MDS Evidence-Based Review of Treatments for Essential Tremor

Joaquim J. Ferreira, MD, PhD,[1,2] Tiago A. Mestre, MD, MSc,[3*] Kelly E. Lyons, PhD,[4] Julián Benito-León, MD,[5] Eng-King Tan, MD,[6] Giovanni Abbruzzese, MD,[7] Mark Hallett, MD,[8] Dietrich Haubenberger, MHSc, MD,[9] Rodger Elble, MD PhD,[10] and Günther Deuschl, MD, PhD,[11]
on behalf of MDS Task Force on Tremor and the MDS Evidence Based Medicine Committee

[1]*Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal*
[2]*CNS-Campus Neurológico Sénior, Torres Vedras, Portugal*
[3]*Parkinson's Disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, Brain and Mind Research Institute, University of Ottawa, Ottawa, Ontario, Canada*
[4]*Parkinson's Disease and Movement Disorder Center, University of Kansas Medical Center, Kansas City, Kansas, USA*
[5]*Department of Neurology, University Hospital 12 de Octubre; Center of Biomedical Network Research on Neurodegenerative diseases (CIBERNED), Department of Medicine, Faculty of Medicine, Complutense University, Madrid, Spain*
[6]*National Neuroscience Institute, Duke NUS Medical School, Singapore*
[7]*Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa–IRCCS Ospedale Policlinico San Martino, Genova, Italy*
[8]*Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA*
[9]*Clinical Trials Unit, Office of the Clinical Director, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA*
[10]*Department of Neurology, Southern Illinois University School of Medicine, Springfield, Illinois, USA*
[11]*Department of Neurology, Universitätsklinikum Schleswig-Holstein, Kiel Campus, Christian Albrechts University Kiel, Kiel, Germany*

ABSTRACT: Background: Essential tremor is one of the most prevalent movement disorders. Many treatments for essential tremor have been reported in clinical practice, but it is uncertain which options have the most robust evidence. The International Parkinson and Movement Disorder Society commissioned a task force on tremor to review clinical studies of treatments for essential tremor.
Objectives: To conduct an evidence-based review of current pharmacological and surgical treatments for essential tremor, using standardized criteria defined a priori by the International Parkinson and Movement Disorder Society.
Methods: We followed the recommendations of the International Parkinson and Movement Disorder Society Evidence Based Medicine Committee.
Results: Sixty-four studies of pharmacological and surgical interventions were included in the review. Propranolol and primidone were classified as *clinically useful*, similar to Topiramate, but only for doses higher than 200 mg/day. Alprazolam and botulinum toxin type A were classified as *possibly useful.* Unilateral Ventralis intermedius thalamic DBS, radiofrequency thalamotomy, and MRI-guided focused ultrasound thalamotomy were considered *possibly useful.* All the above recommendations were made for limb tremor in essential tremor. There was insufficient evidence for voice and head tremor as well as for the remaining interventions.
Conclusion: Propranolol, primidone, and topiramate (>200 mg/day) are the pharmacological interventions in which the data reviewed robustly supported efficacy. Their safety profile and patient preference may guide the prioritization of these interventions in clinical practice. MRI-guided focused ultrasound thalamotomy was, for the first time, assessed and was considered to be *possibly useful.* There is a need to improve study design in essential tremor and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies, and use of nonvalidated clinical scales. © 2019 International Parkinson and Movement Disorder Society

Key Words: clinical trials; essential tremor; evidence-based medicine; systematic review; treatment

*__Correspondence to:__ Dr. Tiago A. Mestre, Parkinson's Disease and Movement Disorders Centre, Division of Neurology, Department of Medicine Civic Campus of the Ottawa Hospital, The Ottawa Hospital Research Institute, University of Ottawa, 1053 Carling Avenue, Room 2174, Ottawa, Ontario, Canada, K1Y4E9; E-mail: tmestre@toh.on.ca

Dr. Joaquim J. Ferreira and Dr. Tiago A. Mestre co-first authors.

