Essential tremor: diagnosis and management

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ABSTRACT

Essential tremor is one of the most common movement disorders in adults and can affect both children and adults. An updated consensus statement in 2018 redefined essential tremor as an isolated action tremor present in bilateral upper extremities for at least three years. Tremor may also be present in other locations, commonly the neck or the vocal cords. Patients with additional neurologic symptoms are now categorized as "essential tremor plus." Additional clinical features associated with the condition include but are not limited to cognitive impairment, psychiatric disorders, and hearing loss. When treatment is needed, propranolol and primidone are considered first line treatments. Patients who are severely affected are often offered deep brain stimulation. Although the ventral intermediate nucleus of the thalamus is the traditional surgical target, the caudal zona incerta is also being studied as a possible superior alternative. Magnetic resonance imaging guided high intensity focused ultrasound is a newer surgical alternative that may be ideal for patients with substantial medical comorbidities. Current research explores novel oral treatments, chemodenervation, and noninvasive neuromodulation for treatment of essential tremor.

Introduction

Essential tremor is a syndrome defined as a "bilateral upper extremity action tremor" and is among the most common movement disorders in adults.[1] As life expectancy increases, the prevalence of essential tremor increases, and the number of patients with essential tremor presenting in the office for treatment is thus growing. The historical practice of grouping all action tremors together may partially explain both the difficulties in identifying genetic causes and patients' variable responses to treatment.

Decades after their initial study, propranolol and primidone remain the first line oral drugs for essential tremor. However, only about half of the patients taking these drugs have a significant reduction in the amplitude of tremor.[2] Little is known about the long term efficacy of treatments, as few trials have had long term follow-up. Very few interventions have class I evidence for their efficacy. The emergence of surgical alternatives for treatment offers new options for the most severely affected patients. In the past decade, novel treatments ranging from chemodenervation to noninvasive neuromodulation bring new excitement into the field. The goal of this review is to summarize the clinical features associated with the condition, the recommended changes in classification, and the current treatment options.

Epidemiology

Worldwide, the crude prevalence rates of essential tremor in adults range from 0.4% to 6%.[3 4] Essential tremor affects approximately 1% of the population and 4-5% of people aged over 65 years.[5 6] Studies suggest a bimodal age of onset.[7] A clinical study of 978 patients with probable or definite essential tremor identified an early onset group with age 24 years or less and an older onset group with age 46 years or above.[8] A retrospective chart review of 211 children found that the onset can be as early as birth, but the mean onset age was 9.7 (SD 5.6) years.[9] Essential tremor in children has a male predominance that ranges from 1.6:1 to 3:1. Although adult onset essential tremor is not thought to have a sex imbalance, a population study of 2117 older adults also found a significant male predominance in the 46 patients with essential tremor (χ^2=5.0, P=0.03).[3]

Sources and selection criteria

Comprehensive search strategies covered the topics of diagnosis, medical and surgical management, and drug treatment in essential tremor. A combination of subject headers and keywords was designed in conjunction with a medical librarian. The searches were executed in the Medline (PubMed) and Embase (Ovid) databases from database inception through 25 February 2019. No date filters were used. Non-English language papers were excluded. Non-systematic reviews were weighted lower than systematic reviews. Studies were prioritized by quality and size. Case reports were excluded. Complete search queries in both databases are reported in the web appendix.

Additional searching was conducted on an as needed basis.

