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REVIEW

The Treatment of Tremor

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Abstract Tremor is a hyperkinetic movement disorder characterized by rhythmic oscillations of one or more body parts. It can be disabling and may impair quality of life. Various etiological subtypes of tremor are recognized, with essential tremor (ET) and Parkinsonian tremor being the most common. Here we review the current literature on tremor treatment regarding ET and head and voice tremor, as well as dystonic tremor, orthostatic tremor, tremor due to multiple sclerosis (MS) or lesions in the brainstem or thalamus, neuropathic tremor, and functional (psychogenic) tremor, and summarize main findings. Most studies are available for ET and only few studies specifically focused on other tremor forms. Controlled trials outside ET are rare and hence most of the recommendations are based on a low level of evidence. For ET, propranolol and primidone are considered drugs of first choice with a mean effect size of approximately 50 % tremor reduction. The efficacy of topiramate is also supported by a large double-blind placebo-controlled trial, while other drugs have less supporting evidence. With a mean effect size of about 90 % deep brain stimulation in the nucleus ventralis intermedius or the subthalamic nucleus may be the most potent treatment; however, there are no controlled trials and it is reserved for severely affected patients. Dystonic limb tremor may respond to anticholinergics. Botulinum toxin improves head and voice tremor. Gabapentin and clonazepam are often recommended for orthostatic tremor. MS tremor responds only poorly to drug treatment. For patients with severe MS tremor, thalamic deep brain stimulation has been recommended. Patients with functional tremor may benefit from antidepressants and are best be treated in a multidisciplinary setting. Several tremor syndromes can already be treated with success. But new drugs specifically designed for tremor treatment are needed. ET is most likely covering different entities and their delineation may also improve treatment. Modern study designs and long-term studies are needed.

Keywords Essential tremor · Dystonic tremor · Propranolol · Primidone · Topiramate

Tremor is a hyperkinetic movement disorder characterized by rhythmic oscillations of one or more body parts. Tremor most commonly affects the hands and arms, but the legs, head, jaw, chin, palate, voice, and trunk may also be affected.

Different Types of Tremor

Different types of tremor are recognized. The diagnosis of tremor is based on the history and the clinical examination, as there are no specific biological markers or diagnostic tests for primary tremor, i.e., tremor without identifiable secondary cause. Essential tremor (ET) is among the most common neurological diseases, with a prevalence of ~0.9 % [1] in people older than 65 years. However, although tremor may have a considerable impact on quality of life [2, 3] by affecting activities of daily living, such as eating, drinking, and writing, only a proportion seeks medical attention. Only 27 % of our population-based cohort in Germany ever saw a doctor for tremor [4] in line with a study in the USA, where only 8.3 % had been prescribed tremor medication [5]. However, the most severe cases cannot even eat or drink without help. Indeed, tremor intensity may range from mild to severe, so treatment decisions need to be made on an individual basis.

The most common cause of tremor at rest is Parkinsonism, the treatment of which is beyond the scope of this review. The most common cause of postural arm tremor is ET, which may be accompanied by tremor of the head and voice in some, with little or no tremor in the lower limbs and torso [6]. Gross signs of ataxia, Parkinsonism, and dystonia are, by definition,

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absent in ET [6, 7]. A common form of kinetic (intention) tremor is cerebellar tremor related to multiple sclerosis (MS), but there are other etiologies of cerebellar tremor. In this review, which extends earlier analyses [8, 9], we will concentrate on the common forms.

Essential tremor may cover different entities which are not separated by the current Tremor Investigation Group (TRIG) and Movement Disorders Society (MDS) consensus criteria. This has to be kept in mind as it may result in heterogeneity of study populations and results of treatment trials. Thus, recent efforts have been made to better delineate and dissect these tremor forms [10, 11] and the MDS has commissioned a new task force on tremor to improve clinical practice and research into the field.

Measurements of Tremor

Tremor severity can be measured using rating scales (i.e., Fahn–Tolosa–Marín tremor rating scale) [12, 13]. Presently, a new scale [the essential tremor rating assessment scale (TETRAS)] is under development for tremor rating [14]. Another tool is accelerometry, which informed early propranolol and primidone trials, and there is good correlation between clinical ratings and log-transformed transducer measures of tremor, as predicted by the Weber–Fechner laws of psychophysics [15]. Action tremor can be reliably measured with spiral drawing [16, 17]. Maybe in the future modern mobile applications [18] will allow long-duration monitoring of treatment effects, which may be helpful considering minute-to-minute variations of tremors including ET [19].

Treatment of Tremor

Treatment of tremor may be challenging. Most treatment studies have been conducted for ET. Accordingly, this review will begin by reviewing treatment studies for ET and, with the lack of data for other tremor syndromes, empirical data of ET are often transferred to other forms of action tremor (i.e., fragile x-associated tremor ataxia syndrome (FXTAS), etc.) [20]. Limb, head, and voice tremor will be discussed separately, followed by separate sections on dystonic tremor, orthostatic tremor (OT), cerebellar tremor in the context of MS, Holmes and thalamic tremor, and, finally, functional (psychogenic) tremor.

Treatment of Limb Tremor in ET

Numerous agents have been studied for potential benefit for ET over the years (Tables 1, 2 and 3). However, only 2 drugs—propranolol and primidone—appear to have sufficient class I support for a level A recommendation of efficacy, and these are thus often recommended as drugs of "first choice" [8, 9, 32]. However, more recent analyses suggest that topiramate may be better established than previously recognized. New drugs in the pipeline for ET tremor treatment are drugs developed analogous to alcohol, which is still the most potent, but dangerous (short-term), treatment of most ET patients.

Table 1 Recommended drugs for essential tremor

Drug	Mean or median effective daily dosage	Estimated percentage improvement in tremor amplitude
Propranolol	40–240 (320) mg/d	32–75
Primidone	<62.5 –750.0 mg/d	42–76
Topiramate	100–333 mg/d	30–41

Having sifted through the literature, we wish to point out that many studies are based on small patient numbers and relatively brief observation periods. Notably, drugs used for tremor treatment in day-to-day practice may not always have approved indications, depending on the country, so when using medications "off label", published guidelines should be followed.

Propranolol and Other Betablockers

Historically, the first treatment, recognized in 1971, for ET was propranolol [33]. Subsequently, other betablockers, including metoprolol [21, 34], nadolol, atenolol, and sotalol were also studied (see below). The majority of studies are cross-over trials comparing propranolol (including long-acting suspensions) or other betablockers against placebo or comparing betablockers in a head-to-head design or against other drugs (i.e., gabapentin, primidone).