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Tremor is a common clinical sign defined as an involuntary, rhythmic, oscillatory movement of a body part.[1] The term essential tremor (ET) has been defined inconsistently, but has been most commonly regarded as a chronic action upper limb tremor, frequently associated with tremor in the head, voice, and elsewhere.[1] In ET, tremor is not associated with other neurological signs, such as dystonia, ataxia, or parkinsonism.[1] ET is one of the most common movement disorders, with an estimated prevalence of 0.9% in the general population.[2] Most people with ET are only mildly affected. Nevertheless, many become disabled to some extent over time.[3]

Recognizing the need to improve clinical practice and research in the field of tremor, the International Parkinson and Movement Disorder Society (MDS) commissioned a task force. In this task force, a working group received the task of conducting an evidence-based review of pharmacological and surgical interventions assessed for the management of patients with ET. In this article, we summarize the evidence available for each intervention and provide recommendations based on the quality of data available for each treatment in ET.

Methods

The methodology of the review followed the recommendations of the MDS Evidence Based Medicine Committee, used in previous published reviews.[4] Literature searches were done using electronic databases, including MEDLINE (1966 to December 2016), the CENTRAL database in the Cochrane Library (1948–2016), and systematic checking of reference lists published in review articles and other clinical reports. Articles selected for review met the following inclusion/exclusion criteria.

Inclusion criteria: (1) any pharmacological, surgical, and nonpharmacological therapies for which there was at least one randomized controlled trial (RCT); (2) nonrandomized controlled or noncontrolled prospective or retrospective studies with blinded ratings for efficacy outcomes were accepted for surgical treatments; (3) patients with a diagnosis of ET; (4) minimum of 10 patients enrolled; (5) minimum of 2 weeks of treatment; (6) use of an established rating scale or a well-described outcome measurement as endpoint; (7) severity and/or disability related with tremor measured by clinical rating scales or patient self-evaluation; and (8) full article available in English language. Exclusion criteria: (1) single-dose studies; (2) ET diagnosis not stated or unclear; (3) duplicated report; (4) technical information reports describing the characteristics and the operational parameters of an intervention and where the evaluation of outcomes is nonexistent or circumstantial; (5) use of unconventional outcome measures; (6) uncertain length of follow-up; (7) unable to track patient subgroups in the report (e.g., which patient had ET vs. other diagnosis; or which patients had unilateral vs. bilateral procedures); (8) abstract, review, or book chapters. Inclusion criteria 4 (n = 10) and 5 (minimum 2 weeks of treatment) were adaptations of the items adopted in the Parkinson's disease MDS Evidence-Based Medicine (MDS-EBM) review (respectively, n = 20 and a minimum 4 weeks of treatment). These changes were agreed upon by consensus of the task force when developing the protocol and accepted by the EBM committee. Adopting more strict criteria would have excluded 50% of the studies. In this first-ever MDS-EBM review on ET, we aimed at providing a broad landscape of therapeutic investigation in ET, while preserving the standards of the MDS-EBM review methodology.

Pairs of members of the task force confirmed the identified studies for inclusion or exclusion and performed the critical appraisal of each study. A consensus was obtained for each article. If the pair of reviewers did not reach agreement, the whole workgroup was called for a consensus.

Classification of Evidence

Clinical evidence was classified into three levels[5]: Level-I studies—randomized, controlled trials; Level-II studies—controlled clinical trials or observational controlled studies such as cohort or case-control studies; and Level-III studies—noncontrolled studies like case series. If sufficient RCTs were available (Level-I studies), studies with lower levels of evidence were only considered secondarily to amplify, but not to establish, efficacy. In instances where RCTs did not exist, lower levels of evidence were used as the primary sources, but the conclusions were less robust.

Rating Study Quality

All studies were rated for study quality. A study quality score was derived from a published checklist of key methodological items[5] relevant to the methodological soundness of the trial. A percentage score (not absolute values) was calculated for each study and used as an indicator of the overall quality of the study. This score was considered for the final evidence-based conclusions (Table 1). To secure consistency across studies, all the ratings were done by two members of the working group. The differences in scores were reviewed and a consensus reached among the reviewers. In this review, there was no cutoff for study inclusion based on quality scores.