Clinical manifestations

Tremor

Limb tremor

The onset and progression of essential tremor are insidious. Arm involvement is kinetic tremor with or without postural tremor affecting both arms. The tremor is a rhythmic oscillation of agonist and antagonist muscles, typically at a frequency between 8 Hz and 12 Hz. In earlier studies, the diagnosis was made on the basis of the presence of either postural or kinetic tremor. However, the amplitude of the kinetic tremor is the most prominent component of limb tremor in essential tremor.[10] In a cross sectional study of 369 patients with essential tremor, kinetic tremor was more severe than postural tremor in around 95%.[11] Although both upper limbs are involved in essential tremor, mild-moderate asymmetry in the amplitude of tremor is common[12]; the postural tremors in the two hands are out of phase, which dampens the tremor when a patient holds items with both hands.[13]

Tremor at rest can occur in patients with longstanding disease. The prevalence of rest tremor in essential tremor was studied in 831 people from four distinct populations. Prevalence ranged from 2% in a population based setting to 46% in a brain bank study.[14] Pathologic study of seven patients with essential tremor who had rest tremor confirmed the lack of parkinsonian pathology.[15]

Intention tremor, the increased amplitude of tremor as a target is neared, is not present at disease onset but is seen later in some patients with essential tremor; its emergence is associated with disease duration.[16] The prevalence of intention tremor in patients with essential tremor is around 44%. It may be associated with head and trunk tremor.[17] A clinical-epidemiologic study of 117 patients with essential tremor found that 40% had intention tremor in the arms. Approximately 27% (95% confidence interval 20% to 36%) of 128 patients with essential tremor enrolled in a clinical-epidemiologic study had intention tremor in one or both legs.[18] A case-control study reported kinetic leg tremor in 44% of 63 patients with essential tremor compared with 14% of controls (P<0.001); tremor was at least moderate in amplitude in about 14% of patients compared with 2% of controls (P=0.008).[19]

Increasing amplitude of tremor or development of intention tremor may affect writing. A case-control study (n=200) reported macrographic handwriting in some patients with essential tremor.[20] Spiral drawings in the office can assess these changes. Although disease progression from year to year may be subtle, prospective studies (n=116, n=83) showed detectable changes in spiral drawings approximately five years later.[21 22] With disease progression, tremor can interfere with activities of daily functioning such as eating and grooming. Tremors in both dominant and non-dominant hands can cause functional disability.[23] Older patients have more rapid progression of tremor.

Head tremor

Many patients with essential tremor develop head tremor. Head tremor is typically a late clinical manifestation of the disease; the presence of isolated head tremor should raise suspicion for an alternate diagnosis (cervical dystonia).[24 25]

Multivariate analysis in a cross sectional clinical-epidemiologic study of 363 patients with essential tremor reported that head tremor, present in 140 (39%) patients was associated with age (odds ratio 1.04, 95% confidence interval 1.02 to 1.06) but not disease duration. Comparing patients with at least 10 years of disease, 2/27 (7%) patients under 40 years of age had tremor compared with 121/283 (43%) over 60.[26] Head tremor is more common in women.[26 27] A clinical-pathologic study (n=137) found women to be at high risk for developing head tremor independent of disease duration (odds ratio 6.5, 2.2 to 19.0). In a video review, 102/386 (26%) patients with essential tremor had head tremor,[28] 70 (69%) of whom had an exacerbation during or immediately after a phonation task in which patients were asked to sustain "ahh" or "eee" for 10-15 seconds; monitoring neck movements during phonation tasks is a helpful clinical pearl to assess the presence of head tremor. Head tremor will most commonly dissipate when the patient is supine, which can help in distinguishing essential tremor from other disease entities in which a resting head tremor is seen.[29] Aside from an action induced tremor, patients with head tremor may have an intention component that can be seen when the patient moves the head forward to sip from a cup.[30] A review of videotaped patients with essential tremor found that almost half of patients with head tremor (19/39) were unaware of its presence.[31] A study of 51 essential tremor patients with head tremor defined movements as "no-no" (horizontal), "yes-yes" (vertical), or mixed directional.[32] Patients with "no-no" tremor generally have short disease duration; mixed and "yes-yes" tremors are associated with older age (P=0.004) and longer disease duration (P=0.018). Patients with mixed direction tremor were reportedly more likely to have a continuous neck tremor and greater severity of tremor.

