MDS Evidence-Based Review of Treatments For Essential Tremor

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MDS Evidence-Based Review of Treatments For Essential Tremor

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ABSTRACT

Background: Essential tremor (ET) is one of the most prevalent movement disorders. Many treatments for ET have been reported in clinical practice, but it is uncertain which options have the most robust evidence. The International Parkinson and Movement Disorder Society (MDS) commissioned a task force on tremor to review clinical studies of treatments for ET.

Objectives: To conduct an evidence-based review of current pharmacological and surgical treatments for ET, using standardized criteria defined *a priori* by the MDS.

Methods: We followed the recommendations of the MDS 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/d. Alprazolam and botulinum toxin type A were classified as *'possibly useful'*. Unilateral *Ventralis intermedius* (Vim) thalamic deep brain stimulation, radiofrequency thalamotomy, and MRI-guided focused ultrasound thalamotomy were considered '*possibly useful'*. All the above recommendations were made for limb tremor in ET. There was insufficient evidence for voice and head tremor as well as for the remaining interventions.

Conclusion: Propranolol, primidone and topiramate (>200 mg/d) 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 ET and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies and the use of non-validated clinical scales.

Background

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 neurologic 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 paper, 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 prior published reviews. (4) Literature searches were done using electronic databases including MEDLINE (1966-Dec 2016), the CENTRAL database in the Cochrane Library (1948-2016), and systematic checking of reference lists published in review articles and other clinical reports. Papers selected for review met the

following inclusion/exclusion criteria. Inclusion criteria: 1. any pharmacological, surgical, and non-pharmacological therapies for which there was at least one randomized controlled trial (RCT); 2. non-randomized controlled or non-controlled 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 two 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; 8. full paper 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 non-existent 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 two 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 four 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; Level-III studies - non-controlled 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 cut-off for study inclusion based on quality scores.

Safety evaluation

The clinical information used to make an overall safety evaluation included primarily the adverse 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 papers. The safety discussion within these sections uses a narrative, unsystematic approach due to 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; 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 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 implication of 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 tremor, unilateral *Ventralis intermedius* (Vim)-thalamic deep brain stimulation 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, 15-25) 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). The average treatment duration was 3.5 weeks (range: 1.5 - 8). 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 - 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 - 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 less than 10% of study participants. Other adverse events with impact in clinical practice are known such as fatigue, lightheadedness and sexual dysfunction. (26) 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. (22)

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 (8 studies)

Primidone was studied in eight Level-I studies (14, 20, 27-32) 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 mg/d and 750 mg/d)(32) was assessed in a 12-month double-blind randomized controlled trial that reported a comparable long-term efficacy and absence of tolerance for the therapeutic effect. In a head-to-head comparison of propranolol 120~~-240~~ mg/d and primidone 250-750 mg/d, 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. (20)

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.(31) The combined use of primidone 250 mg qHS and propranolol 80 mg TID (21) 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) due to the side effect profile and potential high discontinuation rates. Overall, primidone was considered 'clinically useful' for clinical practice.

Topiramate (4 studies)

Topiramate was studied in four placebo-controlled Level-I studies (33-36) 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 – 333 mg/d (n=3). There was a documented improvement in both tremor amplitude and ADL measures in three of the four Level-I studies. (33, 34, 36) 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% for topiramate and 9.5% for placebo. (36) Adverse events were responsible for a percentage of drop-outs ranging from 30 - 54.2%. (33, 36)

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 - 100 mg dose range. Topiramate was considered 'clinically useful' for clinical practice for daily doses higher than 200 mg.

Alprazolam (2 studies)

Alprazolam was studied in two placebo-controlled Level-I studies (30, 37) in a total of 46 patients with ET, as monotherapy with a treatment duration of two and four 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 mg (30) or 0.75 mg (37), and the mean daily effective dose was 0.75 (30) and 1.5 (37) mg. Both studies documented a reduction in non-validated 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%) (37) 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 (3 studies)

Botulinum toxin type A was studied in three placebo-controlled Level-I studies (10, 38, 39) that included a total of 168 patients with ET refractory to oral drugs. Dose ranged from 50 - 100 IU targeting forearm (38, 39) 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 (38, 39) 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, (38) being longer for the postural component of the upper limb tremor. (39) Dose-dependent hand weakness by patient report (38, 39) or by measured grip strength (39) 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) due to conflicting results and with an 'acceptable risk with specialized monitoring' (safety recommendation), as the dose dependent limb weakness is of concern. Botulinum toxin type A was considered 'possibly useful' for clinical practice.

Unilateral Vim – Deep Brain Stimulation (7 studies)

We included seven studies assessing unilateral Vim thalamic deep brain stimulation 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%). (40) The primary outcome was the change from baseline in functional status as measured by the Frenchay Activities Index. (40) 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 ± 3.4 (n=7). Overall, tremor was absent or slight in all seven patients. There was greater improvement in the Frenchay Activities Index with Vim-DBS compared with thalamotomy: 6.6 points, 95% CI: 2.5, 10.7. Adverse events were more

frequent in the thalamotomy group (n=16) than in unilateral 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 out 10 ET patients, with an increased severity of intention and postural tremor. The other remaining six studies (12, 41-45) (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, 41-44) with one study reporting on long-term follow-up up to 6 - 7 years. (45) In five of the studies, the effect of unilateral Vim-DBS was assessed comparing an ON-stimulation with an OFF-stimulation condition. (12, 42-45) 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 microsec (pulse width). There was an improvement in various clinical rating scales of severity and performance of activities. Paresthesia (mean incidence overall: 61%, range: 21 to 100) were the most frequent stimulation-related adverse events and decreased in frequency with time. (42) In terms of long-term effect of unilateral Vim-DBS at 2 and 6 - 7 years, studies document 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 pre-operative evaluations. (45)

Unilateral Vim-DBS alone has been compared with sequential bilateral Vim-DBS, in a case series by Ondo et al (46) (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 ± 0.9; bilateral: 1.3 ± 1.2, $P<0.005$) and leg tremor

(unilateral: 2.3 ± 1.1; bilateral: 0.5 ± 0.5, P<0.005), but not for head or voice tremor. In an open label assessment, there was an improvement in ADLs (unilateral: 25.1 ± 3.6; bilateral: 10.3 ± 3.7) and disability (unilateral: 3.5 ± 0.6; bilateral: 1.3 ± 0.6) from baseline to three months after bilateral Vim-DBS. Adverse events were more frequent with bilateral Vim-DBS (16/21; 76%) compared with unilateral Vim-DBS (11/21; 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 (2 studies)

Radiofrequency thalamotomy has been assessed in two studies. Zirh et al. (47) (Quality score, 64.7%) reported a case series of 21 patients with medically intractable ET not otherwise specified that underwent uni- or bilateral thalamotomy. Assessment at both three 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 two out of three patients with bilateral thalamotomy. Schuurman et al. (40) (Quality score, 95.2%) conducted a randomized parallel Level-I study of Vim-DBS *vs.* thalamotomy with 13 patients with severe upper limb tremor due to ET (see details of the study above

in **Unilateral Vim – Deep Brain Stimulation**). 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, radiofrequency unilateral 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 (1 study)

Elias et al. (48) (Quality score, 84.1%) conducted a randomized parallel study of MRI-guided focused ultrasound thalamotomy *vs.* sham procedure in 81 patients with medically refractory moderate-severe upper limb tremor due to ET. MRI-guided focused ultrasound thalamotomy was associated with an improvement in tremor severity ratings by 47% at three 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 to 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, MRI-guided focused ultrasound unilateral 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 CNS-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'* as three out of four studies reported positive efficacy results. For the fourth study, (35) 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 MRI-guided focused ultrasound unilateral 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 conditioned 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 towards 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, (49) 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. 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, as 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 as 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, (50, 51) open label assessment of perampanel, (52) customized approach for botulinum toxin administration to reduce safety for hand tremor, (53) other deep brain stimulation approaches with assessment of targets such as the Zona Incerta/Posterior Subthalamic area, (54) the subthalamic nucleus, (55) use of constant-current (56) or closed loop stimulation (57) paradigms, and novel MRI-guided approaches for thalamotomy. (58) These interventions will likely merit assessment in a future EBM-MDS review on ET.

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Royalties	None
Other	None

Author: Kelly Lyons	
Stock Ownership in medically-related fields	None
Consultancies	None
Advisory Boards	None
Partnerships	None
Honoraria	None
Grants	None
Intellectual Property Rights	None
Expert Testimony	None
Employment	University of Kansas Medical Center
Contracts	None
Royalties	None
Other	President, International Essential Tremor Foundation

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Stock Ownership in medically-related fields	No
Consultancies	No
Advisory Boards	No
Partnerships	No
Honoraria	No
Grants	No

Intellectual Property Rights	No
Expert Testimony	No
Employment	No
Contracts	No
Royalties	No
Other	No

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Stock Ownership in medically-related fields	No
Consultancies	No
Advisory Boards	No
Partnerships	No
Honoraria	No
Grants	No
Intellectual Property Rights	No
Expert Testimony	No
Employment	No
Contracts	No
Royalties	No
Other	No

Author: Giovanni Abbruzzese	
Stock Ownership in medically-related fields	No

Consultancies	No
Advisory Boards	Zambon (Italy)
Partnerships	No
Honoraria	Abbvie, Chiesi, Zambon.
Grants	No
Intellectual Property Rights	No
Expert Testimony	No
Employment	No
Contracts	No
Royalties	No
Other	No

Author: Mark Hallett	
Stock Ownership in medically-related fields	No
Consultancies	No
Advisory Boards	Medical Advisory Boards of CALA Health and Brainsway.
Partnerships	No
Honoraria	No
Grants	NIH Intramural Program. Merz, Allergan, Medtronic, Inc. CALA Health.
Intellectual Property Rights	US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has

	received license fee payments from the NIH (from Brainsway) for licensing of this patent.
Expert Testimony	No
Employment	No
Contracts	No
Royalties	Cambridge University Press, Oxford University Press, Springer, and Elsevier.
Other	No

Author: Dietrich Haubenberger	
Stock Ownership in medically-related fields	None
Consultancies	None
Advisory Boards	Cadent Pharmaceuticals
Partnerships	None
Honoraria	None
Grants	None
Intellectual Property Rights	None
Expert Testimony	None
Employment	National Institutes of Health
Contracts	None
Royalties	None
Other	None

Author: Günther Deuschl	
Stock Ownership in medically-related fields	None
Consultancies	Boston Scientific, Functional Neuromodulation, Aleva, Cavion, Asarina
Advisory Boards	Boston Scientific
Partnerships	None
Honoraria	None
Grants	Medtronic
Intellectual Property Rights	None
Expert Testimony	None
Employment	None
Contracts	None
Royalties	Thieme Publishers
Other	None

Author: Rodger Elble	
Stock Ownership in medically-related fields	None
Consultancies	Biohaven, Cadent, Cavion, Merz, Praxis Medicines
Advisory Boards	Five Microns
Partnerships	None

Honoraria	None
Grants	Kiwanis Neuroscience Research Foundation, Illinois-Eastern Iowa District
Intellectual Property Rights	None
Expert Testimony	None
Employment	SIU Healthcare
Contracts	None
Royalties	None
Other	None

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TABLES AND FIGURE LEGENDS

Table 1 – Definitions for specific recommendations

Table 2 – Summary of efficacy conclusions and implications for practice for limb tremor in Essential tremor

APPENDIX 1.

