Treatment of essential tremor: current status

Soumya Sharma [1,2] Sanjay Pandey[1]

[1]Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, India
[2]Department of Clinical Neurological Sciences, London Health Sciences Centre, Western University, London, Ontario, Canada

Correspondence to
Dr Sanjay Pandey, Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi 110002, India;
sanjaysgpgi2002@yahoo.co.in

Received 5 April 2019
Revised 14 August 2019
Accepted 13 September 2019

To cite: Sharma S, Pandey S. *Postgrad Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/postgradmedj-2019-136647

ABSTRACT

Essential tremor is the most common cause of tremor involving upper limbs, head and voice. The first line of treatment for limb tremor is pharmacotherapy with propranolol or primidone. However, these two drugs reduce the tremor severity by only half. In medication refractory and functionally disabling tremor, alternative forms of therapy need to be considered. Botulinum toxin injections are likely efficacious for limb, voice and head tremor but are associated with side effects. Surgical interventions include deep brain stimulation; magnetic resonance-guided focused ultrasound and thalamotomy for unilateral and deep brain stimulation for bilateral procedures. Recent consensus classification for essential tremor has included a new subgroup, 'Essential tremor plus', who have associated subtle neurological 'soft signs', such as dystonic posturing of limbs and may require a different treatment approach. In this review, we have addressed the current management of essential tremor with regard to different anatomical locations of tremor as well as different modalities of treatment.

INTRODUCTION

Tremor is one of the most common movement disorders encountered in clinical practice and essential tremor (ET) is the most common cause of a pathological tremor. ET is defined as an isolated tremor syndrome, without other neurological signs, that presents with action tremor of bilateral upper limbs of at least 3 years' duration with or without involvement of head, voice or lower limbs.[1] The symptoms of ET can vary from being mild which may not require any treatment other than reassurance to being severe enough to cause functional disability needing active management. In this review, we have divided the treatment into three major categories, namely pharmacological, botulinum toxin (BoNT) and surgical therapies. Each of these treatment approaches will be described in relation to the anatomical site of involvement, that is, limb, head or voice tremor.

Search strategy

A literature search was performed on PubMed for articles published until April 2019 using the term 'treatment of essential tremor' which yielded 2128 articles. To refine our search, we looked up the following terms and came up with the following number of articles: 261 articles on 'propranolol in essential tremor', 269 articles on 'beta blockers in essential tremor', 159 articles in 'primidone in essential tremor', 65 articles on 'benzodiazepines in essential tremor', 238 articles on 'anticonvulsants in essential tremor', 124 articles on 'botulinum toxin in essential tremor', 246 articles on 'thalamotomy in essential tremor', 139 articles on 'focused ultrasound in essential tremor', 870 articles on 'deep brain stimulation in essential tremor', 51 articles on 'transcranial magnetic stimulation in essential tremor' and 44 articles on 'essential tremor plus'. The study design criteria for inclusion were reviews, systematic reviews, meta-analysis and randomised controlled trials (RCT) published in the English language since 1972 until April 2019. There was no minimal sample size or minimum duration of follow-up for exclusion, however, case reports were omitted. References from articles on treatment recommendations by consensus groups were also scrutinised.

PHARMACOLOGICAL TREATMENT OF ET

Pharmacotherapy of ET depends on several variables like the severity of tremor, situational exacerbations and interference with everyday activities.[2] The two most commonly prescribed drugs, propranolol and primidone, have been available since the 1970s and 1980s; in fact, propranolol was the first treatment to be used for tremor in 1971.[2] A recent evidence-based review of treatment for ET by the Movement Disorder Society concluded that the pharmacological therapies with the most robust efficacy in clinical practice are propranolol and primidone.[3] Most of the studies on pharmacotherapy have predominantly focused on limb tremor. Although pharmacotherapy is the initial treatment of ET, one-third to one-half of the subjects develop pharmacoresistance.[4] A study by Louis and Rios found that nearly one-third of the 528 subjects with ET including those having severe tremor stop their medications.[5] Despite these drawbacks, pharmacotherapy is still the first line of treatment. Here, we review the treatments based on efficacy in managing limb, head or voice tremor (table 1).[3 6 7]

Learning point

- The two most commonly used drugs for ET are propranolol and primidone.
- Treatment of ET is dependent on the limitations in everyday activities and the severity of tremor.

PHARMACOLOGICAL TREATMENT OF LIMB TREMOR

Propranolol and primidone are the mainstay of treatment of limb tremor. A combination of these two drugs yields a better response compared with using either of them alone.[8 9] Both these drugs have shown efficacy in reducing tremor amplitude up to 1 year of treatment.[10–17] However, there are no RCTs done to assess the long-term effects of either propranolol or primidone in ET.[17] Younger subjects, shorter disease duration, lower tremor frequency and higher tremor amplitude at treatment initiation

Table 1 Medical management of essential tremor

	Treatment	Level of evidence[3]	Dosing	Efficacy	Side effects
Essential limb tremor	Propranolol (long/short acting)	Short-acting formulation: efficacious.[3] Long-acting formulation: insufficient evidence.[3]	Short-acting propranolol: start with 10 mg twice/thrice a day increase to 20–30 mg thrice a day, maintenance dose 10–320 mg/day. Long-acting propranolol: 60–80 mg once a day, maintenance dose 60–320 mg/day.	Effective in improving the severity of hand tremor (clinical scores, tremor amplitude, performance score). Reduces tremor amplitude by 50%.	Hypotension, bradycardia, syncope, fatigue, depression, erectile dysfunction in males. Caution in patients with asthma and chronic obstructive pulmonary disease. Can worsen congestive heart failure.
	Primidone	Efficacious[3]	Start with 25 mg/12.5 mg once a day and increase to 50–100 mg thrice a day. Daily dosage range 25–750 mg/day in two or three divided doses.	Improves hand tremors. Reduces tremor amplitude by 50%.	Sedation, cognitive side effects, depression. The first dose effect of nausea, dizziness, malaise, sedation and confusion can be seen in some patients. Start with low dose to overcome initial side effects of cognitive problems and dizziness.
	Topiramate	Efficacious (only for doses more than 200 mg/day).[3]	Start with 25 mg twice a day, maintenance dose of 50–325 mg/day. However, efficacious in higher doses.	Improves clinical rating scale scores for hand tremors. Can be used as a second-line drug.	Patients allergic to sulfa drugs, history of renal stones and angle closure glaucoma need to be cautious. Causes weight loss, paraesthesias.
	Alprazolam	Likely efficacious[3]	Start with 0.125 mg/day, maintenance dose 0.125–3 mg/day.		
	Long-chain alcohol: 1-octanol	No recommendations[3]	Up to 128 mg/kg	Good tolerability. Requires administration of large amount.	Bad oral taste
	Octanoic acid	No recommendations[3]	It is the active metabolite of 1-octanol. Given orally 4 mg/kg.	Delayed effect on tremor reduction.	Well tolerated
	Clozapine[6]	Weak recommendation and low quality of evidence.[7]	50 mg/day	May be used as a second-line treatment in selected patients.	Sedation, which improves on chronic therapy.
	Gabapentin	Insufficient evidence[3]	Start with 50 mg/day, maintenance dose 50–1800 mg/day.	May be tried in limb tremors when other medications have failed especially as an add-on therapy.	Causes dizziness, lethargy.
	Pregabalin, levetiracetam	Non-efficacious[3]			
	Nadolol, metoprolol, atenolol, sotalol, zonisamide, phenobarbitone, amantadine, isoniazid, carisbamate, flunarizine, nimodipine, methazolamide, acetazolamide, mirtazapine.	Insufficient evidence[3]			
Essential head tremor	Zonisamide	Insufficient evidence[3]		May be effective in treating isolated head tremor as compared with propranolol.	
	Propranolol, primidone, topiramate	Insufficient evidence		Can give a trial.	
	Methazolamide	Insufficient evidence			
Essential voice tremor	Propranolol	Insufficient evidence[3]			
	Methazolamide	Insufficient evidence[3]		May be of some benefit; especially if voice tremor is the presenting symptom.	