Chin/jaw tremor

Chin or jaw tremor is uncommon in essential tremor. An estimated 1-2% of patients per year with essential tremor develop head or jaw tremor. The incidence rate for either tremor is 10-20% in a 10 year period.[33] The presence of jaw tremor increases with disease severity, with a reported prevalence of 7.5% (95% confidence interval 3.9% to 14.2%) in a population study, 10.1% (6.8% to 14.7%) in a tertiary care center, and 18% (12.3% to 25.5%) in a brain bank of deceased patients with severe essential tremor (P=0.03).[34] Jaw tremor in essential tremor never appears solely at rest.[34] It is most prominent in posture and may be seen during sustained phonation

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or manifest as a kinetic tremor when the patient is talking. If rest tremor in the jaw is present, the amplitude is never as prominent as during posture or action. Conversely, jaw tremor in Parkinson's disease is prominent at rest and typically disappears with talking. The presence of jaw tremor is associated with older age of onset, greater severity of hand tremor, and rest tremor in the hands. Patients with jaw tremor are more likely to have hand or voice tremor than are those without jaw tremor.

Vocal tremor

Vocal tremor is a clinical manifestation of essential tremor. Older studies included patients who would not meet modern definitions of essential tremor owing to lack of arm involvement. This is concerning, as isolated vocal tremor is typically due to an alternate diagnosis (dystonia). It is more common in women and appears most frequently in the seventh decade. Women are more likely than men to manifest vocal symptoms.

Vocal changes are often described as "weak," "unstable," "shaky," or "hoarse." A descriptive clinical cohort study (n=34) reported that patients commonly complained of challenges maintaining voice volume and increased phonatory effort.[35] Patients with voice tremor are aware of the tremor and often express concern that changes in their voice will be misinterpreted as an anxious or upset emotion. Some patients report alcohol responsive improvements in voice.

Laryngoscopy of essential tremor patients with vocal tremor shows an entrained, oscillatory motion of several anatomic structures during sustained phonation. Many patients have oscillatory movements during quiet respiration. Tremor can involve muscles of the palate, pharynx, tongue, and other articulatory muscles in addition to the larynx. This involvement does not distinguish vocal tremor of essential tremor from spasmodic dysphonia. A cross sectional study of 19 ear, nose, and throat patients with either essential tremor or dystonic tremor found that dystonic patients were more likely to have reduction of tremor in the palate (P=0.02), pharynx (P=0.038), and larynx (P=0.002) when using a higher "falsetto" pitch.[36]

Rating scales are commonly used in research. In the office, clinicians can use rating scales to assist in diagnosis and to provide an objective measure of the severity, progression, and response to treatment of tremor. The Movement Disorder Society established a task force to review available scales. The Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale version 1 was recommended for screening. Five rating scales were recommended for assessing severity of tremor: the Fahn-Tolosa-Marin Tremor Rating Scale, the Bain and Findley Clinical Tremor Rating Scale, the Bain and Findley Spirography Scale, the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale, and the Tremor Research Group Essential Tremor Rating Assessment Scale.[37]

Disease process

Essential tremor is a progressive condition. Despite progression, less than 10% of 335 patients with long disease duration in a cross sectional clinical-epidemiologic study developed significant disability.[38] Predictors of clinical progression include disease duration, asymmetrical tremor, and an isolated limb involvement at onset.[39] Patients with older age of onset may have a more rapid disease course.[8] Pediatric populations are similar to adult populations as they present with bilateral kinetic arm tremor. Some children also develop voice, head, neck, and leg tremor. Children can also have rest tremor. Unlike adults, children rarely report impaired activities due to tremor.[9]

Alcohol responsiveness

In approximately 50% of patients with essential tremor, symptoms improve with alcohol consumption.[40] Responsiveness to alcohol is not pathognomonic for essential tremor. In a cross sectional multicenter trial, 29.3% (369/1258) of patients with isolated dystonia reported improvement with alcohol.[41] Patients with earlier onset are more likely to report alcohol responsiveness.[8] No historical features can help to predict whether a patient will be responsive to alcohol. Despite concerns of increased alcoholism in the essential tremor population, studies have not supported this.[42-44] A test for alcohol responsiveness showed a peak effect at 45 minutes after consumption in 10 patients, with persistent benefit in the initial 90 minutes.[45] It is common for tremor to rebound with increased intensity after more than three hours.[40]