Remaining members of the MDS Task Force on Tremor:

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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
Non-efficacious	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*		
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

* *specialized monitoring* should follow the clinical good sense, and best medical practices in a given jurisdiction.

Table 2: Summary of efficacy conclusions and implications for practice for limb tremor in ET. See further details in Supplemental materials.

Pharmacological class		Efficacy conclusions	Implications for practice	Safety conclusions
ANTICONVULANTS	Carisbamate	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Gabapentin	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Levetiracetam	Non-efficacious	Not useful	Acceptable risk without specialized monitoring
	Pregabalin	Non-efficacious	Not useful	Acceptable risk without specialized monitoring
	Progabide	Unlikely efficacious	Unlikely useful	Acceptable risk without specialized monitoring
	Topiramate	Efficacious (>200 mg/d)	Clinically useful (>200 mg/d)	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 due 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 due of 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. (1-3)(4)(5)*
	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 hematologic reactions. Serum electrolytes should also be periodically monitored.*
	Acetazolamide	Insufficient evidence	Unlikely useful	Acceptable risk with specialized monitoring
	Amantadine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring

OTHER DRUGS	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 – Deep Brain Stimulation	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring
	Bilateral Vim - DBS	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
	Radiofrequency thalamotomy	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring
	Gamma-knife unilateral thalamotomy	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
	MRI-focused ultrasound unilateral thalamotomy	Likely efficacious	Possibly useful	Acceptable risk with specialized monitoring

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Supplemental materials.

Pharmacological interventions (Detailed description)

BETA BLOCKERS

Propranolol (13 studies)

DuPont et al. (1) conducted a randomized placebo-controlled double-blind cross-over study of propranolol (target dose of 120 mg/d by the second month) in 33 patients with ET who were either untreated or on anti-tremor medication (barbiturates or diazepam). ET was defined as "typical benign ET". The efficacy of propranolol was dependent on the sequence of treatments suggesting an order effect. On clinical severity ratings, 10 patients did not improve during the whole trial. Subjectively, most of the study participants reported a greater benefit on propranolol. There was a significant placebo response on patient's subjective report of improvement (≈50%). One of the 3 drops-outs was related with propranolol (lipothymia). During the propranolol treatment period, insomnia (n=6) and sinus bradycardia (n=4) were more frequent. **Quality score, 55.0%.**

Tolosa et al. (2) conducted a randomized double-blind study of propranolol (maximum dose 120 mg/day) for 6 weeks in 11 patients with ET diagnosed by the presence of a chronic postural tremor involving the upper extremities and potential involvement of other body parts. Patients discontinued all anti-tremor medications before study entry. An improvement in tremor was observed in all patients who received propranolol and was most pronounced in the upper extremities, for the averaged results of a 3-week and 6-week assessment. The results obtained in the grooved pegboard test, handwriting evaluated by two blinded raters and patient impression of change also favored

propranolol. With exception of a single case of mild nausea in the placebo group, no other side effects were reported. **Quality score, 60.5%.**

Jefferson et al. (3) conducted a single-blinded placebo-controlled cross-over study to assess the efficacy of two-week treatment periods of propranolol at different doses (range: 30-640 mg/day, mean effective daily dose of 120-240 mg/d in 11 patients with moderately disabling ET diagnosed on the basis of a characteristic postural tremor of the upper limbs without other neurological abnormalities and a known favorable response to propranolol. A head tremor was allowed. The 11 patients presented objective (outstretched hands, handwriting, spiral and sinusoid drawings, and timed performance peg board test) and subjective patient impression of improvement with propranolol (mean value: 51%; range: 25-90%). There were no side effects below the dose of 120 mg/day of propranolol. Above 120 mg/day, lack of energy (n=3) and transient nocturnal hallucinations (n=1) were reported. **Quality score, 73.7%**

Calzetti et al. (4) conducted a randomized placebo-controlled double-blind crossover study to assess the efficacy of propranolol (120 mg/day for 14 days followed by 240 mg/day for 14 days) and metoprolol (150 mg/day for 14 days followed by 300 mg/day for 14 days) in 16 patients with untreated moderate-to-severe ET, diagnosed on the basis of clinical history and detailed general and neurological examination. There was a prior exposure to propranolol as an anti-tremor medication (range 80-240 mg daily, n=9) and/or as part of a research study (n=15). Three patients failed to complete the trial of the higher dose of propranolol due to the occurrence of shortness of breath (n=2) and non-compliance (n=1). Duration of the washout period was unclear. Propranolol 120 mg/d was superior to placebo on performance tests ($P<0.05$) and patient's self-assessment

(P<0.01). Propranolol 240 mg/d was superior to placebo on all evaluations. **Quality score, 69.0%.**

Baruzzi et al. (5) conducted a randomized placebo-controlled double-blind crossover study to test the efficacy of 4 weeks of treatment with propranolol (mean dose 1.7 mg/kg/day) and phenobarbital (mean dose 1.25 mg/kg/day) in 17 patients with untreated moderately disabling ET (mainly hand tremor). Five patients were excluded from the final analysis (drop-outs > 20%). There was no assessment of a carry-over effect. Only propranolol was significantly better than placebo for the clinical evaluation of tremor severity (P <0.01). Propranolol reduced the amplitude of tremor measured by accelerometry (P <0.01) and was associated with a greater subjective improvement (propranolol: P <0.01). There was no difference between propranolol and placebo in functional tests. One patient dropped out from the study due to bradycardia during propranolol treatment. **Quality score, 72.5%.**

Koller et al. (6) conducted a randomized double-blind crossover study to assess the efficacy of a 2-week treatment of propranolol (120 and 240 mg/day in divided doses) or metoprolol (50 - 250 mg/day in divided doses) in 23 patients with ET diagnosed on the basis of a postural tremor predominantly affecting the upper extremities and neck. The presence of cervical dystonia (n=1) was not an exclusion criterion. Prior treatment experience was not reported. Propranolol was associated with a significant reduction of severity ratings. Approximately 50% of patients responded to both metoprolol and propranolol. A class effect is suggested, as the remaining patients did not respond to either intervention. No reference is made to exclusion of a carry-over effect. The most relevant adverse event was respiratory distress that led to the discontinuation of

propranolol in 3 patients. **Quality score, 59.5%.**

Gorman et al. (7) conducted a randomized placebo-controlled double-blind crossover study that compared the efficacy of propranolol (maximum dose of 40 mg three times a day) and primidone (maximum dose 250 mg three times a day) after 10 days of treatment in 19 patients with untreated ET not otherwise specified. Propranolol significantly reduced limb tremor ($P < 0.01$). Five patients dropped out of the study (> 20% study participants). One patient was excluded and described as being on a likely sub-therapeutic propranolol and one due to intolerance to propranolol. Five of the 14 patients preferred propranolol (35.7%) over primidone. **Quality score, 62.5%.**

Koller et al. (8) conducted a randomized single-blind crossover study of 4-week treatment with primidone (target dosage of 250 mg/d), propranolol (target dosage of 240 mg/d), the combined use of propranolol and primidone, and no treatment in 20 patients with ET not otherwise specified. All patients had hand tremor, six had head tremor and three had voice tremor. Some of the study participants had been medically treated for tremor. There was a washout period of 2 weeks between the various periods. Propranolol improved cup drinking, handwriting, Archimedes spiral drawing, and patient's disability for eating and dressing but did not improve finger tapping, the Purdue pegboard and patient's disability for fine manipulations. Scores for embarrassment were not significantly altered by any of the treatments ($P> 0.05$). In accelerometry, the combined and isolated use of propranolol and primidone were associated with a reduction of both postural and kinetic tremors ($p < 0.01$), and the combined treatment of the two drugs decreased postural tremor more than either alone ($p < 0.05$). **Quality score, 52.8%.**

Koller et al. (9) conducted a randomized placebo-controlled parallel trial of 18 men with essential tremor, of which 9 had tremor of both head and hand and 9 had tremor of the head. Propranolol was administered up to 320 mg/d. Propranolol at 160 and 320 mg/d decreased clinical scores for head and hand tremors ($p < 0.05$) compared with baseline. Tremorographic recording documented a reduction of the head and hand of about 50%, without a difference between 160 and 320 mg/d. Side effects were mild, and did not required treatment discontinuation. **Quality score, 63.2%.**

Cleeves et al. (10) conducted a randomized placebo-controlled double-blind crossover trial of conventional propranolol (80 mg tid) and propranolol-long acting (160, 240 or 320 mg qd) in 23 patients with ET defined by a history of postural and action hand tremor in the absence of other neurological signs and obvious etiological factors. Six of these patients withdrew anti-tremor medication prior to the study, and the remaining were treatment *naïve*. Fifteen patients completed the study. At the end of treatment periods, clinical rating of tremor improved significantly with all doses of conventional propranolol, and only the dose of 320 mg/d was associated with an improvement in performance tasks. Patients' self-rating scores improved with conventional propranolol. There was no assessment for a carry-over effect. **Quality score, 60.0%.**

Mally and Stone (11) conducted a randomized double-blind placebo-controlled crossover study of theophylline 150 mg/d and propranolol 80 mg/d in 4-week treatment periods in 10 patients diagnosed *de novo* with ET defined by the presence of a postural tremor, no rest tremor, no significant exacerbation of tremor with action and no signs of Parkinson's disease or cerebellar disease. Tremor was measured by a volumetric

assessment test determined by the amount of water in a cup held between the thumb and fingers. Propranolol was better than placebo ($p<0.05$). Three patients reported dizziness, sleep problems and anxiety with propranolol. **Quality score, 68.4%.**

Gironell et al. (12) conducted a randomized placebo-controlled double-blind cross-over study of propranolol (120 mg/day) and gabapentin (1200 mg/day) in 16 patients with disabling moderate-severe ET. Patients discontinued prior anti-tremor medications (n=10) or were treatment *naïve* (n=6). Patients with dystonia were excluded. There was a 1-week washout period between treatment periods. At day 15, propranolol was associated with a reduction in the composite outcome of tremor clinical severity and task performance (P = 0.007), as well as for activities of daily living (TCRS, P = 0.002) and patients' subjective assessment (only for TCRS, P = 0.006) compared with placebo. The authors point out that propranolol and gabapentin could be associated with a benefit in the same individual patient but in distinct outcome measures. Propranolol was associated with instability (n=3). Daily somnolence was reported with propranolol (n=1) and placebo (n=1). **Quality score, 100%.**

Yetimalar et al. (13) conducted a randomized double-blind crossover study of olanzapine 20 mg/d and propranolol 120 mg/d in 38 patients with ET. ET was diagnosed using the TRIG criteria (14). All anti-tremor medications were discontinued 1 month prior to study initiation. 30-day treatment periods were separated by a 2-week wash-out period. Overall clinical severity of tremor, impact of tasks of daily living and a global quality of life patient assessment significantly improved with both propranolol and olanzapine (P = 0.0001). Tremor improvement was measured globally with no breakdown of the different tremor locations. On day 30, propranolol significantly reduced

all efficacy measures (P = 0.0001). Mean global quality of life was significantly improved with propranolol. Adverse events with propranolol included fatigue (n=8), nausea (n=6), and impotence (n=6). **Quality score, 73.7 %.**