For propranolol, we identified 13 relevant double-blind, placebo-controlled trials using a crossover design [22, 23, 34–41] and 2 studies with a parallel design [34, 42]. Notably, mean duration of treatment (60–240 mg per day) on stable dosages of medication was less than 3 weeks. Furthermore, particularly in early studies, there is sometimes no specific information on washout duration between treatment periods or

Table 2 Drugs for essential tremor with probable or weak efficacy

Drug	Mean or median effective daily dosage	Estimated percentage improvement in tremor amplitude [ref.]	Percentage improvement by accelerometry [ref.]
Atenolol	50–100 mg/d	24–38 [21, 22]	37 [23]
Sotalol	80–240 mg/d	29–51 [21, 22]	–
Gabapentin	1200–1800 mg/d	39 [24]	77
Alprazolam	0.75–1.5 mg/d	48–60 [25, 26]	–

Table 3 Drugs for essential tremor with uncertain efficacy (likely not efficacious)

Level C possibly effective (daily dosage of the respective studies) [ref.]	Agents with recommendations against use	Inadequate evidence to confirm or exclude efficacy
Clonazepam (0.5–4.0 mg) [27]	Acetazolamide/methazolamide	Olanzapine
Clozapine (18–75 mg) [28]	Amantadine	Pregabalin
Flunarizine (10 mg) [29]	Carisbamate	Tiagabine
Nadolol (120–240 mg) [30]	Isoniazid	Sodium oxybate
Nimodipine (120 mg) [31]	Levetiracetam	Zonisamide
Botulinum toxin (depending on injected muscles)	Pindolol	
	Trazodone	
	3,4-Diaminopyridine	
	Mirtazapine	
	Nifedipine	
	Verapamil	

reference made to possible carry-over effects. On average, 18 adults (range, 9–33) were included. There are no randomized controlled trials on the long-term effects of propranolol in ET.

Improvement in the range of 60–70 % has been reported in line with a mean reduction of tremor amplitude of 54 % (range, 32–75 %) measured by accelerometry in 8 controlled studies [23, 34–36, 38, 39]. Occasional dramatic responders have been described [37], but there are no known predictors of response. The side effects of propranolol are well known and frequently dose-limiting, and include bradycardia, syncope, fatigue, and erectile dysfunction. It is thus recommended to begin with a low dose (e.g., 30–60 mg/day) and to gradually increase the dosage as needed. Total daily dosages of 60–240 mg are adequate in most responders.

Clinical trials of other beta blockers (i.e., atenolol, metoprolol, sotalol) are likely efficacious for limb tremor in ET, but none has been found to be superior to propranolol (Table 2). Efficacy comparisons are shown in Fig. 1, and they may be considered when propranolol is contraindicated. There are insufficient data on long-term efficacy. The different betablockers have also helped the understanding of the pharmacology of betablockers. It is likely that betablockers work mainly through central and peripheral beta-blockade and β2-receptors mainly [21–23, 43].

Primidone

We found 6 double-blind, placebo-controlled studies on ET with a crossover design, and none with a parallel design [25, 38, 44–46]. Mean duration of treatment with a stable dosage of medication was, again, rather brief with a duration of 1–5 weeks. Overall, primidone is considered likely efficacious with a benefit of around 60 % reduction in tremor amplitude [25], which correlates with accelerometry findings (59 %; range, 42–76 %) [25, 38, 44–46]. At least 50 % of patients experienced some benefit, and occasional "dramatic responders" have been

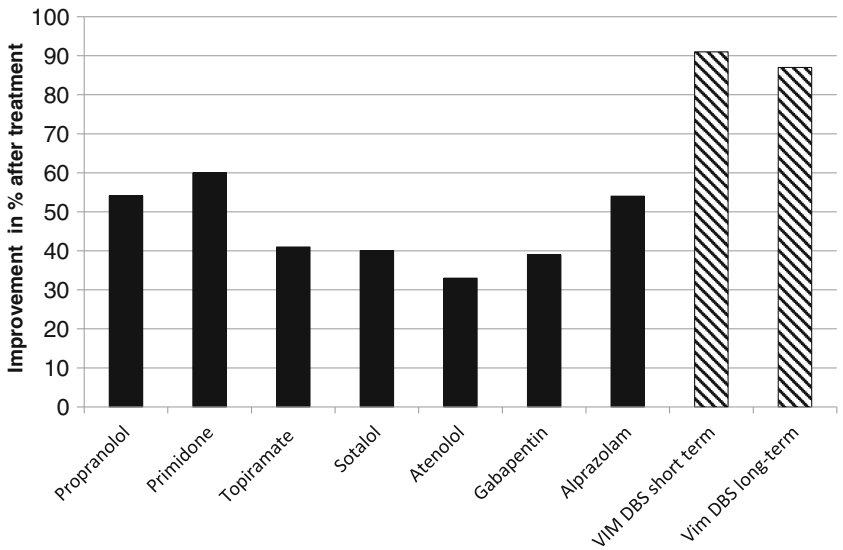

Fig. 1 The estimated percent improvement of tremor amplitude of different interventions is shown. The values show the mean value of the studies reported here. Patients in the surgical studies usually have much higher tremor amplitudes. Tremor amplitude estimation is based on standard algorithms computed as change in tremor rating scale and change in tremor amplitude on accelerometry [9, 15]

described. However, there are no known predictors of response [45].

However, side effects are common and frequently dose-limiting (see below). The average study cohort size was 18 adults (range, 11–22), and thus similar to beta blocker studies, but many randomized patients in studies did not complete the trials. Besides drowsiness and dizziness reported by most patients on total daily dosages of 500 mg or more, children, elderly, and patients with comorbid psychiatric disorders are prone to develop depression, cognitive, and behavioral effects. Unfortunately, acute toxic reaction to the first dose of primidone also frequently occurs and is characterized by nausea, sedation, malaise, ataxia, dizziness, and confusion, and patients may refuse continuation of treatment.

In view of these side effects, it is common practice to start on very low dosages (12.5 or 25 mg) by dividing available (50 mg or 100 mg) tablets into halves or quarters; however, a double-blind, double-dummy trial concluded that even very low initial doses and a graduated titration schedule do not appear to improve primidone tolerability [47]. Thus, caution and patient education are advisable when starting primidone. Total daily dosages of 150 mg or less are often sufficient.

Long-term controlled trials are mostly lacking; one 12-month open-label study found lasting beneficial response in 52 % and tolerance to side effects in 13 % [48]. In another 1-year study comparing different dosages (250 mg/day and 750 mg/day of primidone), 14 % and 31 % of patients on lower and higher doses, respectively, had dropped out [49].

Topiramate

Topiramate is an anticonvulsant, discovered in 1979. Common side effects are weight loss, paresthesias, trouble concentrating, and memory disturbance, as well as an increased risk of kidney stones. Dropout owing to side effects was a problem in reported controlled trials.