Balance difficulties/gait impairment

Some patients with essential tremor report balance difficulties. Studies have tested balance by assessing tandem gait and using posturography.[46-48] Patients with essential tremor perform worse than age matched controls in balance testing. Posturography suggests that balance impairments are present in all patients with essential tremor. Younger patients may be able to use compensatory mechanisms to perform better in clinical tests.

Hearing loss

A population based sample reported hearing impairment in 39% (96/248) of people with essential tremor compared with 29.4% (1371/4669) of controls (P=0.002). Those with impairment were 30% more likely to have essential tremor (odds ratio 1.3, 1.01 to 1.7; P=0.04).[49] A large case-control study with 248 essential tremor patients and 4669 controls found that a significantly greater number of essential tremor patients wore hearing aids compared with patients with Parkinson's disease of similar age and controls (16.8% *v* 1.6% *v* 0.8%). Audiology testing shows high frequency sensorineural hearing loss in essential tremor patients.[50] The average hearing thresholds at 250-500 Hz are higher in patients with essential tremor.[51]

Olfactory changes

Reports of olfactory dysfunction in essential tremor are mixed, which may be due to the heterogeneous causes of the condition. A case-control study of 87 patients with essential tremor and 92 controls reported a mild, but significant, impairment on the University of Pennsylvania Smell Identification Test (UPSIT). This finding was independent of cognitive impairment as assessed by the mini-mental state examination.[52] However, other studies report normal UPSIT scores in patients with essential tremor.[53] A study matching essential tremor patients, Parkinson's disease patients, and controls found impairment in Parkinson's disease patients but no difference between the essential tremor patients and controls.[54] Additionally, in a separate study, essential tremor patients with rest tremor and no signs of parkinsonism had normal UPSIT scores, similar to essential tremor patients without rest tremor.[55] These findings suggest that the UPSIT may be one tool to help clinicians distinguish Parkinson's disease from essential tremor clinically.

Eye findings

Patients with essential tremor may have changes in oculomotor movements. A case-control study of 60 essential tremor patients matched with controls found that patients with essential tremor were more likely to have interruptions with square wave jerks during fixation (P<0.001). In addition, reflexive saccades (saccades triggered exogenously by the introduction of a peripheral stimulus or by the withdrawal of a fixation stimulus) are affected in essential tremor. Latencies and velocities of reflexive saccades were increased in patients with essential tremor.[56] A case-control study of 50 patients with essential tremor reported that the latency of reflexive saccades was associated with severity of tremor. Additionally, an increased incidence of dysmetria was seen during reflexive saccades in patients with more severe disease.[57]

Psychiatric symptoms

Several studies have explored the personality profile and psychiatric comorbidities of essential tremor. A case-control study used the 100 item Tridimensional Personality Questionnaire to assess personality traits; patients with essential tremor scored higher in areas of harm avoidance, worrying/pessimism, and fatigue/asthenia. Because data were collected in affected patients, whether these personality traits emerged before or after onset of tremor is unknown.[58] Almost half of 106 patients with essential tremor from a population sample reported embarrassment, which is an independent predictor of increased drug dosage (odds ratio 1.86; P=0.01).[59]

Depression and anxiety are significantly increased in patients with essential tremor compared with controls and can be similar to what is seen in Parkinson's disease.[60-62] This is true in younger and older populations.[63] Patients may experience anxiety as an internal tremor.[64] A cross sectional case-control study (n=100) showed that, in addition to higher rates of depression (44% *v* 8%, P=0.009) and anxiety (66% *v* 18%, P=0.009), patients with essential tremor also have increased sleep disturbances (46% *v* 8%, P<0.001) and fatigue (30% *v* 8%, P=0.009) compared with healthy controls. Additionally, the study found that patients with essential tremor had increased pain severity as measured on the Brief Pain Inventory-Severity (1.9 (SD 2.3) *v* 0.6 (1.2); P=0.001) compared with controls and more interference from pain as measured on the Brief Pain Inventory-Interference (2.0 (2.9) *v* 0.5 (1.2); P=0.001).[65]