appear to be factors that may determine a favourable outcome following propranolol therapy.[18 19]

Propranolol at a dose of 120–240 mg/day has been proposed to elicit a favourable response but, only short-acting formulations have proven to be efficacious and there is insufficient evidence for the use of long-acting formulations.[3 16 18–22] On the other hand, most studies on primidone caution starting treatment with a low dose of 50–62.5 mg and escalating gradually to a maximum dose of 1000 mg/day.[13 14] However, lower doses of up to 250 mg/day have been found to be equally effective as higher doses.[23] The duration of efficacy is similar for both drugs, but primidone has the advantage of bringing the tremor under control earlier than propranolol after instituting therapy.[24]

The side effect profile differs between the two drugs with acute reactions more common with primidone and chronic reactions with propranolol therapy.[25] The acute side effects associated with primidone are sedation, nausea and vertigo that manifest following the first dose and tend to subside on chronic administration.[13 14 23] However, propranolol is a non-selective beta blocker which may lead to bradycardia, hypotension and breathlessness especially when higher doses are used and are contraindicated in conditions such as chronic obstructive pulmonary disease, asthma, severe peripheral vascular disease and diabetes.[11 26 27] Under these circumstances, a cardioselective beta blocker such as metoprolol could be considered as an alternative. Metoprolol has proven to be equally effective in reducing tremor magnitude as propranolol in a double-blind controlled study.[26 28]

The improvement in tremor magnitude based on accelerometric measurements is comparable for propranolol and primidone with mean improvement of 54.1% (range 32%–75%) and 59.9% (range 42%–76%), respectively.[2 4 29] Primidone could also be effective in those individuals who have had an unsatisfactory response to propranolol or developed adverse reactions to propranolol.[9 23] Therefore, a trial of either propranolol or primidone should be given before resorting to alternative drugs.[2 30]

Learning point

- Although propranolol and primidone are the first-line therapies, their mean efficacy is about 50% in terms of reduction of tremor.
- Primidone is equally efficacious as propranolol in reducing tremor amplitude.
- Long-term side effects are more common with propranolol whereas short-term side effects are seen more often with primidone.
- Cardioselective beta blocker could be used in situations where propranolol, a non-selective beta blocker, is contraindicated.

Several medications have been investigated either to be used as adjunct to the first-line therapies or as individual treatments. Topiramate decreases tremor magnitude and improves functional disability as shown in four placebo-controlled studies.[24 31–33] Therefore, topiramate is considered to be an effective treatment in moderate to severe ET.[3 32 34] However, a higher dose (more than 200 mg/day) of topiramate seems to be more efficient in reducing the tremor compared with a lower dose of 25–100 mg/day.[3 32] Side effect profile of topiramate consists of nausea, paraesthesias and sedation and can limit treatment in as many as one-third of the subjects.[3] Gabapentin, a γ-aminobutyric acid derivative, may be tried as an adjunct to other antitremor medications at doses of 1800 and 3600 mg/day, however, there is insufficient evidence regarding its efficacy.[3 35] Drugs that have shown uncertain efficacy are zonisamide, levetiracetam, clonazepam, flunarizine, nimodipine and pregabalin.[36–44] Newer drugs are being studied for the treatment of ET, including 1-octanol and perampanel.[45–49]

PHARMACOLOGICAL TREATMENT OF VOICE AND HEAD TREMOR

No effective drug therapy is available for either voice or head tremor. Propranolol and primidone are both ineffective in the treatment of voice and head tremor and currently there is insufficient evidence regarding their efficacy in midline tremor treatment.[3 9 41 50 51] Methazolamide, a carbonic anhydrase inhibitor, has been tried in essential voice and head tremor and although found to be of some benefit, the side effect profile leads to its discontinuation in the majority.[52 53]

Learning point

Propranolol and primidone are ineffective in controlling voice and head tremor.

BONT THERAPY FOR ET

The first-line pharmacotherapies fail to produce any functional improvement in nearly one-third of the treated individuals and lead to unwanted side effects in one-third of those who begin treatment. Surgical interventions carry their own risks and are limited due to accessibility.[54] Therefore, the need of the hour is to try an alternative treatment modality like BoNT, but its uses are also limited by side effects like weakness in the injected muscles (table 2).

BONT THERAPY FOR LIMB TREMOR

BoNT has been investigated as a treatment option for essential hand tremor since the early 1990s.[55–60] Several open-label trials have shown that BoNT decreases the tremor amplitude; the improvement is predominantly of the postural component of the tremor.[57 59–61] However, there are certain limitations to treatment of limb tremor with BoNT. The first limitation is the inability of translation of the tremor improvement on clinical rating scales to functional improvement as was shown in two randomised controlled studies.[3 57 60] The other limitation is the development of wrist and finger weakness.[57 59 60] The reason for development of muscle weakness is the standard, fixed selection of muscles (wrist flexors and extensors) as well as a fixed dosing in all subjects based on the assumption that tremor involves the muscles and joints in a uniform pattern in all subjects.[54 62] An individualised muscle selection and dosing may overcome the limitation imposed by muscle weakness. One such technique would be use of motion sensors, which are capable of characterising tremor at individual joints.[54 63] An open-label study by Samotus *et al* has shown functional improvement from reduction in tremor amplitude by using this kinematics technology.[54 63] However, there were certain limitations to this study. Lack of comparison between visually based and kinematically based assessments was not done and the injections were non-blinded. Although the Food and Drug Administration and Health Canada approve the kinematics device, its availability at the basic healthcare level limits its application in clinical use.[63] Since the two first-line drugs, namely propranolol and primidone, decrease the limb tremor amplitude by only half, it is important to investigate alternative therapies such as BoNT (figure 1).[62]

Learning point

BoNT is considered to be 'likely efficacious' in the treatment of essential limb tremor but is limited in its efficacy due to development of muscle weakness.