It has been studied in the largest study for ET so far [50]. Four relevant studies [50–53] assessed the effect of topiramate in limb tremor, providing evidence for therapeutic benefit [50–53]. A placebo-controlled cross-over study in 24 patients using up to 400 mg/d as mono- or adjunct therapy [51] found a significant reduction of tremor subscores. In a subsequent article [53], the same authors report combined results of 3 randomized, double-blind, placebo-controlled, cross-over trials of topiramate for ET (maximum tolerated dose of up to 400 mg/d) in adult patients observed for 10 weeks per treatment arm (active drug then placebo *vs* placebo then active drug). Total tremor scores were significantly improved in the topiramate-treated arms for tremor severity, motor task performance, and functional disability. In contrast, Frima and Grünewald [52] did not find significant differences in favor of topiramate in their double-blind, placebo-controlled, cross-over study at doses of 25, 50, or 100 mg daily. Finally, Ondo et al. [50] reported a multicenter, double-blind, placebo-controlled, parallel-design trial of topiramate with a 24-week treatment plan. More than 100 patients with moderate-to-severe tremor were enrolled per group, making it the largest study of topiramate so far. It is also notable when compared to trials available for betablockers or primidone. Target dose was 400 mg/day; 229 mg/day was the actual average final dose. Outcome measures (tremor rating scales) improved by almost 30 % (compared to 16 % for placebo) for the 6-month duration of this study. Adverse events were common (32 %), but similar to those seen with topiramate for other indications.

Medications with Less Established Efficacy

Numerous other agents have been reported, mostly based on small studies or single cases. No definite conclusions can be drawn from these (Table 3).

Possibly Efficacious Drugs

The calcium channel blocker flunarizine [29], with H1 receptor blocking properties, may reduce tremor; however, side effects include extrapyramidal symptoms. Alprazolam, a benzodiazepine used for treatment of anxiety and panic disorder, led to significant improvement in 2 double-blind placebo-controlled trials in ET [25, 26]. There was no difference compared to primidone. In a double-blind, placebo-controlled, cross-over study [54] tremor was improved by theophylline (dose: 150 mg/day) in 80 % of patients (compared with 60 % of the propranolol-treated arm). One placebo-controlled small study has shown an effect of gabapentin (1800 mg and 3600 mg) [55], while another failed [56], and 1 small crossover study with propranolol has shown similar improvement for both drugs [57].

Likely not Efficacious Drugs

Numerous drugs have been investigated for the treatment of ET; however, results are conflicting or questionable owing to the methodological flaws of studies.

Zonisamide (mean dosage: 160–250 mg/day) produced mixed results ranging from failure of treatment to improvement in postural and kinetic tremor (estimated at 41–46 %) to inconclusive results with lack of clinical improvement, but statistically significant 40 % improvement in accelerometry [58–60]. Thus, results for zonisamide remain inconclusive (level U). Other drugs with inconclusive evidence (level U) include tiagabine (30 mg/day) and sodium oxybate (maximum dosage 4 mg three times a day) [61].

We identified 2 relevant double-blind, placebo-controlled studies for levetiracetam in ET [13, 62]. Overall, no significant effect was found at doses up to 3000 mg/day. Levetiracetam is therefore not recommended.

Similarly, pregabaline [63, 64] (doses up to 600 mg/day) and progabide [65] (at 1800 mg/day and 3600 mg/day), as well as amantadine (dose: 200 mg/day) [66] failed to produce significant benefit. Likewise, the antidepressants trazodone (dose: 100 mg/day), a serotonine reuptake inhibitor [67], and mirtazapine (dose: 45 mg/day) [68] showed no significant results. In a cross-over study comparing olanazpine (20 mg/day) and propranolol, tremor significantly improved in both groups [69]. However, there was no placebo group so it was unclear how much of the improvement may have been placebo-related. The carbonic anhydrase inhibitors acetazolamide (mean dose: 500 mg/day) and methazolamide (dose: 200–300 mg/day) did not produce significant benefits when compared with placebo [25, 70]. A double-blind, placebo-controlled, cross-over study of 20 and 40 mg 3,4-diaminopyridine in 18 patients found no improvement [71]. A multicenter, randomized, double-blind, cross-over, placebo-controlled study of carisbamate 400 mg/d in 62 ET patients also revealed no beneficial effect [72].

The antibacterial isoniazid (used for treatment of tuberculosis) produced no benefit [73], but is associated with unacceptable risks of side effects (including possible fatal hepatitis), so this drug is not recommended for the treatment of ET.

More recently, T2000 (1,3-dimethoxymethyl-5,5-diphenyl-barbituric acid), a new nonsedating barbiturate was explored in double-blind, placebo-controlled trials [74]. Daily doses at 800–1000 mg of T2000 led to significant reduction of tremor in 1 study, but no benefits in the other. In 1 of the studies, 1/12 patients discontinued owing to a rash followed by a febrile illness [74]; in the other study, 6/10 patients withdrew owing to central nervous system-related adverse events. Thus, there is yet insufficient evidence regarding this new compound.

Botulinum Toxin for ET Limb Tremor

There are two relevant published trials of botulinum toxin type A for treatment of limb tremor in ET [75, 76]. This includes one RCT parallel group study [75] using a 2-staged injection pattern with low-dose injections into hand flexors and extensors followed by a higher dose 4 weeks later if patients were unresponsive to the initial dose. Accelerometry revealed around 60–70 % improvement of postural hand tremor, but there were no significant improvements in functional ratings. Eleven of 12 (92 %) patients developed moderate nondisabling wrist or finger weakness. Another study of ET [76] compared low-dose (50 U) and high-dose (100 U) botulinum toxin with placebo in a 12-week randomized, double-blind, controlled trial in 133 patients. Postural and kinetic tremor improved, but without consistent benefit on function. Dose-dependent weakness developed in 30 % after low-dose group and 70 % after high-dose injections. While botulinum toxin may be likely efficacious, side effects are often limiting and, in our experience, efficacy is modest, at best.

Stereotactic Surgery, Gamma Knife Thalamotomy and Experimental Approaches for ET

Thalamotomy and thalamic [ventralis intermedius (Vim)] deep brain stimulation (DBS) have large treatment effects for upper limb tremor in ET with gradual loss of control of tremor over months or years and a mean 0–10 satisfaction rating of more than 8 (10 = extremely satisfied; 0 = not satisfied) [77–83]. Vim, the zona incerta, and the radiation praelemniscalis are all in close proximity and are probably the best targets for ET [9]. Several articles have summarized the long-term results [8, 9]; however, there are no double-blind, placebo-controlled trials, also because true blinding is difficult.