Propranolol Long-Acting (LA) (1 study)

Cleeves et al. (10) (see above for more study details) propranolol LA (160, 240 or 320 mg qd) was assessed. Side effects (skin eruption and exacerbation of tremor) were responsible for two patients not completing the study when taking propranolol-long acting 320 mg/d. Clinical rating of tremor improved significantly with propranolol-long acting 160 mg/d, and only the dose of 320 mg/d was associated with an improvement in performance tasks. Patients' self-rating scores improved with propranolol-long acting. There was no assessment for a carry-over effect. **Quality score, 60.0%.**

Nadolol (1 study)

Koller et al. (15) conducted a randomized placebo-controlled double-blind cross-over study of nadolol (120 mg qd for 2 weeks followed by 240 mg for 2 weeks) in 10 patients with ET who had discontinued anti-tremor medication 2 weeks before study initiation. There was a 1-week washout period between treatment periods. Nadolol was associated with an improvement in the composite score of the clinical severity rating scale as well as tremor amplitude measured by accelerometry (P < 0.05). There was no statistical difference in outcome measures between the two doses of nadolol used in the study. Only patients (n=6) who had previously responded to propranolol experienced significant tremor reduction with nadolol. No adverse events were reported. **Quality score, 72.5%.**

Metoprolol (3 studies)

Calzetti et al. (4) (see above for more study details) conducted a randomized placebo-controlled double-blind crossover study to assess the efficacy of propranolol (120 mg/day for 14 days followed by 240 mg/day for 14 days) and metoprolol (150 mg/day for 14 days followed by 300 mg/day for 14 days) in 16 patients with untreated moderate-to-severe ET, diagnosed on the basis of clinical history and detailed general and neurological examination. Metoprolol was not significantly different from placebo, irrespective of the dosage or the method of assessment. **Quality score, 69.0%.**

Leigh et al. (16) conducted a randomized placebo-controlled double-blind cross-over study to assess the comparative efficacy of atenolol (24 patients 50 mg bid), metoprolol (17 patients 50 mg bid, 7 patients 100 mg bid), sotalol (24 patients 80 mg bid) and no treatment in 24 patients with ET. The diagnosis was established by the presence of a postural hand tremor, with or without an intention tremor and head titubation, in the absence of a rest tremor or other extra-pyramidal and cerebellar features. Anti-tremor medications were discontinued prior to study initiation. Metoprolol ($P<0.05$) were superior to placebo on subjective assessments, but not on the blinded assessment of performance tasks or in the Gibson maze. There were no side effects. **Quality score, 76.3%.**

Koller et al. (6) (see above for more study details) conducted a randomized double-blind crossover study to assess the efficacy of a 2-week treatment of propranolol (120 and 240 mg/day in divided doses) or metoprolol (50, 150, and 250 mg/day in divided doses) in 23 patients with ET. Metoprolol was associated with a significant reduction of clinical

severity ratings. **Quality score, 59.5%.**

Atenolol and Sotalol (1 study)

Leigh et al. (16) (see above for more study details) conducted a randomized placebo-controlled double-blind cross-over study to assess the comparative efficacy of atenolol (50 mg bid), metoprolol (50 – 100 mg bid,) and sotalol (80 mg bid) in 24 patients with ET. Atenolol ($P<0.05$) was superior to placebo on subjective assessments, on the blinded assessment of performance tasks ($P<0.05$) but not in the Gibson maze. Sotalol ($P<0.01$) was superior to placebo on subjective assessments and on the blinded assessment of performance tasks but not in the Gibson maze. There were no side effects. **Quality score, 76.3%.**

PRIMIDONE AND BARBITURATES

Primidone (9 studies)

Findley et al. (17) conducted a randomized placebo-controlled (pyridoxine, 20 mg twice daily) double-blind crossover study to assess the efficacy of primidone (mean daily dosage: 590 mg/d, range: 125-750 mg/d) in 11 patients with moderate to severe ET (not otherwise specified) *naïve* to anti-tremor medication. Results favored primidone compared with placebo for reduction of tremor amplitude. No clinical efficacy data was reported. Only seven of the 11 patients achieved the maximum dose of primidone due to the occurrence of side effects. **Quality score, 63.2%.**

Findley et al. (18) conducted a randomized, placebo-controlled (pyridoxine, 20 mg twice daily) double-blind crossover study to test the efficacy of primidone (62.5 mg/d titrated to a max of 750 mg/d) in 22 patients with moderate to severe ET (chronic monosymptomatic postural tremor affecting the hands and/or the head) that were either *naïve* to treatment or had discontinued propranolol prior to the start of the study. Sixteen patients completed the study. Primidone significantly improved clinical severity assessments ($P < 0.02$), performance tasks ($P < 0.01$), and patient self-evaluation ($P < 0.01$) and was significantly superior to placebo in reducing the amplitude of hand tremor ($P < 0.01$). There were 5 dropouts due to acute toxic reaction after the first 62,5 mg dose of primidone. Of the patients who completed the study, four only tolerated a daily dose of between 125 and 500 mg. Side effects requiring adjustment of the dose of primidone included sedation, day-time sleepiness, tiredness and depression**. Quality score, 75.0%.**

Gorman et al. (7) (see above for more study details) conducted a randomized placebo-controlled double-blind crossover study that compared the efficacy of propranolol (120 mg/day), primidone (maximum dose 750 mg/ day) in 19 patients with untreated ET. Primidone significantly reduced limb tremor ($P < 0.01$). Three out of the five patients that dropped out from the study (> 20% study participants) were due to intolerance to primidone. Nine of the 14 patients preferred primidone (64.3%), but primidone caused more bothersome side effects including malaise, dizziness and unsteadiness at the initial dose of 62.5 mg/day. **Quality score, 62.5%.**

Koller et al. (8) (see above for more study details) conducted a randomized single-blind crossover study of primidone (target dose of 250 mg/d), propranolol (80 mg tid), the combined use of propranolol and primidone, and no treatment in 20 patients with ET not otherwise specified. Primidone improved performance tasks, and patient's disability for eating and dressing but did not improve finger tapping, the Purdue pegboard and patient's disability for fine manipulations. Scores for embarrassment were not significantly altered by primidone ($P> 0.05$). In accelerometry, the combined and isolated use of propranolol and primidone were associated with a reduction of both postural and kinetic tremors ($p < 0.01$) and the combined treatment of the two drugs decreased postural tremor more than either alone ($p < 0.05$). **Quality score, 52.8%.**

Sasso et al. (19) conducted a randomized double-blind placebo-controlled crossover study of phenobarbital (mean maintenance dose = 136±25 mg/day) and primidone (mean maintenance dose = 740 ±35 mg/day) in 16 patients with ET (15 patients treatment *naïve*). ET was defined as chronic symptomatic tremor affecting predominantly the hands, without other neurologic disease or biochemical abnormalities. Primidone was

better than phenobarbital (P<0.05), and the latter did not differ from placebo (P>0.05), using a physician's assessment of postural hand tremor, a patient self-assessment of the functional severity of the tremor and performance tests. The magnitude of effect is unclear, as efficacy results are only displayed in figures. There were three drop-outs due to fatigue (primidone, n= 1; phenobarbital, n=1) and poor compliance (n=1). The most frequent reported adverse events were drowsiness and fatigability (both drugs), ataxia (mostly with phenobarbital), and transient nausea and vertigo (mostly with primidone). A follow-up report of the 11 patients that had a benefit with primidone, reported that the anti-tremor effect of primidone was present up to 12 months measured by accelerometry, although the clinical benefit was less consistent and present only up to 6 months, as measured by physician assessments (20). **Quality score, 65.0%.**

Sasso et al. (21) conducted a double-blind placebo-controlled crossover study of phenobarbital (mean maintenance dose =128 ± 8.2mg/day), primidone (maximum dose: mean maintenance dose = 734 ± 9.8 mg/day) in 18 patients with ET (mono-symptomatic postural hand and/or head tremor). After 5 weeks of treatment, primidone decreased hand tremor amplitude (accelerometry) compared with placebo (P<0.01), but not phenobarbital when compared with placebo. Neither primidone nor phenobarbital was associated with significant changes in the amplitude of head tremor. The magnitude of effect is unclear, as efficacy results for amplitude of head tremor are displayed in a figure. There were three drop-outs due to fatigue (primidone, n=1; phenobarbital, n=1) and poor compliance (n=1). Sedation/drowsiness was more frequently reported as an adverse event with both primidone (8/11 cases with adverse events) and phenobarbital (9/9 cases with adverse events). **Quality score, 67.5%.**

Gunal et al. (22) conducted a placebo-controlled double-blind crossover study of 4-week treatment periods with acetazolamide, alprazolam, primidone (mean dose 406 mg/d) and placebo in 22 patients with ET diagnosed using the Tremor Research Investigation Group (TRIG) criteria.(23) All anti-tremor medications were discontinued two weeks prior to enrolment. Primidone was superior to placebo in functional tasks (writing, spiral drawing, feeding, and social activities) and a patient self-evaluation of global improvement, and there was no significant difference reported between primidone and alprazolam (p=0.062). 42% of the patients (n = 8) developed acute side effects including nausea, ataxia, dizziness, confusion with the initial dose of primidone (62.5 mg), and these patients discontinued treatment. Three patients dropped-out due to treatment non-compliance. **Quality score, 70.0%.**

O'Suilleabhain et al. (24) conducted a randomized double-blind double-dummy study to assess if different titration regimens of primidone were associated with a better tolerability profile and better compliance. 40 patients with ET (MDS consensus criteria) without any anti-tremor medication were randomized to either one of the titration regimens. The relative risk of medication cessation due to side effects was 1.9 (95% confidence interval: 0.4 to 9.2), with a greater risk for the suspension group. Subjective and objective changes in quality of life or tremor amplitude were similar in the suspension and the tablet groups. After 18 months, the trial was stopped due to slow recruitment. **Quality score, 78.9%.**

Serrano Duenas et al. (25) conducted a randomized double-blind parallel trial with 1-year follow-up evaluating two doses of primidone (250 mg/d and 750 mg/d) in 113 ET patients (category II classification proposed by Marsden (26)). 87 patients completed the

study. No difference was found between primidone 250 mg/day and 750 mg/day for the control of ET after 12 months of treatment, as measured by rater and patient global estimations of change and by the Fahn-Tolosa-Marin Tremor Rating (FTM) Scale. Fifteen patients did not complete the study due to undesirable side effects, five due to a negative response, and six were lost to follow-up. The percentage of patients who didn't complete the study was significantly higher for primidone 750 mg/day (P< 0.04) and was more frequently due to undesirable side effects. The side effects were present during the first weeks of the treatment and all patients abandoned the study for these reasons within the first 3 months. **Quality score, 66.7%.**

Phenobarbital and Phenobarbitone (primidone metabolite) (4 studies)

Baruzzi et al. (5) (see above for more study details) conducted a randomized placebo-controlled double-blind crossover study to test the efficacy of propranolol (mean dose 1.7 mg/kg/day) and phenobarbital (mean dose 1.25 mg/kg/day) for one month in 17 patients with untreated moderately disabling ET (mainly hand tremor). Phenobarbital significantly reduced the amplitude of tremor measured by accelerometry (P <0.01) and was associated with subjective improvement (P <0.05), but there was no effect for the clinical evaluation of tremor severity as well as in functional tests. **Quality score, 72.5%.**