Safety Evaluation

The clinical information used to make an overall safety evaluation included primarily the adverse

TABLE 1. Definitions for specific recommendations

Efficacy Conclusions	Definition	Required Evidence
Efficacious	Evidence shows that the intervention has positive effect on studied outcomes without conflicting data.	Supported by data from at least one high-quality (score >75%) RCT *without conflicting Level-I data*
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes.	Supported by data from any Level-I trial without conflicting Level-I data
Unlikely efficacious	Evidence suggests that the intervention does not have a positive effect on studied outcomes.	Supported by data from any Level-I trial without conflicting Level-I data
Nonefficacious	Evidence shows that the intervention does not have a positive effect on studied outcomes.	Supported by data from at least one high-quality (score >75%) RCT without conflicting level I data
Insufficient evidence	There is not enough evidence either for or against efficacy of the intervention.	All the circumstances not covered by the intervention in previous statements
Safety		
Acceptable risk without specialized monitoring		
Acceptable risk with specialized monitoring[a]		
Unacceptable risk		
Insufficient evidence to make conclusions on the safety of the intervention		
Implications for Clinical Practice		
Clinically useful	For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit.	
Possibly useful	For a given situation, evidence available suggests, but insufficient to conclude, that the intervention provides clinical benefit.	
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, but further study may be warranted.	
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit.	
Unlikely useful	For a given situation, available evidence suggests that the intervention does not provide clinical benefit.	

[a]*Specialized monitoring* should follow the best medical practices in a given jurisdiction.

reactions reported in the included studies. Other sources of information to be considered were the adverse reactions described in the product monograph, regulatory measures taken by country or regional authorities based on safety and tolerability profiles of the treatment, and case reports based on non-systematically identified articles. The safety discussion within these sections uses a narrative, unsystematic approach because of the limited data available from clinical studies of ET.

Assessments of efficacy and safety for each therapeutic intervention were made using standardized wording, followed by the specific implications for use in clinical practice and future clinical research. Each intervention was considered for the following indications: symptomatic improvement of limb tremor in ET; symptomatic improvement of head tremor in ET; symptomatic improvement of voice tremor in ET; and symptomatic improvement of tremor in any body segment in specific postures or tasks in ET. A given indication was stated whenever evidence was available. Standardized criteria were used to describe conclusions to avoid subjectivity and inconsistencies across sections. For efficacy, in cases where there was just one Level-I trial included per intervention and there was no possibility to evaluate reproducibility of the trial results, it was decided to follow a conservative approach and downgrade the efficacy conclusion and corresponding implication for clinical practice by one level. We used a consensus-based approach for safety conclusions having as starting point the safety data available in the included studies. The implications for clinical practice considered first efficacy conclusions, and then a consensus decision on how safety recommendations could downgrade a clinical practice recommendation. This approach obtained consent of the EBM committee.

Results

A total of 241 publications were identified by the database search. From these, a total of 66 publications were included in the review that assessed pharmacological and surgical interventions. We further excluded two publications[6,7] that corresponded to a study published elsewhere.[8,9] For this review, we also included studies exclusively on isolated head tremor.[10,11] After reviewing the evidence available for the interventions included in this review, propranolol, primidone, and topiramate were the interventions with sufficient evidence to warrant the recommendation of *clinically useful*. Alprazolam and botulinum toxin type A were considered *possibly useful*. Among the surgical interventions for ET, unilateral *Ventralis intermedius* (Vim)/thalamic DBS and thalamotomy (radiofrequency and MRI-guided focused ultrasound) were considered *possibly useful*. All the above recommendations were made only for limb tremor in ET (see Table 2, for summary of recommendations). A few studies[10-14] had a focus on head tremor, either isolated or in the context of ET, but data available only allowed a conclusion of *insufficient evidence* for head tremor. None of the included studies specifically assessed voice tremor.