Table 2 Summary of studies for treatment of essential limb tremor with botulinum toxin

Authors	Design	Patients, n	Process of selecting target muscles	Process of determining dose	Use of needle EMG to identify and inject muscles	Improvement in clinical rating scales/objective measures	Functional improvement	Improvement in tremor amplitude	Side effect
Essential limb tremor									
Trosch and Pullman[55]	Open label	14	Surface EMG	Previous experience; large muscles and muscles contributing more to tremor got higher dose.	Yes	Not significant/not significant	5/14 reported moderate to marked functional improvement.	Decreased by 25%	Weakness of digit extension after wrist extensor injections.
Pullman *et al*[56]	Prospective	17	Clinical judgement	Previous experience; empirically on muscle size, function and regional anatomy.	Yes	Not significant	–	Decreased by 25%.	Weakness of digit extension after wrist extensor injections.
Jankovic *et al*[57]	Randomised double-blind placebo-controlled study.	25	Fixed dose in wrist flexors and extensors.	Fixed	–	Significant (60%–70%) improvement in clinical rating scales.	Not significant	Decreased by 30%	Insignificant finger weakness
Modugno *et al*[58]	Prospective	10	Wrist flexors and extensors injected.	Empirically chosen based on clinical status or previous experience.	Yes	Some improvement	All subjects reported improvement of average 20%.	–	Mild forearm weakness
Pacchetti *et al*[59]	Open-label study	20	Surface EMG done while doing specific tasks.	Based on mass of selected muscles and previous experience.	No	–	Significant improvement	Significant decrease	Digit extension weakness
Brin *et al*[60]	Double-masked randomised controlled study.	133	Wrist flexors and extensors selected.	Fixed dose (2 groups: low and high dose).	Yes	Significant improvement	Mild improvement	Significant improvement	Grip strength significantly reduced.
Samotus *et al*[54]	Single-centre, single-injector, open-label pilot study.	24	Kinematics assessment	Botulinum toxin A dose decided based on multijoint biomechanical recordings for each patient.	Yes	Significant reduction in scores	Significant improvement	Significant reduction	Insignificant muscle weakness reported by 40% of subjects.
Niemann and Jankovic [61]	Retrospective	91 (53 ET)	Forearm flexors (majority of patients).	Injection pattern was based on tremor aetiology.	Yes, in 5 subjects.	–	Moderate to marked improvement.	–	Transient and non-disabling limb weakness.

EMG, electromyography; ET, essential tremor.

BONT THERAPY FOR VOICE AND HEAD TREMOR

Since pharmacotherapy is not very successful in treating voice and head tremor alternative forms of therapy need to be explored. One such option is BoNT injection (table 3). A remarkable improvement has been shown in subjective clinical rating scales in head tremor treated with BoNT.[64 65] Similarly, a subjective improvement of 50%–65% is reported in voice tremor following BoNT injections as a result of reduced vocal effort due to decreased laryngeal airway resistance.[66–70] Side effects such as neck weakness, soreness, dysphagia and headache occur in less than half the subjects injected for head tremor and do not require any medical intervention.[64 65] On the other hand, mild voice weakness and breathiness occur following BoNT treatment for voice tremor.[66 67 71] Since pharmacological therapy is

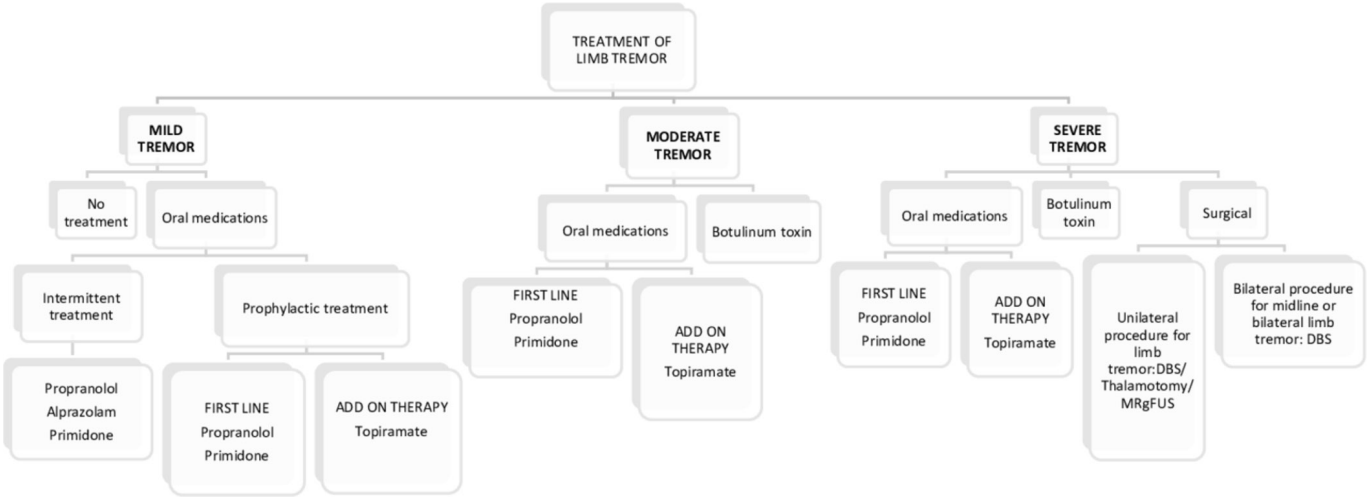

Figure 1 Treatment of limb tremor. DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound.

Table 3 Summary of studies on treatment of essential head and voice tremor with botulinum toxin

Authors	Study design	Patients, n	Muscles injected	Clinical rating scales	Side effects
Essential head tremor					
Pahwa *et al*[64]	Double-blind, placebo-controlled study	10	Sternocleidomastoid and splenius capitis.	Moderate to marked improvement.	Mild side effects and transient (neck weakness, dysphagia, headache).
Wissel *et al*[65]	Prospective	14	Splenius capitis	Significant subjective improvement noted in all patients.	Mild and transient side effects (local pain, dysphagia, neck weakness).
Voice tremor					
Hertegård *et al*[66]	Prospective	15	Thyroarytenoid plus either cricothyroid or thyrohyoid muscles.	Treatment was effective in 50%–65% of cases.	Mild temporary voice weakness noted in majority which improved in 1–2 weeks.
Warrick *et al*[67]	Prospective open-label cross-over study	10	Unilateral or bilateral vocalis.	Subjective reduction in vocal effort noted in majority of patients.	Most common side effect was breathiness.
Adler *et al*[68]	Randomised study	13	Bilateral vocal cord.	All patients reported botulinum toxin to be effective with improvement in mean tremor severity scale scores.	Patients complained of breathiness and dysphagia as side effects.
Gurey *et al*[69]	Retrospective analysis	16	Bilateral thyroarytenoid and strap muscles.	All patients had symptomatic improvement with a reduction in tremor amplitude.	Mild postinjection hoarseness.
Guglielmino *et al*[70]	Prospective	15 (EVT and dystonic voice tremor).	Left thyroarytenoid muscle versus oral propranolol.	EVT did not respond significantly to either intervention.	–

EVT, essential vocal tremor.

not very successful in either voice or head tremor, BoNT could be considered in subjects with disabling axial tremor (figure 2, table 3).[71]

Learning point

BoNT injection for voice tremor is perceived to improve subjective vocal effort. However, more studies should be performed, as the evidence is quite weak. Also, we should offer this treatment to a selective group of patients only in a specialised clinic due to concern regarding development of voice breathiness.