Findley et al. (27) conducted a randomized placebo-controlled (pyridoxine, 20 mg twice daily) double blind crossover study of phenobarbitone (60 mg twice daily), after 5 weeks of treatment in 12 patients with untreated ET, of which 11 patients were treatment *naïve*. ET was defined as chronic symptomatic postural tremor of the hands, with no other neurologic disorder or biochemical abnormality. Phenobarbitone was better than placebo

on accelerometric measurement (P<0.01) and clinical severity (P<0.05) but not as per patient self-assessment or performance tasks (P>0.05). The most frequent adverse events associated with phenobarbitone were mild fatigue (n=5) and drowsiness (n=3). **Quality score, 77.5%**

Sasso et al. (19) (see above for more study details) conducted a randomized double-blind placebo-controlled crossover study of phenobarbital (mean maintenance dose = 136±25 mg/day) and primidone (mean maintenance dose = 740 ±35 mg/day) in 16 patients with ET, of which 15 patients were treatment *naïve*. Phenobarbital did not differ from placebo (P>0.05). There was a drop-out due to fatigue secondary to phenobarbital. The most frequent reported adverse events were drowsiness and fatigability and ataxia. **Quality score, 65.0%.**

Sasso et al. (21) (see above for more study details) conducted a double-blind placebo-controlled crossover study of phenobarbital (mean maintenance dose =128 ± 8.2mg/day), primidone (mean maintenance dose = 734 ± 9.8 mg/day) in 18 patients with ET (mono-symptomatic postural hand and/or head tremor). Phenobarbital did not decrease hand tremor amplitude compared with placebo nor did it change the amplitude of head tremor. There was one drop-outs due to fatigue. Sedation/drowsiness was more frequently reported as an adverse event with (9/9 cases with adverse events). **Quality score, 67.5%.**

T2000 (1,3-dimethoxymethyl-5,5-dephenyl-barbituric acid) (3 studies)

Melmed et al. (28) conducted two double-blind, placebo-controlled studies of T2000 in 34 ET patients diagnosed with NIH criteria (29). In the first study, 12 ET patients there was a significant reduction in tremor with T2000 compared to placebo (p=0.03). One

patient discontinued T2000 due to rash followed by febrile illness. In the second study, in 22 ET patients there was a significant reduction in tremor with T2000 at all assessments from Day 2 through Day 20 compared to baseline ($p<0.001$). At 20 days, there was a reduction of tremor rating scale scores of 8.2 with T2000 and 6.2 with placebo. However, there was no significant difference between T2000 and placebo ($p=0.1647$). One patient developed a rash with T2000. **Quality score, 80.0% (both studies).**

Hadj-Tahar et al. (30) conducted a double-blind, placebo-controlled cross-over study of T2000 in 10 patients with ET (NIH Criteria) that at least moderate in severity (FTM scale). Eight participants withdrew due to adverse events, including CNS-related adverse events. **Quality score, 47.1%.**

BENZODIAZEPINES

Alprazolam (2 studies)

Huber and Paulson (31) conducted a double-blind, placebo-controlled study of 24 ET patients (diagnostic criteria not described). All anti-tremor medications were discontinued one week prior to enrollment. Alprazolam was given for a 2-week period (range, 0.75 to 2.75mg/d). Tremor severity was significantly improved with alprazolam compared to placebo ($p<0.01$) as well as pursuit rotor, anxiety scores ($p<0.05$). and investigator impression of global improvement ($p<0.05$). Patient ratings were also improved but did not reach significance (alprazolam 2.8, placebo 3.5). Fifty percent of the alprazolam group reported drowsiness or sedation, although this was not significantly increased compared to the placebo group. In addition, 2 patients reported constipation and 1 reported dry mouth with alprazolam. **Quality score, 70.0%.**

Gunal et al. (22) (see above for more study details) conducted a double-blind, placebo-controlled, crossover study of alprazolam in 22 definite ET patients diagnosed by Tremor Research Investigation Group (TRIG) criteria (23). There was a significant reduction in tremor with alprazolam compared to placebo ($p=0.03$), and there was no difference in tremor reduction between alprazolam and primidone ($p=0.06$). There were no adverse events reported with alprazolam. **Quality score, 70.0%.**

ANTICONVULSANTS

Carisbamate (1 study)

Elble et al. (32) conducted a multicenter, randomized, double-blind, cross-over, placebo-controlled study of Carisbamate (400 mg/d) in 62 patients with a diagnosis of ET. Carisbamate did not differ from placebo in the change in FTM (P = 0.94) or on measures of affect, mood, or quality of life. Headache was the most commonly reported adverse event, but the adverse event profile was comparable in both the placebo and Carisbamate groups. **Quality score, 94.7%.**

Gabapentin (2 studies)

Pahwa et al. (33) conducted a double-blind crossover study to test the efficacy of gabapentin (1800 mg/day) and placebo in 20 ET patients. Eighteen patients completed the study and two patients dropped out as a result of adverse effects which resolved when the medication was discontinued. There was no significant difference for total FTM SCALE, hand tremor score, handwriting scores, or pouring scores, as well as SIP scores, between placebo and gabapentin. **Quality score, 70.0%.**

Ondo et al. (34) conducted a double-blind, placebo-controlled, cross-over trial evaluating two doses (1800 mg per day and 3600 mg per day) to establish the efficacy and tolerability of gabapentin in 25 patients with ET. Statistically improved pouring scores, ADL scores, tremor amplitude scores were observed when compared with placebo. The results were similar for high and low dosages. Statistical regression models did not demonstrate any significant predictors of response. **Quality score, 85.0%.**

Levetiracetam (2 studies)

Handforth and Martin (35) performed a pilot single-site study assessing the efficacy and safety of levetiracetam (maximum dose: 3000 mg/d) in 12 randomized ET subjects, using a placebo-controlled, double-blind, randomized crossover design. There was no statistically significant difference in response between placebo and levetiracetam on tremor rating scales or accelerometry measure. **Quality score, 72.5%.**

Elble et al. (36) conducted a double-blind, placebo-controlled crossover trial of levetiracetam (maximum dose: 3000 mg/d) in 15 patients with essential hand tremor. Patient enrollment was stopped due to futility after an interim analysis. **Quality score, 81.6%.**

Pregabalin (3 studies)

Zesiewicz et al. (37) performed a pilot, double-blind, placebo-controlled, randomized trial to evaluate the efficacy and tolerability of pregabalin (maximum dose of 600 mg/day), in 22 patients with ET. There was a greater reduction in tremor amplitude in the pregabalin group compared with the placebo group, as measured by accelerometry. Action tremor limb scores on the FTM SCALE part A subsection also improved in the pregabalin group compared with the placebo group. However, there were no significant differences in the FTM SCALE total scores between the two groups, nor in the FTM SCALE parts A, B and C scores. Pregabalin was well tolerated, with about one-third of patients dropping out of the study because of adverse events. **Quality score, 86.8%.**

Ferrara et al. (38) conducted a double-blind, crossover-design study to assess the tolerability and efficacy of pregabalin (150-600 mg/day) in 20 patients with ET. There was no improvement in any of the FTM SCALE measures and a statistically significant worsening of the Quality of Life in ET Questionnaire (QUEST) scores while patients were taking pregabalin. There were no significant differences between the pregabalin and placebo groups with respect to adverse events, the most common being drowsiness and dizziness. **Quality score, 72.5%.**

Zesiewicz et al. (39) performed a double-blind, placebo-controlled randomized study of pregabalin to evaluate the efficacy and tolerability of pregabalin in 29 patients diagnosed with ET (maximum dose of 450 mg/day, mean daily dose: 329 +/- 127 mg). There was no significant change in the pregabalin group compared with placebo for the FTM total score, subscale scores, physician-assessed clinical global impression scale, and pain rating scale. **Quality score, 81.6%.**

Progabide (2 studies)

Mondrup et al. (40) performed a double-blind crossover trial of two 2-week treatment periods, recruiting 18 patients with benign ET to test the efficacy of progabide, a gamma-aminobutyric acid agonist. No statistically significant difference could be shown in any respect between progabide and placebo in tremor score and tremor amplitude. No side-effects were reported. **Quality score, 63.2%.**

Koller et al. (41) conducted a double-blind, placebo-controlled crossover study in ten patients with ET. No improvement in clinical rating scale, accelerometry, and patient self-assessment was observed. **Quality score, 58.3%.**

Topiramate (4 studies)

Connor et al. (42) investigated the safety and efficacy of topiramate (400 mg/d to maximum tolerated dose) as monotherapy or adjunctive treatment of hand ET in a placebo-controlled, crossover study (n = 24). Topiramate induced significantly greater reductions from baseline based in each of the normalized tremor scale subscores (location/severity, specific motor tasks/functional disabilities, and tremor-resultant functional disabilities). Most common adverse events were appetite suppression/weight loss and paresthesias. **Quality score, 82.5%.**

Connor et al. (43) combined the results of three randomized, double-blind, placebo-controlled, crossover trials that followed a common protocol. Study subjects were adults with untreated or treated moderate to severe ET involving the upper extremities. Patients were randomized to a double-blind sequence of topiramate (400 mg/d or maximum tolerated dose) then placebo (n = 30) or placebo then topiramate (n = 32) with a 2-week washout period separating the 10-week double-blind treatment phases. The total tremor score of the FTM scale was significantly lower with topiramate vs. placebo. The change from baseline in FTM SCALE total and subscale scores was significantly greater with topiramate treatment. Adverse events accounted for 13 of 18 discontinuations during topiramate treatment and 5 of 10 discontinuations during placebo exposure. Adverse events reported by two or more patients discontinuing topiramate were nausea (n = 3), paresthesia (n = 3), and concentration/attention difficulty (n = 2). **Quality score, 80.0%.**

Frima and Grünewald (44) conducted a double-blind, placebo-controlled crossover study of topiramate (25 - 100 mg daily) in ET, using accelerometry, spirography, and an

activities of daily living questionnaire. There was no significant difference in the outcome measures. **Quality score, 65.0%.**

Ondo et al. (45) in a multicenter, double-blind, placebo-controlled, parallel-design trial, patients with moderate to severe ET of the upper limbs were randomized to 24 weeks of treatment with placebo or topiramate (target dose, 400 mg/day) as monotherapy or as an adjunct to one anti-tremor medication. Mean percentage improvement in overall FTM SCALE scores was 29% with topiramate at a mean final dose of 292 mg/day and 16% with placebo ($p < 0.001$). Topiramate was associated with greater improvement in function and disability ($p = 0.001$). Adverse events (paresthesia, nausea, concentration/attention difficulty, and somnolence) were treatment limiting in 31.9% of topiramate patients and 9.5% of placebo patients. **Quality score, 90.0%.**

Zonisamide (2 studies)

Zesiewicz et al (46) performed a double-blind placebo-controlled randomized trial to evaluate the efficacy and tolerability of zonisamide in 20 patients with ET who were randomized to receive zonisamide (up to 200 mg/day) or placebo. Zonisamide was effective in reducing tremor amplitude as measured by accelerometry. However, zonisamide did not provide significant improvements in the FTM SCALE total score or its subsections as well as on the Clinical Global Impression-Change (CGI-C) compared to placebo and was only modestly well tolerated. **Quality score, 84.2%.**