The risks and side effects of thalamic DBS are well-documented, although their incidence and severity are somewhat uncertain owing to widely varying methods of follow-up and documentation. They include hardware complications (25 % of patients), paresthesias (6–36 %), dysarthria (3–18 %), ataxia (6 %), limb weakness (4–8 %), balance disturbance (3–8 %), dystonia (2–9 %), and perioperative complications (i.e., intracerebral bleeding, ischemic stroke, infection). The mortality rate of DBS surgery was found to be 0.4 % [83].

For gamma knife thalamotomy controlled trials are scarce: 1 study [84] used blinded rating, but there are no placebo-(sham-) controlled trials. Two recent uncontrolled case series report conflicting results, with efficacy and risks comparable to Vim DBS in 1 [85, 86], but only mild benefit in the other [84]. The risk of uncontrolled long-term enlargement of the lesions has been described [84, 87]. Therefore, we conclude that there is insufficient evidence to recommend the use of gamma knife thalamotomy in the treatment of ET.

Most recently, noninvasive magnetic resonance-guided focused ultrasound has been proposed for treatment of disabling tremor. Lipsman et al. [88] produced ablative lesions by stereotactically-guided focused ultrasound energy in 4 patients with ET and produced immediate and sustained improvement of about 90 %. Elias et al. [89] produced about 45 % improvement of total tremor rating scales (with effects on hand tremor of 20.4 at baseline to 5.2 at 12 months) in 15 ET patients. Larger studies are needed to validate safety and ascertain the efficacy of this interesting approach. Transcranial magnetic stimulation has also been explored [90].

Treatment of Dystonic Limb Tremor

According to current MDS tremor criteria, tremor in dystonia is subclassified as “dystonic tremor” when tremor occurs in a body part that is affected by dystonia, for example head tremor in torticollis or arm tremor in patients with writer's cramp, and as “tremor associated with dystonia” when tremor is present in

a body part not affected by dystonia, for example hand tremor in cervical dystonia patients. However, dystonia may be subtle and ET may be overly generously diagnosed in patients with dystonic (and other types of) tremor. Presence of an irregular jerky tremor with "flurries" or task- or position-specificity may be pointers towards this diagnosis. Asymmetric resting arm tremor with impaired arm swing does not exclude the diagnosis [11] and dopamine imaging may help to differentiate it from Parkinsonian rest tremor.

Few studies have specifically focused on dystonic tremor, but patients may have accidentally been included in ET trials. A recent study of 25 patients with dystonic tremor found that only 40 % of patients benefitted from oral therapy. Anticholinergics [i.e., trihexyphenidyl (range, 3–6 mg/day)] produced the best results; propranolol also produced some benefit [91].

Treatment of Primary Writing Tremor

Primary writing tremor is a condition in which tremor predominantly or only occurs during writing, or also when adopting the hand position normally used for writing. There are no specific drugs for primary writing tremor, so overall treatment is similar to what is discussed above. Main studies and their results are summarized by Hai et al. [92]. In brief, 60 % of patients treated reported that they had obtained some benefit from drug therapy. Better results can probably be obtained with botulinum toxin [93], but there are no controlled studies. Some patients received DBS for writing tremor.

Treatment of Head Tremor in ET and Dystonic Tremor

While hand tremor is usually the predominant symptom in ET [7], head and voice tremor may occur. However, it may also be a feature of dystonic tremor, and patients with cervical dystonia frequently have tremulous head movements (dystonic head tremor); 1 study reported occurrence in 38 % of patients [94]. These patients often also have postural hand tremor (dystonic tremor/tremor associated with dystonia) and this should not be mistaken as ET. Amongst others, essential and dystonic head tremor may be separated by the positive geste antagoniste for dystonic tremor [95]. Temporal discrimination has also been proposed for discrimination [96].

Few studies have specifically addressed treatment of head and voice tremor. From the current literature there is insufficient evidence for beta blockers, including propranolol for the treatment of head tremor in ET or dystonic tremor. Botulinum toxin injections produces good benefit in head tremor in the context of ET [97] and dystonic [95] head tremor, as shown in 29 patients with predominant tremulous torticollis in an open trial. Vim-DBS seems to be a potent treatment, but bilateral surgery is important for severe head tremor [98, 99].

Treatment of Voice Tremor

Similarly, voice tremor may be a feature in ET or associated with dystonic limb or head tremor, but may also occur in isolation. In dystonia, 25–30 % of patients with spasmodic dysphonia have associated vocal tremor [100]. Again, only a few studies specifically focused on treatment of voice tremor. Overall, fewer than 50 % patients with voice tremor respond to oral medication [101]. Botulinum toxin may be helpful, and a treatment algorithm for botulinum toxin use in vocal tremor has recently been proposed [101]. Also, DBS does improve voice tremor [99].

Treatment of OT

OT is a rare form of tremor and is characterized by subjective unsteadiness during standing, which is relieved by sitting or walking. Neurophysiological recording confirms the presence of a fast, 13–18 Hz, tremor [102, 103]. Disease course is often slowly progressive. Notably, about one third of patients have associated other movement disorders (OT-plus) and may go on to develop Parkinsonism [104]. Gabapentin (up to 2400 mg/day) was found to be effective in case series [105–107]. Clonazepam (0.25–3.5 mg/day, median 1 mg/day) may even be more effective, but has more long-term side effects [108, 109]. In those unresponsive to these drugs treatment is challenging as only 12 % in a large series responded to alternative drugs (e.g., valproic acid, acetazolamide, mirtazapine, primidone, and levetiracetam) [110–112]. Levetiracetam has not produced benefit in a controlled trial [111]. Levodopa had no benefit on OT in any of the patients with a diagnosis of Parkinsonism. Thalamic DBS was helpful in few cases but less efficient than in other tremors [113, 114].

Treatment of Cerebellar Tremor Related to MS

Cerebellar tremor is common in MS, with a prevalence ranging around 25–60 % in different studies, with a mean latency between onset of MS and development of tremor of about 11 years [115]. It typically occurs on action as postural and kinetic tremor, while classical rest tremor is usually not found in MS. Tremor most frequently affects the arms, but may also involve head, voice, and trunk. Titubation of the head and trunk are the most severe manifestations. Treatment with pharmacological agents is usually unsuccessful. Small case series or single cases showed improvement after carbamazepine [116], propranolol, topiramate [117], primidone [118], isoniazid, ondansetron, or 4-aminopyridine [119], but there is insufficient evidence to support or refute efficacy of these drugs. A recent randomized, placebo-controlled, cross-over study [120] assessed botulinum toxin for MS-related limb

tremor in 23 patients. Differences in all primary outcomes were highly significant at 6 and 12 weeks. Mild-to-moderate weakness after botulinum toxin injections occurred in 42 %. The most potent treatment is DBS or lesioning of the Vim nucleus of the thalamus [121, 122].