Pharmacological Interventions

Propranolol (13 Studies)

Propranolol was studied in 13 Level-I studies[9,13,20-30] in a total of 255 patients with ET, comparing propranolol with placebo (n = 9) or active comparator only (n = 4: propranolol extended release, metoprolol [n = 2], and olanzapine). Average treatment duration was 3.5 weeks (range, 1.5–8.0). Only two studies were parallel in design. The average quality score was 66.7% (range: 53.7–100). Propranolol was used with various daily doses up to 240 to 360 mg. In terms of efficacy, propranolol was associated with an improvement in limb tremor across the included studies documented in various outcome measures such as clinical rating scales of severity, task performance, measures of activities of daily living (ADLs), patient impression of change, and data collected with accelerometric devices. Responder rate was of 50% to 70% (range, 11–100), though with a lower rate of responders for functional improvement and for a sustained effect. Bradycardia and bronchospasm are among the most common adverse events in these studies. Overall, adverse events led to a discontinuation in <10% of study participants. Other adverse events with impact in clinical practice are known such as fatigue, lightheadedness, and sexual dysfunction.[31] A comparison of the immediate release and long acting formulation of propranolol was done only in one of the included studies, and suggested that the two formulations may be equivalent in terms efficacy and safety.[27]

For upper limb tremor, propranolol was considered efficacious *(efficacy recommendation) with an* acceptable risk without specialized monitoring *(safety recommendation). Overall, propranolol was considered* clinically useful *for clinical practice.*

Primidone (Eight Studies)

Primidone was studied in eight Level-I studies[14,25,32-37] that included a total of 274 patients with ET, comparing primidone with placebo (n = 6) or different formulations/doses of primidone (n = 2). The average treatment duration was 10.1 weeks (range, 3–52). Only two studies were parallel in design. The average quality score was 66.8% (range, 52.8–78.9). Primidone was used with various daily doses ranging from 150 to 750 mg. The different studies showed an improvement in clinical rating of tremor severity, task performance, and measures of ADLs. The long-term effect of primidone (250 and 750 mg/day)[37] was assessed in a 12-month double-blind RCT that reported a comparable long-term efficacy and absence of tolerance for the therapeutic effect. In a head-to-head comparison of propranolol 120 mg/day and primidone 250 to 750 mg/day, patient preference was greater for primidone (n = 9 [64.3%] vs. n = 5 [35.7%]), but primidone caused more bothersome side effects, including malaise, dizziness, and unsteadiness, at the initial dose of 62.5 mg/day.[25]

The most common adverse events were an acute "toxic" reaction occurring at a frequency as high as 22.7%,[14] even after an initial dose of 62.5 mg.[14] Sedation, daytime sleepiness, and fatigue were also commonly reported adverse events. Overall, adverse events led to a discontinuation rate ranging from 7.5% to 42%. There is no evidence on the best titration regimen to reduce the frequency of the initial side effects such as the acute "toxic" reaction.[36] The combined use of primidone 250 mg qHS and propranolol 80 mg TID[26] was associated with a greater benefit in postural limb tremor measured by accelerometry than either drug alone. Safety and tolerability were not reported.

For upper limb tremor, primidone was considered efficacious *(efficacy recommendation) with an* acceptable risk with specialized monitoring *(safety recommendation) attributed to the side-effect profile and potential high discontinuation rates. Overall, primidone was considered* clinically useful *for clinical practice.*

Topiramate (Four Studies)

Topiramate was studied in four placebo-controlled Level-I studies[38-41] in a total of 322 patients with ET, as monotherapy or add-on treatment, and an average treatment duration of 10.5 weeks (range, 2–24). The average quality score was 79.4% (range, 65–90). The mean effective dose of topiramate ranged from 215 to 333 mg/day (n = 3). There was a documented improvement in both tremor amplitude and ADL measures in three of the four Level-I studies.[38,39,41] Paresthesia, concentration/attention difficulty, appetite suppression/weight loss, and nausea were among the most common adverse events. Overall, adverse events were treatment limiting in 31.9% of the cases for topiramate and in 9.5% of the cases for placebo.[41] Adverse events were responsible for a percentage of dropouts ranging from 30% to 54.2%.[38,41]