Song et al. (47) conducted a pilot study to test the efficacy of zonisamide in the treatment of patients with isolated head tremor (n=12). Each subject with isolated head tremor was randomly treated with either zonisamide or propranolol. Statistically significant

differences between the effects of zonisamide and propranolol on the patients' scores on part A of the FTM SCALE were observed. Zonisamide was significantly more effective against isolated head tremor than propranolol. **Quality score, 81.6%.**

CALCIUM CHANNEL BLOCKERS

Flunarizine (1 study)

Biary et al. (48) conducted a double-blind, placebo-controlled, crossover study of 1 month treatment of flunarizine (10 mg) in 17 ET patients, diagnosed as having postural and kinetic hand tremor. Tremor medications were discontinued at least 1 month prior to study entry. In the 15 patients that completed the study (2 lost to follow-up), there was a significant improvement in tremor scores (p=0.0006) and tremor amplitude (p=0.0003) with flunarizine compared to placebo. The only adverse event reported with flunarizine was mild daytime sedation in two patients. **Quality score, 65.0%.**

Nimodipine (1 study)

Biary et al. (49) conducted a double-blind, placebo-controlled, crossover study of a two-week treatment of nimodipine (30 mg four times daily) in 16 de novo ET patients diagnosed as having postural and kinetic hand tremor. In the 15 patients that completed the study, eight improved (53%). Tremor scores significantly improved compared to baseline from 3.3 to 1.8 with nimodipine (p=0.001), and there was no change with placebo (3.3 to 3.2; p=0.33). Tremor amplitude was reduced from 118 to 55 with nimodipine (p=0.0014) and from 118 to 108 with placebo (p=0.075) compared to baseline. The only adverse event reported with nimodipine was headache and heartburn in one patient that was withdrawn from the study. **Quality score, 62.5%.**

CARBONIC ANHYDRASE INHIBITORS

Methazolamide (1 study)

Busenbark et al. (50) conducted a double-blind, placebo-controlled, crossover study of 10-day treatment with methazolamide (mean dose 208mg/d) in 25 ET patients diagnosed as having postural and kinetic hand tremor causing functional disability. All anti-tremor medications were discontinued 1 month prior to enrollment. There were no significant differences reported between methazolamide and placebo on any of the efficacy measures. Ten patients (40%) discontinued methazolamide due to adverse events. Adverse events with methazolamide in those that completed the study included most frequently paresthesias (n=12) and drowsiness (n=8). **Quality score, 62.5%.**

Acetazolamide (1 study)

Gunal et al. (22) conducted a double-blind, placebo-controlled, crossover study of acetazolamide in 22 definite ET patients diagnosed by Tremor Research Investigation Group (TRIG) criteria. The mean dose of acetazolamide was 562mg/d. There were no significant differences reported between acetazolamide and placebo on any of the measures. Tremor intensity was decreased by 8.7% with acetazolamide compared to placebo (p=0.81). The only adverse event reported with acetazolamide was tolerable paresthesias in 3 patients. **Quality score, 70.0%.**

OTHER PHARMACOLOGICAL INTERVENTIONS

Amantadine (1 study)

Gironell et al. (51) conducted a double-blind, placebo-controlled, crossover study of a 14 day treatment with amantadine (200 mg/d) in 16 ET patients diagnosed as chronic, persistent, bilateral postural tremor of the upper extremities with no other neurological disease or no other known cause of tremor confirmed by neurophysiological criteria, of which eleven were taking anti-tremor medications. Fifteen patients completed the study; one discontinued due to anxiety and an increase in postural tremor. There were no significant differences between amantadine and placebo on modified FTM scale(52), patient assessment of change, the Bain self-report of disability scale(53) and accelerometry. Adverse events reported with amantadine were anxiety and postural tremor (n=5), sleep problems (n=4), dry mouth (n=2) and blurred vision (n=1). **Quality score, 85.0%.**

Isoniazid (1 study)

Hallett et al. (54) conducted a double-blind, placebo-controlled, crossover study of isoniazid (maximum dose: 1200 mg/d) in 11 ET patients (diagnostic criteria not described). The authors reported no improvement in the majority of patients; two ET patients had some tremor reduction and two others seemed to improve but discontinued due to AEs. Three patients had elevated liver enzymes and discontinued isoniazid and one other discontinued due to dizziness. **Quality score 62.0%.**

Mirtazapine (1 study)

Pahwa and Lyons (55) conducted a double-blind, placebo-controlled, crossover study of a 4-week treatment of mirtazapine (maximum dose: 45 mg/g) in 17 ET patients with action tremor of the upper extremities, no rest tremor and no other neurological signs (Bain criteria), of which thirteen were taking anti-tremor medications. Four discontinued the study, three due to AEs (nausea, polyuria, gait/balance difficulty; drowsiness, blurred vision; drowsiness, dry mouth and bad taste in mouth) and one discontinued due to addition of an anti-tremor medication. There were no significant differences reported between mirtazapine and placebo on any FTM scale, patient global improvement, depression (BDI) and quality of life (PDQ-39). Adverse events reported with mirtazapine were drowsiness in three subjects, dry mouth, weight gain, polyuria and itching each in 2 subjects and confusion in one subject. **Quality score, 72.5%.**

Olanzapine (1 study)

Yetimalar et al. (13) conducted a double-blind, crossover study comparing 30-day treatment with olanzapine (20mg/d) and propranolol (120 mg/d) in 38 ET patients. (See above for details on study description). Total tremor score was improved from 2.4 ± 0.5 at baseline to 0.6 ± 0.5 with olanzapine. Patients were significantly more improved with olanzapine compared to propranolol on all tasks ($p<0.05$), except hygiene ($p=0.08$). Adverse events with olanzapine included sedation/drowsiness (n=7), fatigue (n=6), dizziness (n=5) and nausea (n=5). **Quality score, 73.7%.**

Theophylline (1 study)

Mally and Stone (11) conducted a double-blind, placebo-controlled, crossover study of a 4–week treatment of 150mg/d of theophylline or 80mg/d of propranolol. (See above for details on study description). There was significant improvement with both theophylline (92.6 ± 16.2) and propranolol (92.2 ± 17.4) compared to placebo (79.9 ± 23.5) ($p<0.05$). Sixty percent reported improvement with propranolol and 80% reported improvement with theophylline. There were no AEs reported with theophylline. **Quality score, 68.4%.**

Trazodone (2 studies)

Koller et al. (56) conducted a double-blind, placebo-controlled, crossover study of 6-week treatment of trazodone (up to 150 mg/d) in 10 ET patients diagnosed by clinical history and examination. All anti-tremor medications were discontinued four weeks prior to enrollment. There were no significant changes with trazodone or placebo in postural or kinetic tremor with clinical ratings or accelerometry. Postural hand tremor amplitude was increased 2.6% with trazodone and 5.1% with placebo compared to baseline. Kinetic hand tremor was decreased by 8.3% with trazodone and 3.2% with placebo compared to baseline. Two patients reported drowsiness with trazodone. **Quality score, 68.4%.**

Cleeves and Findley (57) conducted a double-blind, placebo-controlled, crossover study of a 4-week treatment of trazodone (up to 150 mg/d) in 14 ET patients (diagnostic criteria and body parts affected not described) taking no anti-tremor medications. Only 9 patients completed the study as five (36%) withdrew due to personal reasons, which were not

disclosed. There were no significant differences reported between trazodone and placebo on any of the measures (clinical ratings self-report spirals, accelerometry). Adverse events with trazodone included drowsiness in four patients and constipation in one patient. **Quality score, 52.8%.**

BOTULINUM TOXIN (4 studies)

Pahwa et al. (58) performed a double-blind, placebo-controlled study in 10 patients with head tremor. Of note, only three participants had pure head tremor. The participants received two treatments approximately three months apart, one with botulinum toxin injections (40 IU into each sternocleidomastoid and 60 IU into each splenius capitis muscles) and another with normal saline injections and they were assessed before each treatment and at 2, 4, and 8 weeks after injections. The subjective and clinical rating evaluations as well as accelerometry findings did not differ statistically between the botulinum toxin and placebo groups. **Quality score, 71.0%.**

Jankovic et al. (59) performed a randomized controlled study with a parallel design of botulinum toxin or placebo in 25 patients with moderate to severe essential hand tremor. The participants were randomized to receive either 50 U of botulinum toxin type A or placebo injections into the wrist flexors and extensors of the dominant limb. A second injection (100 U) was administered four weeks later if no response was observed after the first injection; one patient was withdrawn from the study because of pregnancy. Four weeks after treatment injection, there was a significant improvement in the severity of action tremor in patients treated with botulinum toxin as compared with placebo, and this effect was maintained for the duration of the study: -3 (botulinum toxin type A) vs - 0.82 (placebo); $p < 0.05$) There were no significant change in the UTRA. At week 4, mild to moderate finger weakness was observed in the subjects treated with botulinum toxin (42% to 50%) and in none of the subjects treated with placebo. Therefore, the investigators and patients were not truly blinded. **Quality score, 85.0%.**

Brin et al. (60) compared low-dose (50 U) or high-dose (100 U) botulinum toxin type A or vehicle placebo treatment injected into the wrist flexors and extensors in a 16-week randomized, double masked, controlled trial. Clinical assessments included tremor severity rating scales, tremor treatment response, motor tasks and functional ability. Grip strength was evaluated by clinical rating and by a dynamometer. The tremor severity rating scale indicated a significant difference from baseline for the low- and high-dose groups for postural tremor after 4 to 16 weeks and for kinetic tremor only at the 6-week evaluation as compared with the vehicle placebo injection. Measures of motor tasks and functional disability were not consistently improved with botulinum toxin type A treatment. Grip strength was reduced in both the botulinum toxin type A groups as compared with the placebo group. Dose-dependent hand weakness was the main adverse reaction. **Quality score, 95.2%.**

SURGICAL INTERVENTIONS

Unilateral Vim – Deep Brain Stimulation (7 studies)

Hubble et al. (61) reported a case series of 19 patients with a diagnosis of ET and disabling medication-refractory upper limb tremor (FTM scale grade 3-4) who underwent unilateral Vim Deep Brain Stimulation (DBS). Anti-tremor medication was stopped at least one month prior to surgery. At 12 weeks, the average±SD parameters of stimulation were: amplitude = 3.01 ± 1.05 V, frequency = 161.9 ± 29.1 Hz, pulse width = 116.9 ± 86.1 microsec. There was a significant ($p < 0.001$) mean improvement from baseline in the four types of tremor at 12 weeks, in an ON-stimulation condition only on blinded and randomly ordered video ratings: rest tremor (0.89 points), kinetic tremor (1.79 points), distal postural (2.05 points) proximal postural (2.21 points), using the FTM scale. There was no difference between the different kinds of tremor. There were no severe or unexpected DBS-related adverse events. **Quality score, 72.2%**

