < 0.001$; 95 % CI 2.5 to 6.7). Mean percentage improvement in overall TRS score was 29 % during Topiramate treatment and 16 % in the placebo group ($p < 0.01$; 95 % CI 6.5–18.4)	Paresthesia, weight loss, taste perversion, upper respiratory tract infection, fatigue, nausea, appetite decrease, memory difficulty, dizziness, somnolence, diarrhea, headache. Discontinuation for adverse events was 31.9 % after topiramate and 9.5 % after placebo	Moderate
	Cross-over [76, 84]	2	75	Average TRS total score significantly lower after topiramate (28.7) than after placebo. Mean percentage improvement in overall TRS score was 31 % after Topiramate and 8.6 % after placebo [84] No outcome measures improved significantly in the active treatment period as compared with the placebo control period [76]	Discontinuation for adverse events: 24 % (13) of topiramate patients and 10 % (5) of placebo group	Moderate [84] Very low [76]
	Case series [66, 67]	2	12	No effect of topiramate up to 400 mg/die assessed by spirography, ADL and visual analogue scale [66]. Improvement of ET assessed by spirography in three patients treated with low doses (up to 50 mg) [67]	Discontinuation due to adverse events (fatigue, paresthesia): 2/9 patients [66]	Very low

Table 11 continued

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Levetiracetam	RCT [59]	1	12	Line drawing better at 70 and 130 min and spiral drawing better at 130 min in the levetiracetam group than in the placebo group Handwriting at 70 and 130 min and spiral drawing at 70 min did not differ between groups Volume of water spilled was less in the levetiracetam group at 130 but not at 70 min	No acute adverse events	Very low
	Cross-over [169, 170]	2	27	No statistical significant difference in short-term follow-up (2-4 weeks) between levetiracetam and placebo	Worsening of tremor, fatigue, drowsiness, depressed mood, headache, dizziness	Low
	Case series [68–70]	3	30	No significant reduction after treatment (from 48 days to 7 weeks)	Not reported	Very low
Zonisamide	RCT [60]	1	20	Total TRS score decreased from 29 to 15.7 in the zonisamide group and to 29.8 to 26.7 in the placebo group. In the zonisamide group score for TRS subscales improved at study endpoint compared to baseline, but the differences from placebo were not significant	30 % of patients in the zonisamide group discontinued the study due to side-effects taking 100 mg/die. Three additional patients developed side-effects while taking 200 mg/die but no one discontinued the study. Common side-effects were headache, nausea, fatigue, and diarrhea	Low
	Cross-over [47, 85]	2	26	Significant effect of zonisamide in reducing head tremor: mean change of 1.42 point at TRS-A from baseline, after 2 weeks of treatment. Moreover, zonisamide seemed to be more effective than PRP (mean dose 100 $\pm$ 52.22 mg/die) and arotinolol (10 mg/die) in reducing head, voice, face, and tongue tremor	Not reported	Very low
	Case series [71–73]	3	53	Good improvement from baseline (6.5 points at TRS total score, 8.8 points TRS A + B)	Somnolence, poor energy, imbalance, sedation, dizziness, nausea, decreased concentration with increasing dosage	Very low
Gabapentin	Cross-over [164, 171, 172]	3	61	Gabapentin and PRP reduced tremor more than placebo ($p < 0.05$ and $p < 0.02$) without any apparent difference between the two drugs Considering disability, gabapentin more efficacious than placebo and PRP [164] No improvement as add on therapy [171] At low and high doses (from 900 mg/die to 3,600 mg/die divided in three intakes) improvement on global assessments ($p < 0.05$), tremor ($p < 0.005$), water pouring ($p < 005$) and ADL ($p < 0.005$), but not on accelerometer [172]	Fatigue, lethargy, drowsiness, dizziness Discontinuation due to adverse events: 10 %	Very low
	Case series [74]	1	34	Improvement of 2.6 points on TRS items 1–14 and 1.3 points on TRS items 15–21	Not reported	Very low