For upper limb tremor, topiramate was considered efficacious *(efficacy recommendation) for daily doses higher than 200 mg with an* acceptable risk without specialized monitoring *(safety recommendation). These recommendations are based on positive efficacy results documented for daily doses higher than 200 mg, and not in a study assessing a 50- to 100-mg dose range. Topiramate was considered* clinically useful *for clinical practice for daily doses higher than 200 mg.*

Alprazolam (Two Studies)

Alprazolam was studied in two placebo-controlled Level-I studies[35,42] in a total of 46 patients with ET, as monotherapy with a treatment duration of 2 and 4 weeks. One study was parallel in design. The quality score in the two studies was 70.0%. The initial dose of alprazolam was 0.125[35] or 0.75 mg,[42] and the mean daily effective dose was 0.75[35] and 1.5[42] mg. Both studies documented

TABLE 2. Summary of efficacy conclusions and implications for clinical practice for limb tremor in ET[a]

Pharmacological Class		Efficacy Conclusions	Implications for Clinical Practice	Safety Conclusions
Anticonvulants	Carisbamate	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Gabapentin	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Levetiracetam	Nonefficacious	Not useful	Acceptable risk without specialized monitoring
	Pregabalin	Nonefficacious	Not useful	Acceptable risk without specialized monitoring
	Progabide	Unlikely efficacious	Unlikely useful	Acceptable risk without specialized monitoring
	Topiramate	Efficacious (>200 mg/day)	Clinically useful (>200 mg/day)	Acceptable risk without specialized monitoring *The most common adverse effects with topiramate were appetite suppression, weight loss, cognitive impairment, and paresthesias.*
	Zonisamide	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
Beta-lockers	Propranolol	Efficacious	Clinically useful	Acceptable risk without specialized monitoring *Withdrawals were rare and mainly attributed to fatigue and bradycardia.*
	Propranolol long-acting	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Nadolol	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Metoprolol	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Atenolol	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Sotalol	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
Barbiturates	Primidone	Efficacious	Clinically useful	Acceptable risk with specialized monitoring *Consistent withdrawal attributed to adverse effects (first dose acute toxic reaction, sedation, daytime sleepiness, tiredness, nausea, ataxia, dizziness, and confusion).*
	Phenobarbital/phenobarbitone	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring *Phenobarbital may be associated with depression and cognitive and behavioral effects.*
	T2000 (1,3-dimethoxymethyl-5,5-dephenyl-barbituric acid)	Insufficient evidence	Investigational	Insufficient evidence to make conclusions on the safety of the intervention
Benzodiazepines	Alprazolam	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring *Adverse effects with benzodiazepines include sedation, and cognitive and behavioral effects have been well described for other conditions.*
Calcium channel blockers	Flunarizine	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring *Flunarizine been associated with the development of parkinsonism and other movement disorders.*[15-19]
	Nimodipine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
Carbonic anhydrase inhibitors	Methazolamide	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring *CBC and platelets should be measured before starting methazolamide and periodically during use to monitor for hematological reactions. Serum electrolytes should also be periodically monitored.*
	Acetazolamide	Insufficient evidence	Unlikely useful	Acceptable risk with specialized monitoring
Other drugs	Amantadine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Isoniazid	Insufficient evidence	Unlikely useful	Unacceptable risk *Isoniazid can lead to severe and possibly fatal hepatitis.*
	Mirtazapine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Olanzapine	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring *Associated with the induction of parkinsonism, akathisia, and tardive dyskinesia*
	Theophylline	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Trazodone	Unlikely efficacious	Unlikely useful	Acceptable risk without specialized monitoring
Botulinim toxin	Botulinum toxin type A	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring *Hand weakness was a frequent dose-related adverse event.*
Surgery	Unilateral Vim-DBS	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring
	Bilateral Vim-DBS	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
	Unilateral Radiofrequency thalamotomy	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring
	Unilateral Gamma-knife thalamotomy	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
	Unilateral MRI-focused ultrasound thalamotomy	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring

[a]See further details in the Supporting Information.
CBC, complete blood count.

a reduction in nonvalidated clinical rating scales of severity and task performance, but also in anxiety scores. The side-effect profile was concerning for somnolence (as high as 50%)[42] and the known risk of dependence.