Koller at al. (62) reported a case series of 29 patients with a diagnosis of disabling and medically refractory ET who underwent unilateral Vim-DBS. ET was defined as a postural or kinetic hand tremor in absence of other neurologic signs. Anti-tremor medication was stopped at least one month prior to surgery in 28 patients. The average±SD parameters of stimulation were: amplitude = 3.01 ± 1.1 V, frequency = 116.9 ± 86.1 Hz, pulse width=161.9 ± 29.1 microsec. At 12 weeks after surgery, the comparison of blinded ON- and OFF-stimulation conditions showed a significant decrease in tremor severity contralateral to the placement of the electrode, as measured by the FTM Scale (values not provided) and a significant improvement ($P<0.001$) in

some performance activities (physician assessed). In the patient's global assessment of disability, 23 patients (79%) reported a marked improvement (>50%). Six patients were not implanted and were not followed-up in the study because of lack of intraoperative tremor suppression (two patients), hemorrhage (two patients), withdrawal of consent (one patient) and persistent microthalamotomy effect (one patient). Transient paresthesias (79.2%) were the most frequent stimulation-related adverse events but decreased in frequency with time. **Quality score, 88.2%**

Koller at al. (63) reported a case series of 38 patients with medically refractory ET with involvement of the head. ET was defined as the presence of postural or kinetic tremor of the hands without other neurologic signs. Patients with signs of dystonia were excluded. Medications remained stable one month before surgery and for the first twelve weeks after surgery. At 12 weeks after unilateral Vim DBS, only 24 patients were blindly evaluated in ON-stimulation and OFF-stimulation conditions using the FTM Scale, but the results reported correspond to all 38 patients, with the rational that open-label and blinded evaluations yielded similar results. The blinded strategy was the same as in Koller et al., 1997. (62) The average±SD parameters of stimulation were: amplitude =3.5 ± 1.0 V, frequency = 155.9 ± 29.4 Hz; pulse width = 86.1 ± 37.7 microsec. At 12 weeks, there was a significant improvement compared with baseline in the total score of the FTM Scale with stimulation ON and stimulation OFF, and, for head tremor, with stimulation ON only (for both analyses values were not provided, n=38, $p<0.01$). A significant reduction in head tremor was reported by 71% of patients, remained unchanged in 26% of patients and worsened in 3% of patients. Four patients had surgery-related complications, though without persistent morbidity at 3 months. Transient

paresthesias (24/38) were the most frequent stimulation-related adverse events. At 12 months, there was a loss of effect for hand tremor in eight patients, due to device-related issues. **Quality score, 80.6%**

Koller at al. (64) reported a case series of the long-term anti-tremor effects of unilateral Vim DBS (maximum follow-up time of 40 months) 49 patients with medically refractory and significantly disabling ET. ET was defined according to Tremor Investigation Group criteria. At 12 weeks, the average±SD parameters of stimulation were amplitude = 3.4 ± 0.7 V, frequency =157.5 ± 28.2 Hz and pulse width = 78.8 ± 37.3 sec, and the blinded rating for the total score in the FTM Scale was significantly improved comparing ON-stimulation with OFF-stimulation conditions (values not provided, n=25, P<0.001). In addition, at the 24 months follow-up, there were 24 (49.0%) dropouts, of which 10 were due to compromised implantation of the electrodes. Stimulation-related adverse events were mild, transient and the most frequent adverse events were paresthesia (n=21) and headaches (n=15). **Quality score, 70.6%**

Ondo et al. (65) reported a case series of 14 patients with ET. ET was defined according to the Tremor Investigation Group criteria. Tremor medications were discontinued one month before study entry. Patients were randomly allocated to an OFF-stimulation and ON-stimulation with prior established parameters, and tremor severity was rated tremor in the arms, legs, voice, head, face and tongue. (Unified Tremor Rating Assessment/UTRA) At 12 weeks, there was an improvement of tremor from baseline (62.6% decrease, 7.3 ± 1.5 *vs.* 2.8 ± 1.6, p<0.01) for the contralateral arm only and in the group of patients randomized to an ON-stimulation condition. Patient-rated modified ADL score (UTRA) improved by 57.6% (19.8 ± 3.2 *vs.* 8.4 ± 2.3, p<0.0001) and the

disability score (UTRA) improved by 62.2% (3.7 ± 0.5 vs. 1.4 ± 0.6, p<0.0001). The average ± SD parameters of stimulation were: voltage (range) = 2.7 ± 0.9 (1.7 - 6.1) V, frequency (range) = 168.9 ± 16.4 (130 - 170) Hz, pulse width (range) = 256.4 ± 91.6 (90 - 450) microsec. There were no significant surgical complications and stimulation-related adverse events were mild. Device-related complications occurred in 2/14 (14.2%) patients. **Quality score, 76.3%**

Rehncrona et al.(66) reported a case series of 19 patients with medically refractory ET submitted to unilateral Vim-DBS. ET was defined as rest, postural or kinetic tremor present during daytime. Pharmacological treatment was stable for a minimum of 3 months. At 6-7 years, the average ± SD parameters of stimulation were: voltage =2.3±1.0 V, frequency =181.4± 9.1 Hz, pulse width = 90.0 ± 39.0 microsec. At 2 and 6-7 years, there was 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 pre-operative evaluations, using the FTM scale was used. Kinetic and postural tremor of the lower limbs improved only at 2 years (p<0.025). Six patients were lost to follow-up between the 2- and 6-7-year evaluations. **Quality score, 91.7%**

Schuurman et al. (67) conducted a randomized parallel study of Vim-DBS vs. thalamotomy with 13 ET patients with severe upper limb tremor. There was no specification about used diagnostic criteria. The primary outcome was change from baseline in functional status as measured by the Frenchay Activities Index. Clinical severity of tremor was also measured in single-blinded fashion using disease-specifc rating scales. At 24 weeks, Vim-DBS was associated with a change in the Frenchay Activities from baseline of 6.4 ± 3.4 in the ET group (n=7). There was greater

improvement in the Frenchay Activities Index with Vim-DBS compared with thalamotomy: 6.6 points, 95% CI: 2.5, 10.7. Overall, tremor was absent or slight in all seven patients. Adverse events were more frequent in the thalamotomy group (n=16) than in unilateral Vim-DBS (n=6, P = 0.024) in the group of patients with ET. At a 5-year follow-up, in 10 patients with a diagnosis of ET included in the initial study, a reduction of the effect of stimulation was observed in half of these patients, with increased severity of intention and postural tremor. **Quality score, 95.2%**

Bilateral Vim - DBS (1 study)

Ondo et al. (68) reported a case series of 13 patients with ET submitted to sequential bilateral Vim-DBS. The diagnosis of ET was based on the Tremor Investigational Group definition. Tremor medications were discontinued one month before study entry. Compared with baseline unilateral Vim-DBS, in the blinded three months after assessment, the ON-stimulation condition in bilateral Vim-DBS was associated with an improvement in severity of arm (unilateral: 6.7 ± 0.9; bilateral: 1.3 ± 1.2, P<0.005) and leg tremor (unilateral: 2.3 ± 1.1; bilateral: 0.5 ± 0.5, P<0.005), but not in head or voice tremor. Overall, there was an improvement in open label assessment activities of daily living (unilateral: 25.1 ± 3.6; bilateral: 10.3 ± 3.7) and disability (unilateral: 3.5 ± 0.6; bilateral: 1.3 ± 0.6) from baseline to three months after bilateral Vim-DBS. Adverse events were more frequent in bilateral Vim-DBS (16/21; 76%) compared with unilateral Vim-DBS (11/21; 52%). The most problematic stimulation-related adverse events were gait difficulty and dysarthria. **Quality score, 80.0%**

Radiofrequency thalamotomy (2 studies)

Zirh A et al. (69) reported a case series of 21 patients with medically intractable ET not otherwise specified that underwent uni- or bilateral thalamotomy, according to tremor characteristics. 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 FTM Scale. Permanent perioral numbness (n=1) and disequilibrium (n=1) were reported after unilateral thalamotomy, and permanent mild dysarthria occurred in 2 out of 3 patients with bilateral thalamotomy. **Quality score, 64.7%**

Schuurman et al. (67) conducted a randomized parallel study of Vim-DBS vs. thalamotomy with 13 patients with severe upper limb tremor due to ET. (see details of the study above) At 24 weeks, thalamotomy was associated with a change in the Frenchay Activities from baseline of - 0.2 ± 3.3 in the ET group (n=6). Vim-DBS was associated with greater improvement in the Frenchay Activities Index compared with thalamotomy: 6.6 points, 95% CI: 2.5, 10.7. Overall, tremor was absent or slight in all 6 patients submitted to thalamotomy. Adverse events were more frequent in the thalamotomy group (n=16, P = 0.024). **Quality score, 95.2%**

Gamma knife unilateral thalamotomy (1 study)

Lim et al. (70) conducted a retrospective case series of 11 patients with ET. The patients had a disabling postural and/or action limb tremor and were unwilling or deemed unsuitable for stereotactic radiofrequency lesioning or Vim-DBS. Single blinded assessments were made at 6, 12, and 24 months after unilateral gamma knife

thalamotomy using the FTM Scale. ADL scores improved significantly (p=0.03). There was no significant change in other items of the FTM Scale. There were 3 delayed neurologic adverse events, of which one was severe with edema and thalamic hemorrhage at the lesion site. **Quality score, 66.7%**

MRI-guided focused ultrasound unilateral thalamotomy (1 study)

Elias et al. [71] conducted a randomized parallel study of MRI-guided focused ultrasound thalamotomy *vs.* sham procedure with 81 patients with medically refractory moderate-severe upper limb tremor due to ET. MRI-guided focused ultrasound thalamotomy was associated with an improved by 47% at three 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 to 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%). **Quality score, 84.1%**

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Supplemental table 1. Rating Scale for Quality of Evidence

	Yes	Unclear/ Possibly	No	N/A
RESULTS				
1. Is an estimate of the treatment effect given	2	1	0	N/A
2. Is it of clinical importance	2	1	0	N/A
3. Is the estimate of treatment effect sufficiently precise	2	1	0	N/A
VALIDITY: *SELECTION*				
4. Was the spectrum of patients well defined?	2	1	0	N/A
5. Was the diagnosis of the disease well defined?	2	1	0	N/A
6. If pragmatic, were suitably abroad eligible criteria used?	2	1	0	N/A
7. If explanatory, were eligibility criteria suitably narrow?	2	1	0	N/A
MEASUREMENT				
8. Was assignment to treatments stated to be random?	2	1	0	N/A
9. If yes, was the method of randomization explained?	2	1	0	N/A
10. Were all patients accounted for after randomization?	2	1	0	N/A
11. Were losses to follow-up low (<10)?	2	1	0	N/A
12. Were the treatment groups similar in important factors at the start of the trial?	2	1	0	N/A
13. Were all patients otherwise treated alike?	2	1	0	N/A
14. Were patients, health care workers and investigators "blind" to treatment?	2	1	0	N/A
15. Was assessment of outcome "blind"?	2	1	0	N/A
16. Was the occurrence of side effects explicitly looked for?	2	1	0	N/A
17. If yes, were estimates of their frequency/severity given?	2	1	0	N/A
STATISTICAL ANALYSIS				
18. Was the main analysis on "intention to treat"?	2	1	0	N/A
19. If no, was a sensitivity analysis performed?	2	1	0	N/A
20. Were additional clinically-relevant factors allowed for?	2	1	0	N/A
21. Were appropriate statistical methods used?	2	1	0	N/A
22. Were any "unusual" methods used?	2	1	0	N/A
23. If subgroup analyses were done, were they explicitly presented as such?	2	1	0	N/A
UTILITY				
24. Do the results help me choose treatment?	2	1	0	N/A
TOTAL (add ringed scores above):	(A)			
No. of questions which actually applied to this article (maximum=24):	(B)			
Maximum possible score (2 X B)	(C)			
OVERALL RATING (A/C expressed as a percentage)	%			