SURGICAL INTERVENTIONS FOR ET

Medical treatment fails or becomes intolerable due to side effects in nearly half of the subjects with ET. Therefore, surgical intervention is preferred when ET is pharmacoresistant and producing functional limitations in everyday activities. Surgical interventions can be divided into neuromodulation techniques and lesional surgeries. Neuromodulation refers to deep brain stimulation (DBS) surgery and lesional surgeries include radiofrequency thalamotomy, gamma knife radio-induced thalamotomy and magnetic resonance-guided focused ultrasound (MRgFUS) (figures 1 and 2, tables 4 and 5).

DBS of the thalamus is an invasive surgery done in subjects with medication refractory and functionally disabling tremor and has proven to be effective in the short term of over 6–12 months postoperatively.[72–78] But, several studies have pointed out that tolerance develops in 13%–40% of the subjects after chronic ventral intermediate nucleus (VIM) stimulation which

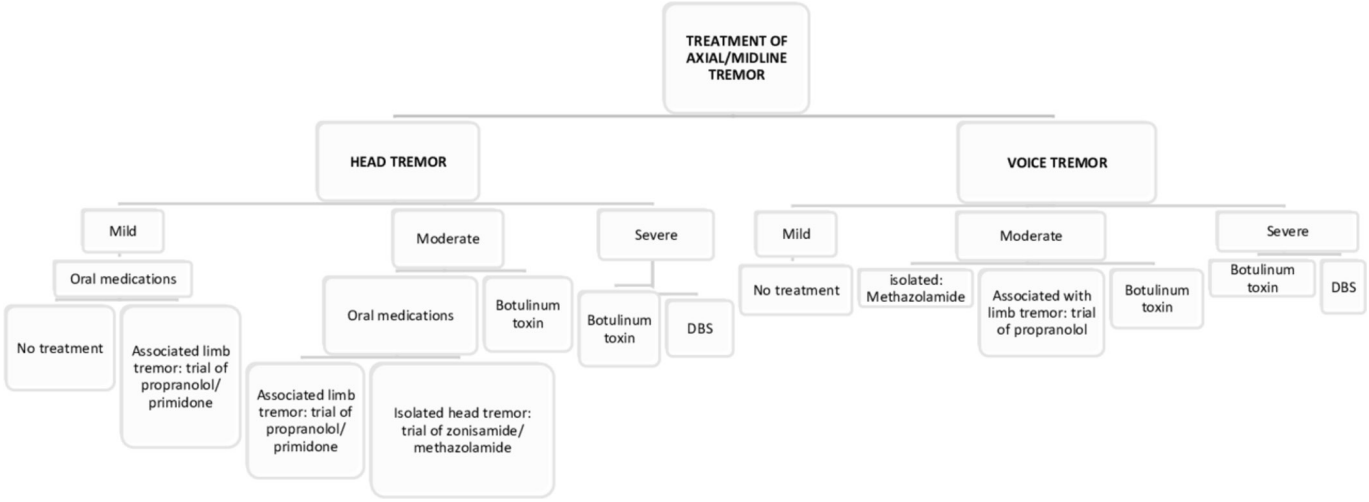

Figure 2 Treatment of axial (midline) tremor. DBS, deep brain stimulation.

Table 4 Magnetic resonance-guided focused ultrasound in the treatment of essential tremor

Authors	Study design	Patients, n	Follow-up duration (months)	Site of ablation	Side effects	Outcome	Conclusion
Lipsman *et al*[103]	Prospective	4	3	Thalamus	One developed postoperative persistent paraesthesia.	Immediate and sustained improvement in tremor which leads to functional improvement.	Safe and effective for medication-resistant ET.
Elias *et al*[104]	Open-label uncontrolled study	15	12	Thalamus	Persistent paraesthesias in 4 patients	Improvement noted in both tremor scores and quality-of-life scores.	Further studies needed to establish the procedure's safety and efficacy.
Elias *et al*[102]	Randomised trial	76	12	Thalamus	9% of patients had persistent gait disturbance and 14% had persistent paraesthesias.	The improvement in hand tremor was noted immediately after focused ultrasound thalamotomy compared with sham procedure. And the improvement was maintained.	Focused ultrasound reduced the severity of hand tremor.
Gallay *et al*[88]	Prospective	21	24	Cerebellothalamic tract in posterior subthalamic area	Mild worsening of previously existing gait instability was seen in 5 subjects.	Tremor reduction was maintained at follow-up. Bilateral lesioning showed good tolerance.	It is safe, effective and minimally invasive treatment and could potentially be used for bilateral treatment.
Kim *et al*[105]	Retrospective	23	12	Thalamus	Least side effects at 12 months when compared with RF thalamotomy and DBS.	Absent/mild tremor at 1 month postoperatively which is maintained at 12 months.	MRgFUS is equally efficacious as RF thalamotomy or DBS with fewer complications.
Schreglmann *et al*[106]	Prospective study	6	6	Unilateral cerebellothalamic tract (CTT)	Mild and transient hand clumsiness and gait impairment that lasted 3 months postoperatively.	Significant reduction of tremor in contralateral arm with improvement in quality of life.	Unilateral MRgFUS of CTT is highly effective.
Zaaroor *et al*[107]	Prospective	18	6–24	Thalamus	Significant side effects but none persisted beyond 3 months.	Immediate cessation of tremor seen. Reappearance of tremor seen in 2 patients although it was less severe.	It is a safe and effective procedure in drug-resistant ET although side effect profile is worse compared with other surgical procedures.
Tian *et al*[108]	Retrospective	8	12	Thalamus	Minimal	Significant improvement in tremor immediately which was maintained. Strong correlation between good outcome and the overlap between induced and tractography-identified location.	Diffusion tractography improves outcome by accurate target location for MRgFUS.
Jung *et al*[109]	Prospective	20	12	Thalamus	Insignificant cognitive decline	Clinical rating scale for tremor and quality of life improved at 12 months.	MRgFUS is an acceptable treatment for ET without causing any significant cognitive decline.