For upper limb tremor, alprazolam was considered likely efficacious *(efficacy recommendation) with an* acceptable risk with specialized monitoring *(safety recommendation). Alprazolam was considered* possibly useful *for clinical practice.*

Botulinum Toxin Type A (Three Studies)

Botulinum toxin type A was studied in three placebo-controlled Level-I studies[10,43,44] that included a total of 168 patients with ET refractory to oral drugs. Dose ranged from 50 to 100 IU targeting forearm[43,44] or neck muscles,[10] with an average treatment duration of 12 weeks (range, 4–16). The three studies were parallel in design. The average quality score was 83.7% (range, 71–95.2). Two studies[43,44] reported an improvement in clinical ratings of upper limb tremor, but no functional improvement. There was no reported benefit for a horizontal head tremor without any evidence of dystonia after administration in each sternocleidomastoid muscle and splenius capitis.[10] The therapeutic effect of botulinum toxin type A was maintained for 16 weeks,[43] being longer for the postural component of the upper limb tremor.[44] Dose-dependent hand weakness by patient report[43,44] or by measured grip strength[44] was the main adverse reaction with an incidence ranging from 30 (for 50 IU) to 69% (for 100 IU).

For upper limb tremor, botulinum toxin type A was considered likely efficacious *(efficacy recommendation) attributed to conflicting results and with an* acceptable risk with specialized monitoring *(safety recommendation), given that the dose-dependent limb weakness is of concern. Botulinum toxin type A was considered* possibly useful *for clinical practice.*

Unilateral Vim-DBS (Seven Studies)

We included seven studies assessing unilateral Vim thalamic DBS as a treatment option for ET. Of note, there was a single randomized parallel Level-I study comparing Vim-DBS with thalamotomy in 13 ET patients with severe upper limb tremor (quality score: 95.2%).[45] The primary outcome was the change from baseline in functional status as measured by the Frenchay Activities Index.[45] The clinical severity of tremor was also measured in single-blinded fashion using the Fahn-Tolosa-Marin scale. At 24 weeks, Vim-DBS was associated with a change in the Frenchay Activities Index from baseline of 6.4 $\pm$ 3.4 (n = 7). Overall, tremor was absent or slight in all 7 patients. There was greater improvement in the Frenchay Activities Index with Vim-DBS compared with thalamotomy (6.6 points; 95% confidence interval [CI]: 2.5, 10.7). Adverse events were more frequent in the thalamotomy group (n = 16) than in the Vim-DBS group (n = 6; P = 0.024). At a 5-year follow-up, a reduction of the benefit of stimulation was observed in 5 of 10 ET patients, with an increased severity of intention and postural tremor. The other remaining six studies[12,46-50] (mean quality score: 79.9%; range, 70.6–91.7) are case series with blinded patient assessments and included a total of 147 patients with a diagnosis of ET and disabling medication-refractory upper limb tremor. The follow-up time was 12 weeks in five studies,[12,46-49] with one study reporting on long-term follow-up up to 6 to 7 years.[50] In five of the studies, the effect of unilateral Vim-DBS was assessed comparing an ON-stimulation with an OFF-stimulation condition.[12,47-50] The mean values of stimulation in each case series ranged from 2.3 to 3.5 V (amplitude), 117 to 181 Hz (frequency) and 79 to 256 μsec (pulse width). There was an improvement in various clinical rating scales of severity and performance of activities. Paresthesia (mean incidence overall: 61%; range,: 21–100) were the most frequent stimulation-related adverse events and decreased in frequency with time.[47] In terms of long-term effect of unilateral Vim-DBS at 2 and 6 to 7 years, one study documents an improvement of upper limb postural or kinetic tremor and hand function ($P < 0.025$) in an ON-stimulation condition compared with OFF-stimulation condition and preoperative evaluations.[50]