Treatment of Holmes Tremor and Thalamic Tremor

Holmes tremor is characterized by the combination of slow (4–5 Hz or less) rest and intention tremor, and is often less "rhythmic" than other tremor variants. Additional postural tremor may be present. Neuroimaging, with special focus on the brainstem, is crucial in the work-up of these patients. In contrast, lesion in the thalamus (typically in the dorsolateral part) causes thalamic tremor typically characterized by a combination of rest, postural and intention tremor, and dystonia, which may be indistinguishable from Holmes tremor purely on clinical grounds. Treatment of both is challenging. Single cases have responded to high-dose levodopa [123], trihexyphenidyl (2–12 mg), clonazepam (0.5–4.0 mg), clozapin (<75 mg), or levetiracetam. Pharmaco-refractory cases may respond to DBS [124–126]; however, in thalamic tremor electrode placement (into the damaged area) is difficult, so opting for 2 targets has been proposed [127, 128].

Tremor in Peripheral Neuropathies

Tremor may be a rare accompanying feature of peripheral neuropathy. In inflammatory neuropathies tremor is found in up to 80 % of cases with IgM paraproteinemic neuropathy [129, 130]. Clinically, neuropathic tremor mostly presents as postural or kinetic tremor [131]. Propranolol may be beneficial. Others reported improvement after pregabalin (30–80 mg) [132, 133]. However, in a recent series no patient responded to medication prescribed for tremor, but some reported improvement after treatment for their neuropathy (intravenous immunoglobulin, rituximab or chemotherapy regimen consisting of cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone plus rituximab (CHOP-R) chemotherapy) [129]. DBS of the thalamus (Vim) has been described successful in cases of hereditary neuropathy [134–136].

Treatment of Functional (Psychogenic) Tremor

Psychogenic tremor is the most common form (55 %) of all functional movement disorders and may be remarkably variable in its presentation. It should be suspected when there is sudden onset and spontaneous remission. Examination shows entrainment, distractibility, or the co-contraction sign. Tremor remission rates have been estimated at only 20–60 % [137–139]. For better outcome, diagnostic delay should be avoided and treatment is best offered in a multidisciplinary approach, including symptom-focused cognitive–behavioral therapy approaches and physical interventions [140, 141]. With respect to pharmacotherapy patients may benefit from antidepressants [142] when there is a history of recent or current depression or anxiety. Overall, there is a terrible need for clinical treatment trials.

Conclusions

Treatment of tremor is challenging. The first step is to establish the correct diagnosis. This may not always be straightforward, particularly because the current definition of ET may cover different subgroups. For many tremors, controlled studies are lacking or the quality of existing trials is poor by modern standards. For ET there are at least 3 drugs (propranolol, topiramate, primidone) that have reasonable evidence to receive a level A recommendation. But, in general, only 50 % of the patients respond to 1 of the drugs. For many other drugs there is insufficient evidence to recommend them for treatment of ET.

Other tremor types show variable response to oral medication. Dystonic limb tremor may respond to anticholinergics. Gabapentin and clonazepam are often used for OT. Similarly, MS tremor may respond to primidone or topiramate, but there are no controlled trials. Botulinum toxin improves head and voice tremor. Finally, patients with functional tremor may benefit from antidepressants, but should best be treated in a multidisciplinary setting.

The most severe organic tremors usually show a poor response to medical treatment. Therefore, surgical treatments have a role for very severe tremors with good success for ET and, probably, dystonic tremor, while they are less favorable for other tremors (MS tremor, neuropathic tremor, and thalamic and Holmes tremor), but still worth trying in severely handicapped patients when drugs have failed.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 2010;25:534–541.
2. Lorenz D, Schwieger D, Moises H, Deuschl G. Quality of life and personality in essential tremor patients. Mov Disord 2006;21:1114–1118.