DBS, deep brain stimulation; ET, essential tremor; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

requires an increase in stimulation parameters.[74 79–86] The reasons postulated for the development of tolerance are progression of the disease and larger distance between the active contact and dentate-rubro-thalamic tract (DRTT), the structure that needs to be stimulated to alleviate the tremor.[79 81 87] In fact, several authors have recommended stimulating the posterior subthalamic area (PSA) as the DRTT passes through the superior portion of PSA before it ends in ventrolateral thalamus and, unlike VIM DBS, tolerance does not develop following PSA stimulation, even up to 3–5 years.[88–96]

Among the lesional surgeries, both radiofrequency and gamma-knife thalamotomy are effective in suppressing limb tremor in 85%–90% of the subjects and the effect is maintained in the long term.[97–100] Another form of lesional surgery is the MRgFUS that uses high-intensity focused ultrasound (table 4).[101–109] MRgFUS-thalamotomy has been reported to produce significant improvement in hand tremor, clinical rating scales and quality of life and the benefits have been maintained at 2 years' follow-up.[102 110] The side effects from unilateral MRgFUS-thalamotomy are paraesthesias and imbalance whereas bilateral targeting causes cognitive, gait, balance and speech disturbances.[102 111–113] In summary, the side effects from lesioning surgeries are more pronounced and permanent after bilateral compared with unilateral procedures, thus they are currently performed only unilaterally.[97 101 102 109 111 113]

The decision to select one procedure over another depends on several factors. For unilateral procedures looking to alleviate asymmetrical upper limb tremor, thalamotomy, MRgFUS-thalamus or VIM/PSA DBS can be considered.[97 114 115] For axial tremor (voice or head), bilateral DBS of VIM or PSA is a better

Table 5 Studies of ventral intermediate (VIM) nucleus deep brain stimulation (DBS) in essential tremor with long-term follow-up of more than 3 years

Authors	Study design	Patients, n	Follow-up duration	Site of stimulation	Side effects	Outcome	Development of tolerance
Koller *et al*[72]	Prospective	49	3–40.2 months	VIM	Mild stimulation-related adverse events	Significant improvement in tremor scores	Yes
Sydow *et al*[84]	Multicentre	37	6 years	Thalamus	Mild stimulation-related side effects	Markedly significant reduction in tremor scores and improvement in activities of daily living.	No
Rehncrona *et al*[85]	Prospective	19	6.5±0.3 years	VIM	Significant improvement in hand function	Mild	No
Pahwa *et al*[73]	Prospective	26	5 years	VIM	Significant improvement in hand tremor	Unilateral implants: paraesthesia and pain; bilateral implants: dysarthria and balance difficulty.	–
Blomstedt *et al*[79]	Prospective	19	84–118 months	VIM	Significant improvement in tremor scores	Lead breakage seen in 6 subjects	Yes
Zhang *et al*[86]	Prospective	34	Average 56.9 months	VIM	Significant improvement in tremor	Hardware-related complications seen in 23.5% cases	Yes
Børretzen *et al*[74]	Retrospective	46	Median 6 years	VIM	Significant improvement in tremor scores	Mild	Yes

and effective option.[89 116 117] MRgFUS may provide certain advantages over other surgical interventions due to it being a non-invasive procedure.[101 108 118] A recent systematic literature review concluded that the efficacy in tremor control as well as improving quality of life with unilateral MRgFUS-thalamotomy might be comparable to unilateral DBS in the short term up to 12 months after procedure.[119] On the other hand, DBS is the favoured treatment in subjects with bilateral and axial tremor as well as in those with contraindications to undergo MRI before the procedure.[72 73 76–78 83 101 115]

Learning point

- Both radiofrequency and gamma-knife thalamotomy are effective in reducing limb tremor, however, it is performed only unilaterally as complications are significant after bilateral procedures.
- DBS is preferred treatment option in individuals with bilateral moderate to severe limb tremor in addition to midline tremor.
- MRgFUS-thalamotomy has comparable efficacy to DBS of the VIM in the short term when performed unilaterally.

NON-INVASIVE THERAPIES FOR ET

The non-invasive brain stimulation investigated in ET involves transcranial direct current stimulation, repetitive transcranial magnetic stimulation and theta burst stimulation.[120] These non-invasive procedures have been found to be effective in the reduction of clinical tremor rating scales.[120] The site of stimulation is either the posterior cerebellum or motor cortical regions.[120] However, these studies have been done on small number of subjects with ET and the population studied have been heterogeneous and not well defined. Further studies should focus on patient selection criteria in addition to optimising and individualising the protocols for the non-invasive stimulation.

Another non-invasive form of treatment is the handheld assistive device using active cancellation of tremor technology, which has shown some promise in reducing tremor amplitude and severity while performing tasks in a limited pilot trial.[121] Efficacy of non-invasive peripheral nerve stimulation was assessed in a randomised controlled study by Pahwa *et al*.[122] Subjects receiving a single in-office session of peripheral nerve stimulation showed transient relief in hand tremor symptoms. Although some of these techniques and devices have shown some encouraging results, future studies are required to confirm the efficacy of non-invasive stimulation therapies.

TREATMENT OF ET PLUS

In addition to classical presentation of bilateral upper limb action tremor, some patients demonstrate subtle or 'soft' neurological signs of uncertain significance such as mild dystonic posturing of arms, impaired tandem gait and are now classified as ET plus.[1] The treatment of such cases would then depend on the predominant symptom. In a published case report, Patel *et al* described a 64-year-old woman who had a disabling postural-action tremor with subtle dystonic posturing which responded very well to VIM DBS.[123] Interestingly, a recent retrospective study by Rajalingam *et al* revealed that ET plus might be more common than pure ET.[124] Out of the 283 subjects diagnosed as ET, 110 were reclassified as ET plus based on the recent criteria for ET and ET plus.[1] They pointed out to the fact that there is no clear definition of the 'soft signs' associated with ET. Also, some of the apparent soft signs like gait dysfunction or memory impairment could be related to ageing. They, however, did not mention the treatment responses of this study cohort. Therefore, further studies are needed to better define the neurological soft signs that are associated with ET and the response to conventional treatment of this subset of patients.

CONCLUSION

ET is one of the most common movement disorders encountered in clinical practice. It has a very varied presentation in terms of severity and anatomical site of involvement. Treatment options depend on the tremor severity, functional disability, anatomical localisation of tremor, other medical comorbidities and, most importantly, subjects' desire to be treated. For mild to moderate limb tremor, pharmacotherapy can be started; if symptoms are intermittent, then treatment can be administered accordingly. For moderate to severe limb tremor option is either BoNT injections or surgical. If unilateral surgery is considered for the dominant hand, thalamotomy, VIM/PSA DBS or MRgFUS could be the treatment options. For bilateral limb involvement DBS is a more suitable option. For head and voice tremor, pharmacotherapy is not very beneficial, and these subjects require either BoNT injections or bilateral DBS.

Main messages

- Treatment of essential tremor is based on the severity of tremor, disability experienced as a result of tremor and, most importantly, the desire of the patient to be treated.
- Pharmacotherapy with primidone and/or propranolol is the first-line treatment for essential tremor.
- In moderate to severe tremor, botulinum toxin and surgical interventions could be offered.

Current research questions

- What are the therapeutic options for patients with essential tremor plus?
- Should botulinum toxin therapy be offered as first-line treatment instead of oral medications as the latter are associated with insufficient efficacy as well as side effects?
- Should deep brain stimulation (DBS) of the posterior subthalamic area be the preferred site of stimulation instead of the conventional thalamic DBS?