Unilateral Vim-DBS alone has been compared with sequential bilateral Vim-DBS, in a case series by Ondo and colleagues[51] (quality score: 80.0%) that included 13 patients with ET. Compared with baseline unilateral Vim-DBS, the ON-stimulation condition in bilateral Vim-DBS was associated with an improvement in the single-blinded assessment of the severity of arm tremor (unilateral, 6.7 $\pm$ 0.9; bilateral, 1.3 $\pm$ 1.2; $P < 0.005$) and leg tremor (unilateral, 2.3 $\pm$ 1.1; bilateral, 0.5 $\pm$ 0.5; $P < 0.005$), but not of head or voice tremor. In an open label assessment, there was an improvement in ADLs (unilateral, 25.1 $\pm$ 3.6; bilateral, 10.3 $\pm$ 3.7) and disability (unilateral, 3.5 $\pm$ 0.6; bilateral, 1.3 $\pm$ 0.6) from baseline to three months after bilateral Vim-DBS. Adverse events were more frequent with bilateral Vim-DBS (16 of 21; 76%) compared with unilateral Vim-DBS (11 of 21; 52%), the most disabling being gait difficulty and dysarthria.

For upper limb tremor, unilateral Vim-DBS was considered likely efficacious *(efficacy recommendation). There was an* acceptable risk with specialized monitoring *(safety recommendation). Unilateral Vim-DBS was considered* possibly useful *for clinical practice.*

Radiofrequency Thalamotomy (Two Studies)

Radiofrequency thalamotomy has been assessed in two studies. Zirh and colleagues[52] (quality score: 64.7%) reported on a case series of 21 patients with medically intractable ET not otherwise specified that underwent uni- or bilateral thalamotomy. Assessment

at both 3 and 12 months after thalamotomy documented an improvement compared with baseline for handwriting, drawing (single blinded assessment), functional scores ($P < 0.001$), as well as clinical severity (action and posture; $P < 0.05$) rated by the Fahn-Tolosa-Marin Scale. Permanent perioral numbness (n = 1) and disequilibrium (n = 1) were reported after unilateral thalamotomy and permanent mild dysarthria occurred in 2 of 3 patients with bilateral thalamotomy. Schuurman and colleagues[45] (quality score: 95.2%) conducted a randomized parallel Level-I study of Vim-DBS versus thalamotomy with 13 patients with severe upper limb tremor attributed to ET (see details of the study above in the Unilateral Vim-DBS section). Tremor was absent or slight in all 6 patients treated with thalamotomy. Vim-DBS was associated with a greater improvement in the Frenchay Activities Index compared with thalamotomy (6.6 points; 95% CI: 2.5, 10.7). Adverse events were more frequent in the thalamotomy group (total number: 16; $P = 0.024$).

For upper limb tremor, unilateral radiofrequency thalamotomy was considered likely efficacious *(efficacy recommendation) with an* acceptable risk with specialized monitoring *(safety recommendation). Radiofrequency thalamotomy was considered* possibly useful *for clinical practice.*

Unilateral MRI-Guided Focused Ultrasound Thalamotomy (One Study)

Elias and colleagues[53] (quality score: 84.1%) conducted a randomized parallel study of unilateral MRI-guided focused ultrasound thalamotomy versus sham procedure in 81 patients with medically refractory moderate-severe upper limb tremor attributed to ET. MRI-guided focused ultrasound thalamotomy was associated with an improvement in tremor severity ratings by 47% at 3 months (from 18.1 ± 4.8 to 9.6 ± 5.1) with a between-group difference at 3 months of 8.3 points (95% CI: 5.9–10.7; $P < 0.001$). MRI-guided focused ultrasound thalamotomy was also associated with improvement in function and quality of life at 3 months. The most frequent adverse events in the thalamotomy group were paresthesia or numbness (38%), and gait impairment either objective or subjective (36%).