3. Troster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. Parkinsonism Relat Disord 2005;11:367–373.
4. Lorenz D, Poremba C, Papengut F, Schreiber S, Deuschl G. The psychosocial burden of essential tremor in an outpatient- and a community-based cohort. Eur J Neurol 2011;18:972–979.
5. Louis ED, Ford B, Wendt KJ, Cameron G. Clinical characteristics of essential tremor: data from a community- based study. Mov Disord 1998;13:803–808.
6. Deuschl G, Elble R. Essential tremor – Neurodegenerative or nondegenerative disease towards a working definition of ET. Mov Disord 2009;24:2033–2041.
7. Elble RJ. Tremor: clinical features, pathophysiology, and treatment. Neurol Clin 2009;27:679–676vi.
8. 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;77:1752–1755.
9. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol 2011;10:148–161.
10. Elble RJ. Defining dystonic tremor. Curr Neuropharmacol 2013;11: 48–52.
11. Schneider SA, Edwards MJ, Mir P, et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). Mov Disord 2007;22: 2210–2215.
12. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E (eds) Parkinson's disease and movement disorders. Williams & Wilkins, Baltimore, MD, 1993, pp. 271–280.
13. Stacy MA, Elble RJ, Ondo WG, Wu SC, Hulihan J. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in essential tremor. Mov Disord 2007;22:833–838.
14. Elble R, Comella C, Fahn S, et al. The essential tremor rating assessment scale (TETRAS). Mov Disord 2008;23(Suppl.1):S1–S6.
15. Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain 2006;129:2660–2666.
16. Haubenberger D, Kalowitz D, Nahab FB, et al. Validation of digital spiral analysis as outcome parameter for clinical trials in essential tremor. Mov Disord 2011;26:2073–2080.
17. Raahave D, Christensen E, Loud FB, Knudsen LL. Correlation of bowel symptoms with colonic transit, length, and faecal load in functional faecal retention. Dan Med Bull 2009;56:83–88.
18. Daneault JF, Carignan B, Codere CE, Sadikot AF, Duval C. Using a smart phone as a standalone platform for detection and monitoring of pathological tremors. Front Hum Neurosci 2013;6:357.
19. Mostile G, Fekete R, Giuffrida JP, et al. Amplitude fluctuations in essential tremor. Parkinsonism Relat Disord 2012;18:859–863.
20. Hall DA, O'Keefe JA. Fragile x-associated tremor ataxia syndrome: the expanding clinical picture, pathophysiology, epidemiology, and update on treatment. Tremor Other Hyperkinet Mov (N Y) 2012;2.
21. Leigh PN, Jefferson D, Twomey A, Marsden CD. Beta-adrenoreceptor mechanisms in essential tremor; a double-blind placebo controlled trial of metoprolol, sotalol and atenolol. J Neurol Neurosurg Psychiatry 1983;46:710–715.
22. Jefferson D, Jenner P, Marsden CD. beta-Adrenoreceptor antagonists in essential tremor. J Neurol Neurosurg Psychiatry 1979;42: 904–909.
23. Larsen TA, Teravainen H, Calne DB. Atenolol vs. propranolol in essential tremor. A controlled, quantitative study. Acta Neurol Scand 1982;66:547–554.
24. Kulisevsky J, Berthier ML, Avila A, Gironell A, Escartin AE. Unrecognized Tourette syndrome in adult patients referred for psychogenic tremor. Arch Neurol 1998;55:409–414.
25. Gunal DI, Guleryuz M, Bingol CA. Reversible valproate-induced choreiform movements. Seizure 2002;11:205–206.
26. Huber SJ, Paulson GW. Efficacy of alprazolam for essential tremor. Neurology 1988;38:241–243.
27. Thompson C, Lang A, Parkes JD, Marsden CD. A double-blind trial of clonazepam in benign essential tremor. Clin Neuropharmacol 1984;7:83–88.
28. Ceravolo R, Salvetti S, Piccini P, Lucetti C, Gambaccini G, Bonuccelli U. Acute and chronic effects of clozapine in essential tremor. Mov Disord 1999;14:468–472.
29. Biary N, al Deeb SM, Langenberg P. The effect of flunarizine on essential tremor. Neurology 1991;41:311–312.
30. Koller WC. Nadolol in essential tremor. Neurology 1983;33:1076–1077.
31. Fukuda M, Barnes A, Simon ES, et al. Thalamic stimulation for parkinsonian tremor: correlation between regional cerebral blood flow and physiological tremor characteristics. Neuroimage 2004;21: 608–615.
32. Ferreira JJ, Sampaio C. Essential tremor. Clin Evid (Online) 2007;2007.
33. Winkler GF, Young RR. The control of essential tremor by propranolol. Trans Am Neurol Assoc 1971;96:66–68.
34. Calzetti S, Findely LJ, Gresty MA, Perucca E, Richens A. Effect of a single oral dose of propranolol on essential tremor: a double-blind controlled study. Ann Neuol 1983;13:165–171.
35. Baruzzi A, Procaccianti G, Martinelli P, et al. Phenobarbital and propranolol in essential tremor: a double-blind controlled clinical trial. Neurology 1983;33:296–300.
36. Cleeves L, Findley LJ, Koller W. Lack of association between essential tremor and Parkinson's disease. Ann Neurol 1988;24:28.
37. Dupont E, Hansen HJ, Dalby MA. Treatment of benign essential tremor with propranolol. A controlled clinical trial. Acta Neurol Scand 1973;49:75–84.
38. Gorman G, Fairgrieve S, Birchall D, Chinnery PF. Fragile X premutation presenting as essential tremor. J Neurol Neurosurg Psychiatry 2008;79:1195–1196.
39. Winkler GF, Young RR. Efficacy of chronic propranolol therapy in action tremors of the familial, senile or essential varieties. N Engl J Med 1974;290:984–988.
40. Murray TJ. Long-term therapy of essential tremor with propranolol. Can Med Assoc J 1976;115:892–894.
41. Sweet RD, Blumberg J, Lee JE, Mc Dowell FH. Propranolol treatment of essential tremor. Neurology 1974;24:64–67.
42. Tolosa ES, Loewenson RB. Essential tremor: treatment with propranolol. Neurology 1975;25:1041–1044.
43. Larsen TA, Teravainen H. Beta 1 versus nonselective blockade in therapy of essential tremor. Adv Neurol 1983;37:247–251.
44. Findley LJ, Calzetti S. Double-blind controlled study of primidone in essential tremor: preliminary results. Br Med J (Clin Res Ed) 1982;285:608.
45. 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;48:911–915.
46. Pfefferbaum A, Rosenbloom MJ, Fama R, Sassoon SA, Sullivan EV. Transcallosal white matter degradation detected with quantitative fiber tracking in alcoholic men and women: selective relations to dissociable functions. Alcohol Clin Exp Res 2010;34:1201–1211.
47. O'Suilleabhain PE, Matsumoto JY. Time-frequency analysis of tremors. Brain 1998;121:2127–2134.
48. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology 1989;39: 1587–1588.
49. Martinez-Martin P, Serrano-Duenas M, Forjaz MJ, Serrano MS. Two questionnaires for Parkinson's disease: are the PDQ-39 and PDQL equivalent? Qual Life Res 2007;16:1221–1230.