Cognitive symptoms

Although early descriptions of essential tremor did not identify cognitive impairments, pre-surgical neuropsychological assessments identified impairments, sparking further studies. The impairment is typically mild and is often not recognized by the patient.[66 67] A 2012 literature review of cognition in essential tremor reported that mild executive dysfunction was a consistent finding in studies. Impairments of attention and working memory were commonly seen. A 2017 cross sectional analysis of 128 older patients with essential tremor found that both amnestic and non-amnestic mild cognitive impairment (MCI) subtypes were represented (n=24); amnestic MCI, single and multi-domain, represented about 70% (n=17) of cases.[68] Multi-domain amnestic MCI was the most common subtype (n=13; 54%) Five neuropsychological tests that are sensitive to mild cognitive deficits in patients with essential tremor (as defined by a Clinical Dementia Rating of 0.5) are the California Verbal Learning Test II Total Recall, Logical Memory II, Verbal-Paired Associates I, category Switching Fluency, and Color-Word Inhibition.[69]

Signs of other movement disorders

A small portion of patients with essential tremor have clinical findings that are features of other movement disorders. An examination of 678 patients with essential tremor reported the co-existence of Parkinson's disease (~6%), dystonia (~7%), and myoclonus (1.8%) in this population.[70] A 600 person case-control study found that, compared with healthy controls, patients with Parkinson's disease had higher odds of developing essential tremor (odds ratio 5.43, 1.16 to 25.39). Patients with Parkinson's disease were five to 10 times more likely to develop essential tremor.[71] Many studies have explored the association of Parkinson's disease and essential tremor through study of the clinical features, imaging, and genetics. What, if any, factors influence the development of essential tremor or Parkinson's disease in the presence of the other is still uncertain.[72]

Diagnosis

Essential tremor is a clinical diagnosis. The office history and examination are the sole components needed for diagnosis. The clinician asks about

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tremor during different modalities and the effect on activities of daily living. Symptoms described above are queried. Alcohol responsiveness and family history can be helpful clues, but neither feature is specific to essential tremor. Patients with dystonia can have alcohol responsiveness and a family history of tremor. Approximately 50% of patients with essential tremor have a family history. Accuracy of this history is not reliable, as a family study showed that probands poorly identified tremor in family members, missing tremor in affected members and recalling tremor in family members who did not have symptoms. The age of onset of essential tremor may be lower in patients with a family history.[73 74]

A study of several bedside tests performed in 154 patients (42 essential tremor, 112 controls), including assessments using arm extension, finger-to-nose movements, spiral drawing, pouring water, drinking water, and using a spoon, showed variability of the tremor in different settings. Because of performance variability, asking patients to perform several tasks in the office may lead to a more accurate assessment of tremor.[75] A video is provided with this review to show essential tremor when pouring and writing, and figure 1 shows spiral drawings. Voice and neck tremor are also shown.

A complete neurologic examination is needed. The tremor of essential tremor can be confused in the office with Parkinson's disease and dystonic tremor. Several clinical pearls can help to guide the clinician to the correct diagnosis. A cross sectional study including 50 patients with essential tremor and 50 with Parkinson's disease found that during arm extension, essential tremor is more likely an extension-flexion at the wrist rather than movements at the metacarpal-phalangeal or phalangeal joints.[76] In addition, more than 25% of patients with essential tremor showed an intention tremor in finger-to-nose testing, whereas the presence of intention tremor in Parkinson's disease was about 4% (P<0.001). In writing and Archimedes spiral samples, the axis of essential tremor is commonly in the 8-2 o'clock in right handed drawing and 10-4 o'clock in left handed drawings (see video). This is seen in script writing, especially with vertical letters such as "h," "l," and "p."[77] This can help to differentiate essential tremor from dystonia, in which this axis is uncommon. On examination, up to 20% of patients with essential tremor will have a unidirectional, non-oscillatory head jerk ("head snap") during the finger-to-nose examination as the finger nears the nose. A cross sectional study of 50 patients with Parkinson's disease and 50 with essential tremor found that the "head snap" was seen in some essential tremor cases (20%) but no Parkinson's disease cases.[78]Table 1 lists some pearls for differentiating essential tremor from Parkinson's disease and dystonia.