For upper limb tremor, unilateral MRI-guided focused ultrasound thalamotomy was considered likely efficacious *(efficacy recommendation) with an* acceptable risk with specialized monitoring *(safety recommendation). MRI-guided focused ultrasound unilateral thalamotomy was considered* possibly useful *for clinical practice.*

Discussion

In this EBM review of pharmacological and surgical interventions for ET, we found sufficient evidence only for upper limb tremor. For this indication, propranolol and primidone were considered *clinically useful*, together with topiramate for a daily dose higher than 200 mg (see Table 2, for summary of recommendations). There is an *acceptable risk with specialized monitoring* namely regarding the frequent occurrence of hand weakness with botulinum toxin type A and central nervous system–related adverse events with primidone and alprazolam. While applying the methodology of the EBM review in a consistent fashion, the task force decided to consider topiramate *clinically useful* because three out of four studies reported positive efficacy results. For the fourth study,[40] the daily dose of topiramate was smaller (50–100 mg) than the mean effective dose of topiramate reported in the other studies (range, 215–333 mg), which may explain the observed negative efficacy results in the former. The task force concluded that the overall evidence available for topiramate was stronger for efficacy compared to alprazolam and botulinum toxin type A, which were considered *possibly useful.*

In terms of surgical interventions, unilateral Vim-DBS, radiofrequency thalamotomy, and the recently developed unilateral MRI-guided focused ultrasound thalamotomy were *possibly useful* for the treatment of limb tremor in ET, with an *acceptable risk with specialized monitoring.* These surgical interventions have a single Level-I study and thus would require additional Level-I evidence to achieve a recommendation of *clinically useful.*

We also conclude that for the majority of the other interventions included in this EBM review, there is insufficient evidence for any conclusions to be drawn. It is worth noting that in some instances the conclusions herein may differ from other available guidelines or therapeutic recommendations on the same topic. This fact reflects the intrinsic differences in adopted methodologies for the different evidence-based reviews and guidelines. To identify areas that are understudied and/or where evidence is lacking, a clear understanding of what has been established through clinical research is required. This task force recognizes possible factors that may have undermined therapeutic development in ET and precluded the existence of more robust and higher-quality evidence. Examples are: (1) the lack of assessment of a long-term therapeutic effect in ET, (2) predominance of small sample sizes with a known bias toward false-positive results, (3) the predominance of crossover trials that are methodologically flawed when there is no assessment of a carry-over effect, (4) the use of scales that were sufficiently described to warrant inclusion in this review, but lacked comprehensive clinimetric validation,[54] and (5) the lack of knowledge about the clinical relevance of a difference in tremor score for the various rating scales used in these studies. The frequent finding that

an improvement in clinical severity was not associated with a gain in functional ability further strengthens the need to determine what are clinically significant changes in a clinical rating scale in ET studies. The ability to compare the efficacy of interventions is a gap that needs to be addressed. Typically, clinical trials portraying a head-to-head comparison provide this information in MDS-EBM reviews. If randomized controlled comparative trials are unavailable, the use of measures such as effect size may permit a comparative efficacy analysis. These issues warrant a comprehensive discussion that will help to develop a framework for future interventional studies in ET to overcome these challenges and/or limitations.

In addition, given that new standards such as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach are emerging to optimize the process of summarizing clinical evidence, future MDS-EBM reviews will be able to integrate data with a heterogeneous quality of evidence and establish conclusions with greater flexibility and accuracy.

The MDS Task Force on Tremor acknowledges the existence of other interventions with new or ongoing therapeutic development that are a sign of hope for new therapeutic options in ET. These studies were not included because they did not meet inclusion criteria or have been reported since we concluded the review process. Examples are the assessment of interventions administered on an as-needed regimen, including the more recently studied octanol and its derivatives,[55,56] open label assessment of perampanel,[57] customized approach for botulinum toxin administration to improve safety in the treatment of hand tremor,[58] other DBS approaches with assessment of targets such as the Zona Incerta/Posterior Subthalamic area,[59] the STN,[60] use of constant-current[61] or closed loop stimulation[62] paradigms, and novel MRI-guided approaches for thalamotomy.[63] These interventions will likely merit assessment in a future MDS-EBM review on ET. ■

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Appendix 1

Remaining members of the MDS Task Force on Tremor
Kailash Bhatia
Peter G. Bain
Nin Bajaj
Maria João Forjaz
Elan D. Louis
Jan Raethjen
Maria Stamelou
Claudia M. Testa
Elan Louis
The chair of the EBM committee
Regina Katzenschlager

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.