Table 11 continued

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Phenobarbital	Cross-over [52, 82, 173]	3	45	No significant improvement at clinical evaluation. Significant improvement of tremor amplitude assessed by accelerometer (−82.00 using arbitrary units) No differences between the treatments considering the performance tests [52] but reduction in tremor magnitude at accelerometry (mean reduction of 52.6 %) [173]. No improvement in any variable [82]	Drowsiness, hypotonia, constipation, dizziness, sedation	Very low
Alprazolam	RCT [61]	1	22	Significant improvement in tremor severity ($p < 0.01$) and in total clinical rating score ($p = 0.01$). Subjective improvement ($p < 0.05$)	Sedation or drowsiness in 50 % of treated patients, not significantly greater compared to the placebo group	Very low
	Cross-over [83]	1	24	Improvement of 25 % using the clinical assessment and 46 % at the self-evaluation, reporting an equal efficacy when alprazolam is compared to primidone	Very low incidence of adverse effects (10 % of patients reported paresthesias) compared to primidone (40 % complained nausea, dizziness, confusion)	Very low
Clonazepam	RCT [62]	1	15	Significant improvement assessed during the induction phase, but no statistically significant differences between the scores at the end of the induction phase and those after the double-blind period	High incidence: two discontinuations at 0.5 mg daily because of intolerable drowsiness, seven for sedation. Side-effects worse in older patients. Three cases of impotence	Very low
	Cross-over [160]	1	14	Significant improvement of clinical scores, amplitude, and performance tests	Not reported	Very low
Barbiturate T2000	RCT [64]	1	34	Only 400 mg BID appear to improve tremor ($p = 0.03$)	Skin rash and pruritus. Two discontinuations due to rash and febrile illness	Low
Pregabalin	RCT [63]	1	22	No significant improvement in the TRS total score or in the TRS subscales. Six patients reported improvement in tremor on the CGI scale In the placebo group, 20 % reported improvement	Side-effects at a dosage of 100 mg or more were dizziness, flu, malaise, fatigue, and palpitation Three patients dropped out of the study	Very low
	Cross-over [174]	1	20	No improvement in any of the TRS measures	Nausea, postural instability, drowsiness and dizziness. Three patients dropped out of the study and one died	Very low
Progabide	Cross-over [175, 176]	2	28	No significant improvement of tremor amplitude	Not reported	Very low

Characteristics of the included studies

RCT randomized controlled trial, *TRS* Tremor Rating Scale

Appendix 4

See Table 12.

Table 12 Neuroleptics

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Clozapine	Cross-over [86]	1	15	13/15 patients presented more than 50 % improvement in tremor score and were admitted to the chronic, open phase A significant reduction in tremor scores pre- and post-treatment	Sedation was the only side-effect reported during clozapine test; statistical analysis showed significant differences in the induction of sedation between clozapine and placebo	Low
	Case series [88]	1	25	Approximately 45 % reduction in tremor amplitude measured by accelerometer acutely	All patients complained of sedation. No cases of agranulocytosis	Very low
Olanzapine	Cross-over [87]	1	38	On day 30, both PRP and olanzapine significantly improved all evaluation measures. At the end of the study, olanzapine significantly improved all tremor parameters, except hygiene compared to PRP 87 % improvement in the global assessment scale by self-evaluation in olanzapine group, whereas 63 % amelioration in global assessment scales was found in the PRP group	Olanzapine: sedation/drowsiness (7 patients), fatigue (6 patients), nausea (5 patients)	Low
	Case series [89]	1	37	Olanzapine 5–20 mg daily provided an amelioration of symptoms. Median tremor score after treatment decreased significantly	Sedation (20 % of patients), tended to disappear in approximately 7 days; three patients complained of weight gain	Very low
Quetiapine	Case series [90]	1	10	Six patients completed the study with full doses (75 mg/day). No statistical differences between pre- and post-treatment evaluations	Somnolence (3 patients), anguish (1 patient), hallucinations/delusions (1 patient who discontinued the treatment)	Very low

Characteristics of included studies

PRP propranolol

Appendix 5

See Table 13.

Table 13 Amantadine

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Amantadine	Cross-over [91]	1	16	TCRS part 1-2 at study end: 33.6 (SD 16.4) in the amantadine group and 33.2 (SD 15.1) in the placebo group. Mean difference (MD) at the end of the study between the two groups: 0.40 [15.05–15.85]. The analysis of variance showed no significant time ($p = 0.543$) and treatment effects ($p = 0.940$) TCRS Part 3 at study end: 13.0 (SD 2.9) in the amantadine group and 13.7 (SD 2.8) in the placebo group MD at the end of the study between the two groups was of 0.70 [3.49–2.09]. The analysis of variance showed no significant time ($p = 0.414$) and treatment effects ($p = 0.907$) Subjective assessment by the patient (TCRS Part 4) and global patient appraisal showed no significant differences	During amantadine: Six cases of anxiety, nervousness and an increase in postural tremor; 4 insomnia; 2 dry mouth; 1 blurred vision. One discontinuation due to adverse events No adverse events occurred while in the placebo group	Very low
	Case series [92, 93]	2	14	Tremor improved (clinical evaluation) in just 5 of the 8 patients [92] Five patients in the two studies stated that the drug worsened their tremor	No adverse events reported	Very low

Characteristics of the included studies

TCRS Tremor Clinical Rating Scale

Appendix 6

See Table 14.