A magnetic resonance imaging (MRI) scan of the brain could be considered to exclude a secondary source of onset of tremor, especially when additional neurologic symptoms are present. No guidelines are available for the use of functional imaging (^{123}I-FP-CIT SPECT (DaTscan)) or accelerometry. In the US, the DaTscan has approval from the Food and Drug Administration for use as an adjunctive evaluation tool to differentiate essential tremor from a tremor due to a parkinsonian syndrome. The development of consumer grade accelerometry, which can be helpful in distinguishing essential tremor from Parkinson's disease tremor, may emerge as a viable clinical diagnostic tool as the technology becomes more accessible. Spiral drawings can be performed directly on digital tablets capable of analyzing the characteristics and severity of tremor.[90-92] Accessibility and cost represent a barrier to the use of imaging and other technology.

Classification of essential tremor

The variability in clinical presentations and disease course, the inconsistency in pathologic study findings, and the lack of diagnostic electrophysiologic and radiologic findings argue against essential tremor being a single disorder.[93] In 2018 an updated consensus statement from the task force on tremor of the International Parkinson and Movement Disorder Society redefined essential tremor as a syndrome. The classification was an attempt to recognize the heterogeneity of these symptoms, which are unified

Fig 1 | This sample of an Archimedes spiral and continuous loop drawing performed by a patient with essential tremor demonstrates a unidirectional tremor axis

Table 1 | Clues to distinguish essential tremor from other tremor disorders

Feature	Essential tremor	Parkinson tremor	Dystonic tremor
Activating condition on presentation of limb tremor[1]	Action tremor	Rest tremor	Action tremor
Common upper limb presentation at onset[79]	Bilateral; mild asymmetry; wrist involvement; no finger involvement; flexion/extension movement; no directionality	Unilateral or bilateral; marked asymmetry; wrist involvement; finger involvement; rotary movement; no directionality	Unilateral or bilateral; marked asymmetry; elbow, wrist, or finger involvement + directionality
Other areas frequently involved in tremor	Neck; voice	Mouth/tongue; jaw; leg	Neck; voice; jaw
Common tremor activation	Kinetic tremor amplitude ≥ postural; posture in wing may be greater than posture with arm extension[80]	Rest tremor ≥ postural tremor; when moving from rest to posture, there is often a pause before recurrence of tremor	Kinetic › › postural
Common alleviating factors	Rest; alcohol	Activity	Sensory trick (decreased tremor with light touch)[81]; null point (position where tremor decreases/remits)
Limb tremor: handwriting/spirals[82]	Normal size or macrographic; pen pressure normal or mildly increased; 2-3 o'clock axis on right hand spirals; 10-12 o'clock axis on left hand spirals[77]	Micrographic, decrementing[83-85]; pen pressure reduced[86]; unilateral axis on spirals	Variable quality: can be cramped and tight; pen pressure increased[87]; multidirectional axis on spirals
Intention tremor[76]	May be present, especially after longer disease duration	Not usually present	Not usually present
Associated limb symptoms/signs	None	Bradykinesia; rigidity	Tightness and posturing in limb; sensory trick[81]
Voice (when affected)[36 88]	Intensity fluctuations with perception of increased effort	Hypophonic; patient perceives speaking as normal	Strained, strangled, or breathy quality
Neck tremor	No pain or muscle hypertrophy; often anosognosia to tremor[31]; dissipates when supine[29]	Rare; persists when supine	Associated with pain and muscle hypertrophy[89]; patient aware of neck tremor; persists when supine, if not in null position

only by the presence of action tremor in the arms.[1] In the new criteria, essential tremor is defined as an isolated tremor syndrome with only action tremor present for at least three years. The presence of tremor in other locations such as the legs, head, or voice is allowed. The tremor is identified as an isolated postural or kinetic tremor if it has been present for less than three years. No signs of other neurologic disease such as dystonia, ataxia, or parkinsonism are allowed to be designated as essential tremor.