50. Ondo WG, Jankovic J, Connor GS, et al. Topiramate in essential tremor: a double-blind, placebo-controlled trial. Neurology 2006;66:672–677.
51. Connor GS. A double-blind placebo-controlled trial of topiramate treatment for essential tremor. Neurology 2002;59:132–134.
52. Frima N, Grünewald RA. A double-blind, placebo-controlled, crossover trial of topiramate in essential tremor. Clin Neuropharmacol 2006;29:94–96.
53. Connor GS, Edwards K, Tarsy D. Topiramate in essential tremor: findings from double-blind, placebo-controlled, crossover trials. Clin Neuropharmacol 2008;31:97–103.
54. Mally J, Stone TW. Efficacy of an adenosine antagonist, theophylline, in essential tremor: comparison with placebo and propranolol. J Neurol Sci 1995;132:129–132.
55. Dahl AM, Klein C, Andres PG, et al. Expression of bcl-X(L) restores cell survival, but not proliferation off effector differentiation, in CD28-deficient T lymphocytes. J Exp Med 2000;191:2031–2038.
56. Pahwa R, Lyons K, Hubble JP, et al. Double-blind controlled trial of gabapentin in essential tremor. Mov Disord 1998;13: 465–467.
57. Gironell A, Kulisevsky J, Barbanoj M, Lopez-Villegas D, Hernandez G, Pascual-Sedano B. A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. Arch Neurol 1999;56:475–480.
58. Handforth A, Martin FC, Kang GA, Vanek Z. Zonisamide for essential tremor: an evaluator-blinded study. Mov Disord 2009;24: 437–440.
59. Morita S, Miwa H, Kondo T. Effect of zonisamide on essential tremor: a pilot crossover study in comparison with arotinolol. Parkinsonism Relat Disord 2005;11:101–103.
60. Ondo WG. Zonisamide for essential tremor. Clin Neuropharmacol 2007;30:345–349.
61. Louis ED, Barnes L, Wendt KJ, et al. A teaching videotape for the assessment of essential tremor. Mov Disord 2001;16:89–93.
62. Handforth A, Martin FC. Pilot efficacy and tolerability: a randomized, placebo-controlled trial of levetiracetam for essential tremor. Mov Disord 2004;19:1215–1221.
63. Ferrara JM, Kenney C, Davidson AL, Shinawi L, Kissel AM, Jankovic J. Efficacy and tolerability of pregabalin in essential tremor: a randomized, double-blind, placebo-controlled, crossover trial. J Neurol Sci 2009;285:195–197.
64. Zesiewicz TA, Sullivan KL, Hinson V, et al. Multisite, double-blind, randomized, controlled study of pregabalin for essential tremor. Mov Disord 2013;28:249–250.
65. Mondrup K, Dupont E, Pedersen E. The effect of the GABA-agonist, progabide, on benign essential tremor. A controlled clinical trial. Acta Neurol Scand 1983;68:248–252.
66. Koller WC. Amantadine in essential tremor. Ann Neurol 1984;16: 621–622.
67. Koller WC. Tradozone in essential tremor. Probe of serotoninergic mechanisms. Clin Neuropharmacol 1989;12:134–137.
68. Pahwa R, Lyons KE. Mirtazapine in essential tremor: a double-blind, placebo-controlled pilot study. Mov Disord 2003;18:584–587.
69. Yetimalar Y, Irtman G, Kurt T, Basoglu M. Olanzapine versus propranolol in essential tremor. Clin Neurol Neurosurg 2005;108:32–35.
70. Pahwa R, Busenbark K, Gray C, Koller WC. Identical twins with similar onset of Parkinson's disease: a case report. Neurology 1993;43:1159–1161.
71. Lorenz D, Hagen K, Ufer M, Cascorbi I, Deuschl G, Volkmann J. No benefit of 3,4-diaminopyridine in essential tremor: a placebo-controlled crossover study. Neurology 2006;66:1753–1755.
72. Elble RJ, Biondi DM, Ascher S, Wiegand F, Hulihan J. Carisbamate in essential tremor: brief report of a proof of concept study. Mov Disord 2010;25:634–638.
73. Hallett M, Ravits J, Dubinsky RM, Gillespie MM, Moinfar A. A double-blind trial of isoniazid for essential tremor and other action tremors. Mov Disord 1991;6:253–256.
74. Melmed C, Moros D, Rutman H. Treatment of essential tremor with the barbiturate T2000 (1,3-dimethoxymethyl-5,5-diphenyl-barbituric acid). Mov Disord 2007;22:723–727.
75. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord 1996;11:250–256.
76. 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;56:1523–1528.
77. Wardell K, Blomstedt P, Richter J, et al. Intracerebral microvascular measurements during deep brain stimulation implantation using laser Doppler perfusion monitoring. Stereotact Funct Neurosurg 2007;85:279–286.
78. Pilitsis JG, Metman LV, Toleikis JR, Hughes LE, Sani SB, Bakay RA. Factors involved in long-term efficacy of deep brain stimulation of the thalamus for essential tremor. J Neurosurg 2008;109:640–646.
79. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurosurg 2006;104:506–512.
80. Zhang K, Bhatia S, Oh MY, Cohen D, Angle C, Whiting D. Long-term results of thalamic deep brain stimulation for essential tremor. J Neurosurg 2010;112:1271–1276.
81. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001;16:464–468.
82. Kumar R, Lozano AM, Sime E, Lang AE. Long-term follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor. Neurology 2003;61:1601–1604.
83. Voges J, Hilker R, Botzel K, et al. Thirty days complication rate following surgery performed for deep-brain-stimulation. Mov Disord 2007;22:1486–1489.
84. Lim SY, Hodaie M, Fallis M, Poon YY, Mazzella F, Moro E. Gamma knife thalamotomy for disabling tremor: a blinded evaluation. Arch Neurol 2010;67:584–588.
85. Kondziolka D, Ong JG, Lee JY, Moore RY, Flickinger JC, Lunsford LD. Gamma knife thalamotomy for essential tremor. J Neurosurg 2008;108:111–117.
86. Young RF, Li F, Vermeulen S, Meier R. Gamma knife thalamotomy for treatment of essential tremor: long-term results. J Neurosurg 2010;112:1311–1317.
87. Shoulson I, Penney J, McDermott M, et al. A randomized, controlled trial of remacemide for motor fluctuations in Parkinson's disease. Neurology 2001;56:455–462.
88. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Lancet Neurol 2013;12:462–468.
89. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2013;369:640–648.
90. Popa T, Russo M, Vidailhet M, et al. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. Brain Stimul 2013;6:175–179.
91. Schwingenschuh P, Ruge D, Edwards MJ, et al. Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study. Mov Disord 2010;25:560–569.
92. Hai C, Yu-ping W, Hua W, Ying S. Advances in primary writing tremor. Parkinsonism Relat Disord 2006;16:561–565.
93. Papapetropoulos S, Argyriou AA, Chroni E. No correlation between the clinical severity of autonomic symptoms (SCOPA-AUT) and electrophysiological test abnormalities in advanced Parkinson's disease. Mov Disord 2006;21:430–431.