N/A=not applicable establishing conclusions

Supplemental table 2. Quality score of Evidence for each included study in the MDS Evidence-Based Review of Treatments For Essential Tremor

Title of included study	1st author	year publication	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Item 24	A)	B)	Quality score
Phenobarbital and propranolol in essential tremor: a double-blind controlled clinical trial	Baruzzi	1983	2	2	2	2	0	N/A	N/A	2	2	2	2	N/A	2	1	1	2	2	0	0	0	2	2	N/A	1	29	20	72.5%
The effect of flunarizine in essential tremor	Biary	1991	2	1	0	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	1	26	20	65.0%
The effect of nimodipine on essential tremor	Biary	1995	2	1	0	0	1	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	0	2	1	1	N/A	1	25	20	62.5%
A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor	Brin	2011	2	2	2	2	2	N/A	N/A	2	2	2	2	2	2	2	2	2	2	2	N/A	2	2	2	0	2	40	21	95.2%
Double-blind controlled study of methazolamide in the treatment of essential tremor	Busenbark	1993	2	2	2	2	2	N/A	N/A	2	0	2	0	N/A	1	2	2	2	2	0	0	0	1	1	N/A	0	25	20	62.5%
Controlled study of metoprolol and propranolol during prolonged administration in patients with essential tremor	Calzetti	1982	2	2	0	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	0	2	29	21	69.0%
Trazodone is ineffective in essential tremor	Cleeves	1990	2	0	0	1	0	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	N/A	N/A	N/A	1	19	18	52.8%
Propranolol and propranolol-LA in essential tremor: a double-blind comparative study	Cleeves	1988	0	0	0	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	0	0	2	2	N/A	1	24	20	60.0%
A double-blind placebo-controlled trial of topiramate treatment for essential tremor	Connor	2002	2	2	2	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	2	0	2	2	N/A	1	33	20	82.5%
Topiramate in essential tremor: findings from double-blind, placebo-controlled, crossover trials	Connor	2008	2	2	2	2	2	N/A	N/A	2	0	2	0	1	2	2	2	2	2	2	N/A	0	2	2	N/A	1	32	20	80.0%
Treatment of benign essential tremor with propranolol. A controlled clinical trial.	Dupont	1973	0	1	0	0	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	1	22	20	55.0%
Levetiracetam is not effective for essential tremor	Elble	2007	2	2	2	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	0	2	2	N/A	0	31	19	81.6%
Carbamate in essential tremor: brief report of a proof of concept study	Elble	2010	2	2	2	2	2	N/A	N/A	2	2	2	2	N/A	2	2	2	2	2	2	N/A	2	2	2	N/A	0	36	19	94.7%
A randomized trial of focused ultrasound thalamotomy for essential tremor	Elias	2016	2	2	2	2	1	N/A	2	2	1	2	0	2	2	2	2	2	2	0	2	2	2	2	N/A	1	37	22	84.1%
Efficacy and tolerability of pregabalin in essential tremor: a randomized, double-blind, placebo-controlled, crossover trial	Ferrara	2009	2	2	2	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	0	0	2	2	N/A	0	29	20	72.5%
Double-blind controlled study of primidone in essential tremor: preliminary results	Findley	1982	2	1	1	2	1	N/A	N/A	2	0	2	2	N/A	2	2	2	0	N/A	0	0	0	2	2	N/A	1	24	19	63.2%
Primidone in essential tremor of the hands and head: a double-blind controlled clinical study.	Findley	1985	2	1	2	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	2	2	2	N/A	2	30	20	75.0%
Phenobarbitone in essential tremor	Findley	1985	2	1	2	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	2	2	2	N/A	1	31	20	77.5%
A double-blind, placebo-controlled crossover trial of topiramate in essential tremor	Frima	2006	2	1	0	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	0	26	20	65.0%
Effect of amantadine in essential tremor: a randomized, placebo-controlled trial	Gironell	2006	2	2	2	2	2	N/A	N/A	2	2	2	2	N/A	2	2	2	2	2	0	0	2	2	2	N/A	0	34	20	85.0%
A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor	Gironell	1999	2	2	2	2	2	N/A	N/A	2	2	2	2	N/A	2	2	2	2	2	2	N/A	2	2	2	2	2	40	20	100.0%
A comparison of primidone, propranolol, and placebo in essential tremor, using quantitative analysis	Gorman	1986	2	2	0	0	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	1	25	20	62.5%
New alternative agents in essential tremor therapy: double-blind placebo-controlled study in alprazolam and acetazolamide	Gunal	2000	2	2	2	0	2	N/A	N/A	2	0	1	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	2	28	20	70.0%
Efficacy and safety of T2000 in older patients with essential tremor	Hadj-Tahar	2013	0	0	0	1	1	N/A	N/A	2	0	0	1	N/A	N/A	2	2	2	2	1	N/A	N/A	0	2	N/A	0	16	17	47.1%
A double-blind trial of isoniazid for essential tremor and other action tremors	Hallett	1983	0	0	0	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	2	N/A	N/A	N/A	0	21	17	62.0%
Pilot efficacy and tolerability: a randomized, placebo-controlled trial of levetiracetam for essential tremor	Handforth	2004	2	2	2	2	2	N/A	N/A	2	1	2	2	N/A	2	2	2	2	2	0	0	0	2	0	N/A	0	29	20	72.5%
Effects of thalamic deep brain stimulation based on tremor type and diagnosis	Hubble	1997	2	2	0	2	2	N/A	N/A	0	N/A	2	2	N/A	2	0	2	1	1	N/A	N/A	2	2	2	0	2	26	18	72.2%
Efficacy of alprazolam for essential tremor	Huber	1988	2	2	2	0	0	N/A	N/A	2	0	2	2	1	2	2	2	1	2	1	N/A	0	2	2	N/A	1	28	20	70.0%
A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor	Jankovic	1996	2	2	2	1	1	N/A	N/A	2	0	2	2	2	2	2	2	1	2	1	N/A	2	2	2	N/A	2	34	20	85.0%
Relationship between plasma propranolol concentration and relief of essential tremor	Jefferson	1979	2	2	2	1	1	N/A	N/A	2	0	2	2	N/A	2	0	2	1	2	2	N/A	0	2	2	N/A	1	28	19	73.7%
Disability in essential tremor - effect of treatment	Koller	1986	2	2	2	0	0	N/A	N/A	2	0	2	2	N/A	2	0	1	0	N/A	1	N/A	0	1	1	N/A	1	19	18	52.8%
Metoprolol compared with propranolol in the treatment of essential tremor	Koller	1984	1	1	0	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	0	0	2	2	0	1	25	21	59.5%
Propranolol therapy for essential tremor of the head	Koller	1984	2	2	2	0	0	N/A	N/A	2	0	2	0	N/A	2	1	2	1	2	1	N/A	0	2	2	N/A	1	24	19	63.2%
Nadolol in essential tremor	Koller	1983	2	2	2	0	0	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	1	N/A	2	2	2	0	1	29	20	72.5%
Trazodone in essential tremor	Koller	1989	2	2	0	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	1	N/A	0	2	2	N/A	0	26	19	68.4%
Pharmacologic probe with Progabide of GABA mechanisms in essential tremor	Koller	1987	2	2	0	1	1	N/A	N/A	2	0	2	0	N/A	2	2	2	0	N/A	1	N/A	0	2	2	N/A	0	21	18	58.3%
Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor	Koller	2001	2	2	2	2	2	N/A	N/A	0	N/A	2	0	N/A	2	0	2	1	2	N/A	N/A	0	2	2	N/A	1	24	17	70.6%
High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor	Koller	1997	2	2	200%	2	2	N/A	N/A	0	N/A	2	2	N/A	2	2	2	2	2	N/A	N/A	0	2	2	N/A	2	30	17	88.2%
Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor	Koller	1999	2	2	200%	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	N/A	N/A	0	2	2	N/A	2	29	18	80.6%
Beta-adrenoreceptor mechanisms in essential tremor: a double-blind placebo-controlled trial of metoprolol, sotalol and atenolol	Leigh	1983	2	1	2	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	0	2	2	N/A	1	29	19	76.3%
Gamma knife thalamotomy for disabling tremor: a blinded evaluation	Lim	2010	2	2	2	1	1	N/A	N/A	0	N/A	N/A	N/A	N/A	2	0	2	1	2	N/A	N/A	0	2	2	N/A	1	20	15	66.7%
Efficacy of an adenosine antagonist, theophylline, in essential tremor: comparison with placebo and propranolol	Mally	1995	2	1	2	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	1	N/A	0	1	1	N/A	1	26	19	68.4%
Treatment of essential tremor with barbiturate T2000 (1,3-dimethoxymethyl-5,5-diphenyl-barbituric acid) - 2 studies	Melmed	2007	2	1	2	2	2	N/A	N/A	2	1	2	2	2	1	2	2	1	2	2	N/A	2	1	0	N/A	1	32	20	80.0%
The effect of the GABA-agonist, progabide, on benign essential tremor - a controlled clinical-trial	Mondrup	1983	1	2	0	1	1	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	0	1	1	N/A	0	24	19	63.2%
Randomized trial comparing primidone initiation schedules for treating essential tremor	O'Suilleabhain	2002	2	2	2	0	2	N/A	N/A	2	1	2	2	N/A	2	2	2	2	2	0	1	N/A	0	2	2	N/A	2	30	19	78.9%
Topiramate in essential tremor: a double-blind, placebo-controlled trial	Ondo	2006	2	2	2	2	2	N/A	N/A	2	2	2	0	0	2	2	2	2	2	2	N/A	2	2	2	N/A	2	36	20	90.0%
Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial	Ondo	2000	2	2	2	1	2	N/A	N/A	2	2	2	2	N/A	2	2	2	1	2	0	0	2	2	2	N/A	2	34	20	85.0%
Thalamic deep brain stimulation: comparison between unilateral and bilateral placement	Ondo	1998	2	2	2	1	2	N/A	N/A	2	2	2	2	1	2	0	2	1	2	1	N/A	0	2	2	N/A	2	32	20	80.0%
Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor	Ondo	1998	2	2	200%	1	2	N/A	N/A	2	0	2	2	1	2	0	2	1	2	N/A	N/A	0	2	2	N/A	2	29	19	76.3%
Double-blind controlled trial of gabapentin in essential tremor	Pahwa	1998	2	0	2	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	0	0	0	2	2	N/A	1	28	20	70.0%
Mirtazapine in essential tremor: a double-blind, placebo-controlled pilot study	Pahwa	2003	2	2	2	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	0	29	20	72.5%
Botulinum toxin treatment of essential head tremor	Pahwa	1995	2	2	0	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	0	1	1	N/A	1	28	19	71.0%
Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments	Rehncrona	2003	2	2	2	2	1	N/A	N/A	2	2	2	2	N/A	2	2	2	2	2	N/A	N/A	0	2	2	N/A	2	33	18	91.7%
Double-blind comparison of primidone and phenobarbital in essential tremor	Sasso	1988	1	2	0	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	1	26	20	65.0%
Quantitative comparison of barbiturates in essential hand and head tremor	Sasso	1991	1	2	2	1	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	0	0	0	2	2	N/A	0	27	20	67.5%
A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor	Schuurman	2000	2	2	2	2	2	N/A	N/A	2	2	2	2	2	2	0	2	2	2	2	N/A	2	2	2	2	2	40	21	95.2%
Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor. Double-blind comparative study with one-year follow-up	Serrano-Duenas	2003	2	1	2	1	2	N/A	N/A	2	0	2	0	1	2	2	2	1	2	0	0	0	2	2	N/A	2	28	21	66.7%
Effects of zonisamide on isolated head tremor	Song	2008	2	2	2	2	2	N/A	N/A	2	0	2	2	N/A	2	2	2	1	2	1	N/A	0	2	2	N/A	1	31	19	81.6%
Essential tremor: treatment with propranolol	Tolosa	1975	1	2	0	1	1	N/A	N/A	2	0	2	2	1	2	2	2	2	2	0	0	0	N/A	N/A	N/A	1	23	19	60.5%
Olanzapine versus propranolol in essential tremor	Yetimalar	2005	2	2	2	0	2	N/A	N/A	2	0	2	2	N/A	2	2	2	2	2	1	N/A	0	1	1	N/A	1	28	19	73.7%
A pilot, double-blind, placebo-controlled trial of pregabalin (Lyrica) in the treatment of essential tremor	Zesiewicz	2007	2	1	2	2	2	N/A	N/A	2	2	2	2	N/A	2	2	2	1	2	2	N/A	0	2	2	N/A	1	33	19	86.8%
A double-blind placebo-controlled trial of zonisamide (Zonegran) in the treatment of essential tremor	Zesiewicz	2006	2	1	2	2	2	N/A	N/A	2	2	2	2	N/A	2	2	2	1	2	2	N/A	0	2	2	N/A	0	32	19	84.2%
Multisite, double-blind, randomized, controlled study of pregabalin for essential tremor	Zesiewicz	2013	2	1	2	2	2	N/A	N/A	2	2	2	0	N/A	2	2	2	1	2	2	N/A	0	2	2	N/A	1	31	19	81.6%
Stereotactic thalamotomy in the treatment of essential tremor of the upper extremity: reassessment including a blinded measure of outcome	Zirh	1999	2	2	2	1	1	N/A	N/A	0	N/A	2	0	N/A	2	0	2	1	2	N/A	N/A	0	2	2	N/A	1	22	17	64.7%