Key references

1. Bhatia KP, Bain P, Bajaj N, *et al*. Consensus statement on the classification of tremors, from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord* 2018;33:75–87.
2. Ferreira JJ, Mestre TA, Lyons KE, Benito-león J. MDS evidence-based review of treatments for essential tremor. *Mov Disord* 2019;2018:1–9.
3. Deuschl G, Raethjen J, Hellriegel H, *et al*. Treatment of patients with essential tremor. *Lancet Neurol* 2011;10:148–161.
4. Schneider SA, Deuschl G. The treatment of tremor. *Neurotherapeutics* 2014;11:128–38.
5. Niemann N, Jankovic J. Botulinum toxin for the treatment of hand tremor. *Toxins* 2018;10:299.

Self assessment questions

1. Seventy-five per cent of the subjects with essential tremor fail pharmacotherapy.
2. Propranolol and primidone are an add-on therapy for essential limb tremor.
3. Botulinum toxin is a good treatment option for essential limb, voice and head tremor.
4. MRgFUS-thalamotomy is indicated in midline tremor.
5. Posterior subthalamic area DBS is considered to be more effective than the conventional thalamic DBS.

Contributors SS and SP contributed in manuscript preparation by writing the first draft, review and critique and are responsible for the overall content as guarantors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Soumya Sharma http://orcid.org/0000-0003-3580-8504

REFERENCES

1 Bhatia KP, Bain P, Bajaj N, *et al*. Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and movement disorder Society. *Mov Disord* 2018;33:75–87.
2 Zesiewicz TA, Elble RJ, Louis ED, *et al*. Evidence-Based guideline update: treatment of essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2011;77:1752–5.
3 Ferreira JJ, Mestre TA, Lyons KE, *et al*. Mds commissioned review MDS evidence-based review of treatments for essential tremor. *Mov Disord* 2018;2019:1–9.
4 Deuschl G, Raethjen J, Hellriegel H, *et al*. Treatment of patients with essential tremor. *Lancet Neurol* 2011;10:148–61.
5 Louis ED, Rios EHC. How are we doing with the treatment of essential tremor (et)? persistence of et patients on medication: data from 528 patients in three settings. *Eur J Neurol* 2010;17:882–4.
6 Ceravolo R, Salvetti S, Piccini P, *et al*. Acute and chronic effects of clozapine in essential tremor. *Mov. Disord.* 1999;14:468–72.
7 Zappia M, Albanese A, Bruno E, *et al*. Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian movement disorders association. *J Neurol* 2013;260:714–40.
8 Bain PG. The effectiveness of treatments for essential tremor. *Neurologist* 1997;3:305–21.
9 Findley LJ, Cleeves L, Calzetti S. Primidone in essential tremor of the hands and head: a double blind controlled clinical study. *J Neurol Neurosurg Psychiatry* 1985;48:911–5.
10 Paparella G, Ferrazzano G, Cannavacciuolo A, *et al*. Differential effects of propranolol on head and upper limb tremor in patients with essential tremor and dystonia. *J Neurol* 2018;265:2695–703.
11 Winkler GF, Young RR. Efficacy of chronic propranolol therapy in action tremors of the familial, senile or essential varieties. *N Engl J Med* 1974;290:984–8.
12 O'Brien MD, Upton AR, Toseland PA. Benign familial tremor treated with primidone. *BMJ* 1981;282:178–80.
13 Findley LJ, Calzetti S. Double-Blind controlled study of primidone in essential tremor: preliminary results. *BMJ* 1982;285:608.
14 Sasso E, Perucca E, Fava R, *et al*. Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990;13:67–76.
15 Calzetti S, Sasso E, Baratti M, *et al*. Clinical and computer-based assessment of long-term therapeutic efficacy of propranolol in essential tremor. *Acta Neurol Scand* 1990;81:392–6.
16 Murray TJ. Long-Term therapy of essential tremor with propranolol. *Can Med Assoc J* 1976;115:892–4.
17 Schneider SA, Deuschl G. The treatment of tremor. *Neurotherapeutics* 2014;11:128–38.
18 Dupont E, Hansen HJ, Dalby MA. Treatment of benign essential tremor with propranolol: a controlled clinical trial. *Acta Neurol Scand* 1973;49:75–84.
19 Calzetti S, Findley LJ, Perucca E, *et al*. The response of essential tremor to propranolol: evaluation of clinical variables governing its efficacy on prolonged administration. *J Neurol Neurosurg Psychiatry* 1983;46:393–8.
20 Murray TJ. Treatment of essential tremor with propranolol. *Can Med Assoc J* 1972;107:984–6.
21 Tolosa ES, LOEWENSON RB. Essential tremor: treatment with propranolol. *Neurology* 1975;25:1041–4.
22 Koller WC. Long-Acting propranolol in essential tremor. *Neurology* 1985;35:108–10.
23 Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986;36:121–4.
24 Dietrichson P, Espen E. Primidone and propranolol in essential tremor: a study based on quantitative tremor recording and plasma anticonvulsant levels. *Acta Neurol Scand* 1987;75:332–40.
25 Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology* 1989;39:1587–8.
26 Calzetti S, Findley LJ, Gresty MA, *et al*. Metoprolol and propranolol in essential tremor: a double-blind, controlled study. *J Neurol Neurosurg Psychiatry* 1981;44:814–9.
27 Koller WC, Biary N. Metoprolol compared with propranolol in the treatment of essential tremor. *Arch Neurol* 1984;41:171–2.
28 Calzetti S, Findley LJ, Perucca E, *et al*. Controlled study of metoprolol and propranolol during prolonged administration in patients with essential tremor. *J Neurol Neurosurg Psychiatry* 1982;45:893–7.
29 Zesiewicz TA, Elble R, Louis ED, *et al*. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005;64:2008–20.
30 Koller WC. Nadolol in essential tremor. *Neurology* 1983;33:1076–7.
31 Connor GS. A double-blind placebo-controlled trial of topiramate treatment for essential tremor. *Neurology* 2002;59:132–4.