94. Godeiro-Junior C, Felicio AC, Aguiar PC, Borges V, Silva SM, Ferraz HB. Head tremor in patients with cervical dystonia: different outcome? Arq Neuropsiquiatr 2008;66:805–808.
95. Wissel J, Masuhr F, Schelosky L, Ebersbach G, Poewe W. Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. Mov Disord 1997;12:722–726.
96. Tinazzi M, Fasano A, Di Matteo A, et al. Temporal discrimination in patients with dystonia and tremor and patients with essential tremor. Neurology 2013;80:76–84.
97. Pahwa R, Busenbark K, Swanson-Hyland EF, et al. Botulinum toxin treatment of essential head tremor. Neurology 1995;45:822–824.
98. Obwegeser AA, Uitti RJ, Turk MF, Strongosky AJ, Wharen RE. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. Neurology 2000;54:2342–2344.
99. Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999;66:289–296.
100. Kendall KA, Leonard RJ. Interarytenoid muscle botox injection for treatment of adductor spasmodic dysphonia with vocal tremor. J Voice 2011;25:114–119.
101. Gurey LE, Sinclair CF, Blitzer A. A new paradigm for the management of essential vocal tremor with botulinum toxin. Laryngoscope 2013;123:2497–2501.
102. Thompson PD, Rothwell JC, Day BL, et al. The physiology of orthostatic tremor. Arch Neurol 1986;43:584–587.
103. Deuschl G, Lãcking CH, Quintern J. Orthostatic tremor: clinical aspects, pathophysiology and therapy. EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete 1987;18:13–19.
104. Gerschlager W, Brown P. Orthostatic tremor – a review. Handb Clin Neurol 2011;100:457–462.
105. Rodrigues JP, Edwards DJ, Walters SE, et al. Blinded placebo crossover study of gabapentin in primary orthostatic tremor. Mov Disord 2006;21:900–905.
106. Evidente VG, Adler CH, Caviness JN, Gwinn KA. Effective treatment of orthostatic tremor with gabapentin. Mov Disord 1998;13:829–831.
107. Di FA, Tassorelli C, De MM, et al. Comprehensive analysis of the LRRK2 gene in sixty families with Parkinson's disease. Eur J Hum Genet 2006;14:322–331.
108. FitzGerald PM, Jankovic J. Orthostatic tremor: an association with essential tremor. Mov Disord 1991;6:60–64.
109. McManis PG, Sharbrough FW. Orthostatic tremor: clinical and electrophysiologic characteristics. Muscle Nerve 1993;16:1254–1260.
110. Rodrigues JP, Edwards DJ, Walters SE, et al. Gabapentin can improve postural stability and quality of life in primary orthostatic tremor. Mov Disord 2005;20:865–870.
111. Hellriegel H, Raethjen J, Deuschl G, Volkmann J. Levetiracetam in primary orthostatic tremor: A double-blind placebo-controlled crossover study. Mov Disord 2011;26:2431–2434.
112. Gerschlager W, Münchau A, Katzenschlager R, et al. Natural history and syndromic associations of orthostatic tremor: A review of 41 patients. Movement Disorders 2004;19:788–795.
113. Espay AJ, Duker AP, Chen R, et al. Deep brain stimulation of the ventral intermediate nucleus of the thalamus in medically refractory orthostatic tremor: Preliminary observations. Mov Disord 2008;23:2357–2362.
114. Guridi J, Rodriguez-Oroz MC, Arbizu J, et al. Successful thalamic deep brain stimulation for orthostatic tremor. Mov Disord 2008;23:1808–1811.
115. Alusi SH, Aziz TZ, Glickman S, Jahanshahi M, Stein JF, Bain PG. Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study. Brain 2001;124:1576–1589.
116. Sechi GP, Zuddas M, Piredda M, et al. Treatment of cerebellar tremors with carbamazepine: a controlled trial with long-term follow-up. Neurology 1989;39:1113–1115.
117. Schroeder A, Linker RA, Lukas C, Kraus PH, Gold R. Successful treatment of cerebellar ataxia and tremor in multiple sclerosis with topiramate: a case report. Clin Neuropharmacol 2010;33:317–318.
118. Naderi F, Javadi SA, Motamedi M, Sahraian MA. The efficacy of primidone in reducing severe cerebellar tremors in patients with multiple sclerosis. Clin Neuropharmacol 2012;35:224–226.
119. Schniepp R, Jakl V, Wuehr M, et al. Treatment with 4-aminopyridine improves upper limb tremor of a patient with multiple sclerosis: a video case report. Mult Scler 2013;19:506–508.
120. Van Der Walt A, Sung S, Spelman T, et al. A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. Neurology 2012;79:92–99.
121. Schuurman PR, Bosch DA, Merkus MP, Speelman JD. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. Mov Disord 2008;23:1146–1153.
122. Hooper AK, Okun MS, Foote KD, et al. Venous air embolism in deep brain stimulation. Stereotact Funct Neurosurg 2009;87:25–30.
123. Boelmans K, Gerloff C, Munchau A. Long-lasting effect of levodopa on holmes' tremor. Mov Disord 2012;27:1097–1098.
124. Diederich NJ, Verhagen ML, Bakay RA, Alesch F. Ventral intermediate thalamic stimulation in complex tremor syndromes. Stereotact Funct Neurosurg 2008;86:167–172.
125. Kudo M, Goto S, Nishikawa S, et al. Bilateral thalamic stimulation for Holmes' tremor caused by unilateral brainstem lesion. Mov Disord 2001;16:170–174.
126. Nikkhah G, Prokop T, Hellwig B, Lucking CH, Ostertag CB. Deep brain stimulation of the nucleus ventralis intermedius for Holmes (rubral) tremor and associated dystonia caused by upper brainstem lesions. Report of two cases. J Neurosurg 2004;100:1079–1083.
127. Lim DA, Khandhar SM, Heath S, Ostrem JL, Ringel N, Starr P. Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. Stereotact Funct Neurosurg 2007;85:144–149.
128. Foote KD, Okun MS. Ventralis intermedius plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic Holmes tremor: two leads may be better than one: technical note. Neurosurgery 2005;56:E445.
129. Saifee TA, Schwingenschuh P, Reilly MM, et al. Tremor in inflammatory neuropathies. J Neurol Neurosurg Psychiatry 2013;84:1282–1287
130. Dalakas MC, Teravainen H, Engel WK. Tremor as a feature of chronic relapsing and dysgammaglobulinemic polyneuropathies. Incidence and management. Arch Neurol 1984;41:711–714.
131. Bain PG, Britton TC, Jenkins IH, et al. Tremor associated with benign IgM paraproteinaemic neuropathy. Brain 1996;119:789–799.
132. Alonso-Navarro H, Fernandez-Diaz A, Martin-Prieto M, Ruiz-Ezquerro JJ, Lopez-Alburquerque T, Jimenez-Jimenez FJ. Tremor associated with chronic inflammatory demyelinating peripheral neuropathy: treatment with pregabalin. Clin Neuropharmacol 2008;31:241–244.
133. Coltamai L, Magezi DA, Croquelois A. Pregabalin in the treatment of neuropathic tremor following a motor axonal form of Guillain-Barre syndrome. Mov Disord 2010;25:517–519.
134. Ruzicka E, Jech R, Zarubova K, Roth J, Urgosik D. VIM thalamic stimulation for tremor in a patient with IgM paraproteinaemic demyelinating neuropathy. Mov Disord 2003;18:1192–1195.
135. Weiss D, Govindan RB, Rilk A, et al. Central oscillators in a patient with neuropathic tremor: evidence from intraoperative local field potential recordings. Mov Disord 2011;26:323–327.
136. Breit S, Wachter T, Schols L, et al. Effective thalamic deep brain stimulation for neuropathic tremor in a patient with severe demyelinating neuropathy. J Neurol Neurosurg Psychiatry 2009;80:235–236.
137. Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol 2008;7:827–840.
138. Gupta A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2009;22:430–436.

139. Roper LS, Saifee TA, Parees I, Rickards H, Edwards MJ. How to use the entrainment test in the diagnosis of functional tremor. Pract Neurol 2013. doi:10.1136/practneurol-2013-000549.
140. Edwards MJ, Bhatia KP. Functional (psychogenic) movement disorders: merging mind and brain. Lancet Neurol 2012;11:250–260.
141. Dallocchio C, Arbasino C, Klersy C, Marchioni E. The effects of physical activity on psychogenic movement disorders. Mov Disord 2010;25:421–425.
142. Voon V, Lang AE. Antidepressant treatment outcomes of psychogenic movement disorder. J Clin Psychiatry 2005;66:1529–1534.