MDS Evidence-Based Review of Treatments For Essential Tremor

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EBM review of treatment of Essential Tremor

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Relevant disclosures and conflicts of interest are listed at the end of this article.

ABSTRACT

Background: Essential tremor (ET) is one of the most prevalent movement disorders. Many treatments for ET have been reported in clinical practice, but it is uncertain which options have the most robust evidence. The International Parkinson and Movement Disorder Society (MDS) commissioned a task force on tremor to review clinical studies of treatments for ET.

Objectives: To conduct an evidence-based review of current pharmacological and surgical treatments for ET, using standardized criteria defined *a priori* by the MDS.

Methods: We followed the recommendations of the MDS 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/d. Alprazolam and botulinum toxin type A were classified as *'possibly useful'*. Unilateral *Ventralis intermedius* (Vim) thalamic deep brain stimulation, radiofrequency thalamotomy, and MRI-guided focused ultrasound thalamotomy were considered '*possibly useful'*. All the above recommendations were made for limb tremor in ET. There was insufficient evidence for voice and head tremor as well as for the remaining interventions.

Conclusion: Propranolol, primidone and topiramate (>200 mg/d) 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 ET and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies and the use of non-validated clinical scales.

Background

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 neurologic 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 paper, 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 prior published reviews. (4) Literature searches were done using electronic databases including MEDLINE (1966-Dec 2016), the CENTRAL database in the Cochrane Library (1948-2016), and systematic checking of reference lists published in review articles and other clinical reports. Papers selected for review met the

following inclusion/exclusion criteria. Inclusion criteria: 1. any pharmacological, surgical, and non-pharmacological therapies for which there was at least one randomized controlled trial (RCT); 2. non-randomized controlled or non-controlled 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 two 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; 8. full paper 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 non-existent 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 two 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 four 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; Level-III studies - non-controlled 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 cut-off for study inclusion based on quality scores.

Safety evaluation

The clinical information used to make an overall safety evaluation included primarily the adverse 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 papers. The safety discussion within these sections uses a narrative, unsystematic approach due to 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; 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** ~~or~~ 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 implication of 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 tremor, unilateral *Ventralis intermedius* (Vim)-thalamic deep brain stimulation 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, 15-25) 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). The average treatment duration was 3.5 weeks (range: 1.5 - 8). 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 - 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 - 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 less than 10% of study participants. Other adverse events with impact in clinical practice are known such as fatigue, lightheadedness and sexual dysfunction. (26) 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. (22)

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 (8 studies)

Primidone was studied in eight Level-I studies (14, 20, 27-32) 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 mg/d and 750 mg/d)(32) was assessed in a 12-month double-blind randomized controlled trial that reported a comparable long-term efficacy and absence of tolerance for the therapeutic effect. In a head-to-head comparison of propranolol 120~~-240~~ mg/d and primidone 250-750 mg/d, 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. (20)

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.(31) The combined use of primidone 250 mg qHS and propranolol 80 mg TID (21) 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) due to the side effect profile and potential high discontinuation rates. Overall, primidone was considered 'clinically useful' for clinical practice.

Topiramate (4 studies)

Topiramate was studied in four placebo-controlled Level-I studies (33-36) 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 – 333 mg/d (n=3). There was a documented improvement in both tremor amplitude and ADL measures in three of the four Level-I studies. (33, 34, 36) 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% for topiramate and 9.5% for placebo. (36) Adverse events were responsible for a percentage of drop-outs ranging from 30 - 54.2%. (33, 36)

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 - 100 mg dose range. Topiramate was considered 'clinically useful' for clinical practice for daily doses higher than 200 mg.

Alprazolam (2 studies)

Alprazolam was studied in two placebo-controlled Level-I studies (30, 37) in a total of 46 patients with ET, as monotherapy with a treatment duration of two and four 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 mg (30) or 0.75 mg (37), and the mean daily effective dose was 0.75 (30) and 1.5 (37) mg. Both studies documented a reduction in non-validated 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%) (37) 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 (3 studies)

Botulinum toxin type A was studied in three placebo-controlled Level-I studies (10, 38, 39) that included a total of 168 patients with ET refractory to oral drugs. Dose ranged from 50 - 100 IU targeting forearm (38, 39) 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 (38, 39) 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, (38) being longer for the postural component of the upper limb tremor. (39) Dose-dependent hand weakness by patient report (38, 39) or by measured grip strength (39) 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) due to conflicting results and with an 'acceptable risk with specialized monitoring' (safety recommendation), as the dose dependent limb weakness is of concern. Botulinum toxin type A was considered 'possibly useful' for clinical practice.

Unilateral Vim – Deep Brain Stimulation (7 studies)

We included seven studies assessing unilateral Vim thalamic deep brain stimulation 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%). (40) The primary outcome was the change from baseline in functional status as measured by the Frenchay Activities Index. (40) 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 ± 3.4 (n=7). Overall, tremor was absent or slight in all seven patients. There was greater improvement in the Frenchay Activities Index with Vim-DBS compared with thalamotomy: 6.6 points, 95% CI: 2.5, 10.7. Adverse events were more

frequent in the thalamotomy group (n=16) than in unilateral 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 out 10 ET patients, with an increased severity of intention and postural tremor. The other remaining six studies (12, 41-45) (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, 41-44) with one study reporting on long-term follow-up up to 6 - 7 years. (45) In five of the studies, the effect of unilateral Vim-DBS was assessed comparing an ON-stimulation with an OFF-stimulation condition. (12, 42-45) 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 microsec (pulse width). There was an improvement in various clinical rating scales of severity and performance of activities. Paresthesia (mean incidence overall: 61%, range: 21 to 100) were the most frequent stimulation-related adverse events and decreased in frequency with time. (42) In terms of long-term effect of unilateral Vim-DBS at 2 and 6 - 7 years, studies document 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 pre-operative evaluations. (45)

Unilateral Vim-DBS alone has been compared with sequential bilateral Vim-DBS, in a case series by Ondo et al (46) (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 ± 0.9; bilateral: 1.3 ± 1.2, $P<0.005$) and leg tremor

(unilateral: 2.3 ± 1.1; bilateral: 0.5 ± 0.5, P<0.005), but not for head or voice tremor. In an open label assessment, there was an improvement in ADLs (unilateral: 25.1 ± 3.6; bilateral: 10.3 ± 3.7) and disability (unilateral: 3.5 ± 0.6; bilateral: 1.3 ± 0.6) from baseline to three months after bilateral Vim-DBS. Adverse events were more frequent with bilateral Vim-DBS (16/21; 76%) compared with unilateral Vim-DBS (11/21; 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 (2 studies)

Radiofrequency thalamotomy has been assessed in two studies. Zirh et al. (47) (Quality score, 64.7%) reported a case series of 21 patients with medically intractable ET not otherwise specified that underwent uni- or bilateral thalamotomy. Assessment at both three 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 two out of three patients with bilateral thalamotomy. Schuurman et al. (40) (Quality score, 95.2%) conducted a randomized parallel Level-I study of Vim-DBS *vs.* thalamotomy with 13 patients with severe upper limb tremor due to ET (see details of the study above

in **Unilateral Vim – Deep Brain Stimulation**). 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, radiofrequency unilateral 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 (1 study)

Elias et al. (48) (Quality score, 84.1%) conducted a randomized parallel study of MRI-guided focused ultrasound thalamotomy *vs.* sham procedure in 81 patients with medically refractory moderate-severe upper limb tremor due to ET. MRI-guided focused ultrasound thalamotomy was associated with an improvement in tremor severity ratings by 47% at three 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 to 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, MRI-guided focused ultrasound unilateral 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 CNS-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'* as three out of four studies reported positive efficacy results. For the fourth study, (35) 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 MRI-guided focused ultrasound unilateral 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 conditioned 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 towards 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, (49) 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. 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, as 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 as 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, (50, 51) open label assessment of perampanel, (52) customized approach for botulinum toxin administration to reduce safety for hand tremor, (53) other deep brain stimulation approaches with assessment of targets such as the Zona Incerta/Posterior Subthalamic area, (54) the subthalamic nucleus, (55) use of constant-current (56) or closed loop stimulation (57) paradigms, and novel MRI-guided approaches for thalamotomy. (58) These interventions will likely merit assessment in a future EBM-MDS review on ET.

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Employment	SIU Healthcare
Contracts	None
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Other	None

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TABLES AND FIGURE LEGENDS

Table 1 – Definitions for specific recommendations

Table 2 – Summary of efficacy conclusions and implications for practice for limb tremor in Essential tremor

APPENDIX 1.

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