32 Connor GS, Edwards KTD. Topiramate in essential tremor: findings from double-blind, placebo-controlled, crossover trials. *Clin Neuropharmacol* 2008;31:97–103.
33 Frima N, Grünewald RA. A double-blind, placebo-controlled, crossover trial of topiramate in essential tremor. *Clin Neuropharmacol* 2006;29:94–6.
34 Ondo WG, Jankovic J, Connor GS, *et al*. Topiramate in essential tremor. *Neurology* 2006;66:672–7.
35 Ondo W, Hunter C, Vuong KD, *et al*. Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 2000;15:678–82.
36 Handforth A, Martin FC, Kang GA, *et al*. Zonisamide for essential tremor: an evaluator-blinded study. *Mov Disord* 2009;24:437–40.
37 Sanz-Cartagena P. Effectiveness and safety of levetiracetam in patients with essential tremor: data from an open 11-week follow-up trial]. *Rev Neurol* 2007;45:134–6.
38 Elble RJ, Lyons KE, Pahwa R. Levetiracetam is not effective for essential tremor. *Clin Neuropharmacol* 2007;30:350–6.
39 Biary N, Bahou Y, Sofi MA, *et al*. The effect of nimodipine on essential tremor. *Neurology* 1995;45:1523–5.
40 Thompson C, Lang A, Parkes JD, *et al*. A double-blind trial of clonazepam in benign essential tremor. *Clin Neuropharmacol* 1984;7:83–8.
41 Huber SJ, Paulson GW. Efficacy of alprazolam for essential tremor. *Neurology* 1988;38:241–3.
42 Biary N, Al Deeb SM, Langenberg P. The effect of flunarizine on essential tremor. *Neurology* 1991;41:311–2.
43 Biary N, Al Deeb SM, Bahou Y. Long-Term therapy of essential tremor with flunarizine. *Eur Neurol* 1995;35:217–9.
44 Zesiewicz TA, Sullivan KL, Hinson V, *et al*. Multisite, double-blind, randomized, controlled study of pregabalin for essential tremor. *Mov Disord.* 2013;28:249–50.
45 Bushara KO, Goldstein SR, Grimes GJ, *et al*. Pilot trial of 1-octanol in essential tremor. *Neurology* 2004;62:122–4.
46 Shill HA, Bushara KO, Mari Z, *et al*. Open-Label dose-escalation study of oral 1-octanol in patients with essential tremor. *Neurology* 2004;62:2320–2.
47 Gironell A, Pascual-sedano B, Marín-lahoz J. Perampanel,a new hope for Essential tremor: An open label trial. *Park Relat Disord* 2018:1–2.
48 Rajput AH, Jamieson H, Hirsh S, *et al*. Relative efficacy of alcohol and propranolol in action tremor. *Can J Neurol Sci* 1975;2:31–5.
49 Haubenberger D, McCrossin G, Lungu C, *et al*. Octanoic acid in alcohol-responsive essential tremor: a randomized controlled study. *Neurology* 2013;80:933–40.
50 Koller W, Graner D, Mlcoch A. Essential voice tremor: treatment with propranolol. *Neurology* 1985;35:106–8.
51 Calzetti S, Sasso E, Negrotti A, *et al*. Effect of propranolol in head tremor: quantitative study following single-dose and sustained drug administration. *Clin Neuropharmacol* 1992;15:470–6.
52 Busenbark K, Ramig L, Dromey C, *et al*. Methazolamide for essential voice tremor. *Neurology* 1996;47:1331–2.
53 Muenter MD, DAUBE JR, CAVINESS JN, *et al*. Treatment of essential tremor with methazolamide. *Mayo Clin Proc* 1991;66:991–7.
54 Samotus O, Rahimi F, Lee J, *et al*. Functional ability improved in essential tremor by incobotulinumtoxinA injections using kinematically determined biomechanical patterns – a new future. *PLoS One* 2016;11:e0153739.
55 Trosch RM, Pullman SL. Botulinum toxin A injections for the treatment of hand tremors. *Mov Disord* 1994;9:601–9.
56 Pullman SL, Greene P, Fahn S, *et al*. Approach to the treatment of limb disorders with botulinum toxin A. experience with 187 patients. *Arch Neurol* 1996;53:617–24.
57 Jankovic J, Schwartz K, Clemence W, *et al*. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996;11:250–6.
58 Modugno N, Priori A, Berardelli A, *et al*. Botulinum toxin restores presynaptic inhibition of group IA afferents in patients with essential tremor. *Muscle Nerve* 1998;21:1701–5.
59 Pacchetti C, Mancini F, Bulgheroni M, *et al*. Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000;21:349–53.
60 Brin MF, Lyons KE, Doucette J, *et al*. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001;56:1523–8.
61 Niemann N, Jankovic J. Botulinum toxin for the treatment of hand tremor. *Toxins* 2018;10:299.
62 Zakin E, Simpson D. Botulinum toxin in management of limb tremor. *Toxins* 2017;9:365.
63 Samotus O, Lee J, Jog M. Long-Term tremor therapy for Parkinson and essential tremor with sensor-guided botulinum toxin type A injections. *PLoS One* 2017;12:e0178670.
64 Pahwa R, Busenbark K, Swanson-Hyland EF, *et al*. Botulinum toxin treatment of essential head tremor. *Neurology* 1995;45:822–4.
65 Wissel J, Masuhr F, Schelosky L, *et al*. Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. *Mov Disord* 1997;12:722–6.
66 Hertegård S, Granqvist S, Lindestad PA. Botulinum toxin injections for essential voice tremor. *Ann Otol Rhinol Laryngol* 2000;109:204–9.
67 Warrick P, Dromey C, Irish JC, *et al*. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: a crossover design study of unilateral versus bilateral injection. *Laryngoscope* 2000;110:1366–74.
68 Adler CH, Bansberg SF, Hentz JG, *et al*. Botulinum toxin type A for treating voice tremor. *Arch Neurol* 2004;61:1416–20.
69 Gurey LE, Sinclair CF, Blitzer A. A new paradigm for the management of essential vocal tremor with botulinum toxin. *Laryngoscope* 2013;123:n/a–501.
70 Guglielmino G, Moraes BT, Villanova LC, *et al*. Comparison of botulinum toxin and propranolol for essential and dystonic vocal tremors. *Clinics* 2018;73:1–6.
71 Sulica L, Louis ED. Clinical characteristics of essential voice tremor: a study of 34 cases. *Laryngoscope* 2010;120:516–28.
72 Koller WC, Lyons KE, Wilkinson SB, *et al*. Long-Term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord* 2001;16:464–8.
73 Pahwa R, Lyons KE, Wilkinson SB, *et al*. Long-Term evaluation of deep brain stimulation of the thalamus. *J Neurosurg* 2006;104:506–12.
74 Børretzen MN, Bjerknes S, Sæhle T, *et al*. Long-Term follow-up of thalamic deep brain stimulation for essential tremor – patient satisfaction and mortality. *BMC Neurol* 2014;14:1–6.
75 Pahwa R, Lyons KE, Wilkinson SB, *et al*. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. *Mov Disord* 2001;16:140–3.
76 Ondo W, Jankovic J, Schwartz K, *et al*. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. *Neurology* 1998;51:1063–9.
77 Koller W, Pahwa R, Busenbark K, *et al*. High-Frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Ann Neurol* 1997;42:292–9.
78 Pahwa R, Lyons KL, Wilkinson SB, *et al*. Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology* 1999;53:1447–50.
79 Blomstedt P, Hariz G-M, Hariz MI, *et al*. Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. *Br J Neurosurg* 2007;21:504–9.
80 Hariz MI, Shamsgovara P, Johansson F, *et al*. Tolerance and tremor rebound following long-term chronic thalamic stimulation for parkinsonian and essential tremor. *Stereotact Funct Neurosurg* 1999;72:208–18.
81 Benabid AL. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir Suppl* 1993;58:39–44.
82 Benabid AL, Pollak P, Gao D, *et al*. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg* 1996;84:203–14.
83 Baizabal-Carvallo JF, Kagnoff MN, Jimenez-Shahed J, *et al*. The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. *J Neurol Neurosurg psychiatry* 2014;85:567–72.
84 Sydow O, Thobois S, Alesch F. Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *J Neurol Neurosurg Psychiatry* 2003;74:1387–91.
85 Rehncrona S, Johnels B, Widner H, *et al*. Long-Term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord* 2003;18:163–70.
86 Zhang K, Bhatia S, Oh MY, *et al*. Long-Term results of thalamic deep brain stimulation for essential tremor. *J Neurosurg* 2010;112:1271–6.
87 Pilitsis JG, Metman LV, Toleikis JR, *et al*. Factors involved in long-term efficacy of deep brain stimulation of the thalamus for essential tremor. *J Neurosurg* 2008;109:640–6.
88 Gallay MN, Moser D, Rossi F, *et al*. Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J Ther Ultrasound* 2016;4:1–10.
89 Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. *J Neurol Neurosurg psychiatry* 2008;79:504–13.
90 Fytagoridis A, Åström M, Samuelsson J, *et al*. Deep brain stimulation of the caudal zona incerta: tremor control in relation to the location of stimulation fields. *Stereotact Funct Neurosurg* 2016;94:363–70.
91 Herzog J, Hamel W, Wenzelburger R, *et al*. Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. *Brain* 2007;130:1608–25.
92 Blomstedt P, Lindvall P, Linder J, *et al*. Peer-Review short reports reoperation after failed deep brain stimulation for essential tremor. *World Neurosurg* 2012;78:554.e1–5.
93 Hamel W, Herzog J, Kopper F, *et al*. Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor. *Acta Neurochir* 2007;149:749–58.
94 Holslag JAH, Neef N, Beudel M, *et al*. Deep brain stimulation for essential tremor: a comparison of targets. *World Neurosurg* 2018;110:e580–4.
95 Anthofer JM, Steib K, Lange M, *et al*. Distance between active electrode contacts and Dentatorubrothalamic tract in patients with habituation of stimulation effect of deep brain stimulation in essential tremor. *J Neurol Surg A Cent Eur Neurosurg* 2017;78:350–7.
96 Fenoy AJ, Schiess MC. Deep brain stimulation of the Dentato-Rubro-Thalamic tract: outcomes of direct targeting for tremor. *Neuromodulation* 2017;20:429–36.
97 Zirh A, Reich SG, Dougherty PM, *et al*. Stereotactic thalamotomy in the treatment of essential tremor of the upper extremity: reassessment including a blinded measure of outcome. *J Neurol Neurosurg Psychiatry* 1999;66:772–5.