Table 14 Botulinum toxin type A

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
BTXA	RCT [94, 95]	2	158 (hand ET)	At 4 weeks, mild improvement of postural and kinetic tremor (UTRA scale), greater for postural tremor (−1.67) than for kinetic tremor (−1.17) [94] Mild improvement of postural tremor at all 6, 12, and 16 weeks of follow-up; not statistically different between low- and high-dose experimental arms [95]	Mild-moderate forearm muscle weakness in 30–50 % of patients at lower dosage, and 70 % of patients at higher dosage. Other adverse events (pain at injection site, stiffness, cramping, rash, hematoma, and paresthesias) were overall slightly more frequent in patients treated with BTXA (at any dose) than in placebo-treated patients [95] No patient withdrawal due to adverse effects	Low
	Cross-over [96]	1	10 (head ET)	Subjective and objective assessment of treatment response yielded a judgment of mild-to-moderate improvement in the BTXA group; there was a slightly significant difference from placebo for subjective assessment ($p = 0.03$), but not for objective assessment ($p = 0.06$)	Neck weakness: 70 % of subjects following BTXA injection, 10 % of subjects following placebo injections	Very low
	Case series [97–102]	6	44 (hand ET) 28 (head ET) 15 (voice ET)	Reduction of tremor magnitude (clinical and accelerometric measures) in most reports of hand ET and head ET 'Relevant' clinical benefit reported in only one of two case reports of voice ET-treated	Weakness of muscle forearm, neck, and vocal muscles	Very low

Characteristics of the included studies

ET essential tremor, *BTXA* botulinum toxin A, *RCT* randomized controlled trial, *UTRA* Unified Tremor Rating Scale

Appendix 7

See Table 15.

Table 15 Thalamotomy

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
Thalamotomy	RCT [103, 104]	1	13	Thalamotomy and VIM-DBS significantly improved disability, with little superiority of VIM-DBS (weighted mean difference of 6.6 $p < 0.0004$), 6 months after treatment. No differences after 2 and 5 years of follow-up	Paresthesias, paresis, dystonia, gait disorder, arm ataxia, dysarthria, cognitive deterioration. Death: three patients (unrelated to surgery). Side-effect after 6 months: VIM-DBS had fewer adverse effects than thalamotomy	Low
	Case series [105–114]	10	343	Both thalamotomy and VIM-DBS were effective in reducing tremor severity or disability [105] The other studies reported disappearance of tremor in the majority of patients	Only immediate surgical complications were reported. Surgical complications were higher in the thalamotomy group Four patients (2 deaths) lost at follow-up in the thalamotomy group and 18 patients excluded before the analysis [105] In two studies [110, 113] the adverse events were not reported. In the other seven studies [106–109, 111, 112, 114], 69 adverse events, 16 of which were permanent	Very low

Characteristics of the included studies

VIM-DBS ventralis intermedius nucleus deep-brain stimulation, *RCT* randomized controlled trial

Appendix 8

See Table 16.

Table 16 Deep-brain stimulation

Treatment	Design (references)	Number of studies	Number of participants	Efficacy	Safety	Quality of evidence
THALAMIC DBS SUBTHALAMIC NUCLEUS DBS	RCT [103, 104]	1	13	Thalamotomy and VIM-DBS significantly improved disability, with little superiority of VIM-DBS (weighted mean difference of 6.6 $p < 0.0004$), 6 months after treatment. No differences after 2 and 5 years [103, 104]	Paresthesias, paresis, dystonia, gait disorder, arm ataxia, dysarthria, cognitive deterioration. Death in three patients (unrelated to surgery). Side-effect after 6 months: VIM-DBS had fewer adverse effects than thalamotomy	Low
	Case series [105, 115–150]	36	629	Significant tremor reduction (TRS and ADL) on contralateral upper limb, with effect reduction over 7 years of follow-up [137]. Significant tremor reduction after bilateral implant compared with unilateral [105] Significant head and voice tremor reduction after bilateral DBS implant [119, 140] Significant tremor voice reduction in 60 % of cases [143]	Paresthesias (9–100 %), disequilibrium (50 %), dysarthria (10–20 %), dystonia (10 %), 8 total deaths, 1 caused by surgery [105]; reoperation or device replacement (30–60 %); Paresthesias, dysarthria, disequilibrium, lead displacement, dystonia, mild cognitive defects Ataxia, dysarthria, and gait disturbances were more common after thalamotomy [141]	Very low
	Case series [153, 154]	2	26	Improvement of 80.1 % of the total tremor score (from baseline mean score of 63 ± 15.1 to a score of 11.8 ± 3.9 at 12 months postoperatively) Excellent tremor reduction for up to 9 years of follow-up [154]	No adverse events reported. Unsafe for patients older than 70 years old	Very Low

Characteristics of the included studies

VIM-DBS ventralis intermedius nucleus deep-brain stimulation, *RCT* randomized controlled trial, *TRS* Tremor Rating Scale

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