98 Jankovic J, Cardoso F, Grossman RG, *et al*. Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. *Neurosurgery* 1995;37:680–7.
99 Witjas T, Carron R, Krack P, *et al*. A prospective single-blind study of gamma knife thalamotomy for tremor. *Neurology* 2015;85:1562–8.
100 Kondziolka D, Ong JG, Lee JYK, *et al*. Gamma knife thalamotomy for essential tremor. *J Neurosurg* 2008;108:111–7.
101 Rohani M, Fasano A. Focused Ultrasound for Essential Tremor : Review of the Evidence and Discussion of Current Hurdles. *Tremor and Other Hyperkinetic Movements* 2017;7:1–12.
102 Elias WJ, Lipsman N, Ondo WG, *et al*. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* 2016;375:730–9.
103 Lipsman N, Schwartz ML, Huang Y, *et al*. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol* 2013;12:462–8.
104 Elias WJ, Huss D, Voss T, *et al*. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* 2013;369:640–8.
105 Kim M, Jung NY, Park CK, *et al*. Comparative evaluation of magnetic resonance-guided focused ultrasound surgery for essential tremor. *Stereotact Funct Neurosurg* 2017;95:279–86.
106 Schreglmann SR, Bauer R, Hägele-Link S, *et al*. Unilateral cerebellothalamic tract ablation in essential tremor by MRI-guided focused ultrasound. *Neurology* 2017;88:1329–33.
107 Zaaroor M, Sinai A, Goldsher D, *et al*. Magnetic resonance–guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg* 2017;128:202–10.
108 Tian Q, Wintermark M, Jeffrey Elias W, *et al*. Diffusion MRI tractography for improved transcranial MRI-guided focused ultrasound thalamotomy targeting for essential tremor. *Neuroimage Clin* 2018;19:572–80.
109 Jung NY, Park CK, Chang WS, *et al*. Effects on cognition and quality of life with unilateral magnetic resonance–guided focused ultrasound thalamotomy for essential tremor. *Neurosurg Focus* 2018;44:E8.
110 Federau C, Goubran M, Rosenberg J, *et al*. Transcranial MRI-guided high-intensity focused ultrasound for treatment of essential tremor: a pilot study on the correlation between lesion size, lesion location, thermal dose, and clinical outcome. *J Magn Reson Imaging* 2018;48:58–65.
111 Chang JW, Park CK, Lipsman N, *et al*. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: results at the 2-year follow-up. *Ann Neurol* 2018;83:107–14.
112 Krack P, Martinez-fernandez R, Alamo M, *et al*. Current applications and limitations of surgical treatments for movement disorders surgery for movement disorders. *Mov Disord* 2017;32:36–52.
113 Mohammed N, Patra D, Nanda A. A meta-analysis of outcomes and complications of magnetic resonance–guided focused ultrasound in the treatment of essential tremor. *Neurosurg Focus* 2018;44:E4.
114 Schuurman PR, Bosch DA, Bossuyt PMM, *et al*. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000;342:461–8.
115 Huss DS, Dallapiazza RF, Shah BB, *et al*. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. *Mov Disord*. 2015;30:1937–43.
116 Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. *J Neurosurg* 1999;91:68–72.
117 Hägglund P, Sandström L, Blomstedt P, *et al*. Voice tremor in patients with essential tremor: effects of deep brain stimulation of caudal zona incerta. *J voice* 2016;30:228–33.
118 Gallay MN, Moser D, Jeanmonod D. Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments. *J Neurosurg* 2018;1:1–10.
119 Langford BE, Ridley CJA, Beale RC, *et al*. Focused ultrasound thalamotomy and other interventions for Medication-Refractory essential tremor: an indirect comparison of short-term impact on health-related quality of life. *Value Heal* 2018;21:1168–75.
120 Chalah MA, Lefaucheur J-P, Ayache SS, *et al*. Non-Invasive central and peripheral stimulation: new hope for essential tremor? *Front Neurosci* 2015;9:1–11.
121 Pathak A, Redmond JA, Allen M, *et al*. A noninvasive handheld assistive device to accommodate essential tremor: a pilot study. *Mov Disord* 2014;29:838–42.
122 Pahwa R, Dhall R, Ostrem J, *et al*. *An acute randomized controlled trial of noninvasive peripheral nerve stimulation in essential tremor*. Neuromodulation: Technology at the Neural Interface, 2019: 22. 537–45.
123 Patel A, Deeb W, Okun MS, *et al*. Deep brain stimulation management of essential tremor with dystonic features. *Tremor Other Hyperkinet Mov* 2018;8.
124 Rajalingam R, Breen DP, Lang AE, *et al*. Essential tremor plus is more common than essential tremor: insights from the reclassification of a cohort of patients with lower limb tremor. *Parkinsonism Relat Disord* 2018:1–2.

Answers

1. False; 50% fail pharmacotherapy.
2. False; they are the first-line therapy.
3. True.
4. False; thalamic DBS is indicated in midline tremor.
5. True.