A second disorder, labeled "essential tremor plus," maintains the criteria of essential tremor but allows for the presence of other neurologic signs such as dystonia or cognitive impairment. Exclusion criteria for essential tremor and essential tremor plus include the presence of isolated focal tremors in the head or voice, orthostatic tremor with a frequency above 12 Hz, task and position specific tremors, and a sudden onset of symptoms with a stepwise deterioration. The consensus statement did not define the range and quality of these additional "soft" neurologic signs. This has generated new concerns and questions. For example, a patient who develops a rest tremor is classified as essential tremor plus; although the presence of this tremor could be a parkinsonian sign, it could also be the evolution of essential tremor.[94] One study reassigned patients with essential tremor to the newly defined classifications; challenges interpreting cerebellar symptoms and possible dystonic posturing were reported.[95]

Treatment of essential tremor

Many patients report symptoms of tremor as mild and opt to delay intervention. Because tremor often improves with alcohol consumption, patients may choose to have an alcoholic drink before social situations. When symptoms are socially bothersome or interfere with activities of daily living, patients often seek medical intervention. Available interventions can only treat the symptoms.

Drug treatment

Oral drugs are the first line of treatment. Few advances in the development of oral drugs used in the treatment of essential tremor have been made over the past two decades. Many of the landmark trials of the first line drugs were done in the 1970s and 1980s under older definitions of the disease that could have included patients with enhanced physiologic tremor. These trials tended to be small, often containing fewer than 20-30 patients in a treatment arm. Most of these trials measured efficacy only for short periods of time. The true long term response to treatment for most drugs used in essential tremor is unknown. Because essential tremor is a syndrome with many causes, the fact that response to available treatments is variable is not surprising. Some drugs had benefit in small trials, but evidence is insufficient to make recommendations. At the time of this review, both the American Academy of Neurology (AAN) and the Italian Movement Disorders Association (IMDA) had produced guidelines for the management of essential tremor.[96-98] Only recommended drugs will be highlighted in this review. Table 2 summarizes the main recommended treatments used in essential tremor.

Existing drugs for essential tremor are suboptimal. Many patients do not respond to them, and those who do may not have a significant improvement in their daily life. A study reviewing response to treatment of 528 patients in three different research settings reported that approximately one in three patients discontinued drugs prescribed for essential tremor.[2] Polytherapy should be considered when monotherapy provides a partial response but is insufficient. The

side effect profile of drugs used in essential tremor may limit both monotherapy and polytherapy.

β blockers

Propranolol is one of two recommended first line therapies for essential tremor. Propranolol is given in divided doses, three times daily. Table 3 summarizes a sample of studies with level 1 evidence assessing the response of limb tremor to propranolol. The table highlights the small sample size, short periods of assessment, and variability or lack of definition of essential tremor stated in the studies. Head tremor and voice tremor do not objectively respond to chronic propranolol therapy.[114 115]

Small studies indicate that long acting propranolol is as effective as the short acting formulation; patients with exposures to both prefer the ease of the long acting formulation.[110 116] One year follow-up

Table 2 | Treatment recommendations

	Recommended dosing	Common side effects	AAN guideline[96 97]	IMDA guidelines[99]	Notes
Drugs					
Propranolol, propranolol LA: non-selective β adrenergic receptor antagonist	Start 10 mg orally TID; up to 360 mg in divided doses; LA given once daily	Bradycardia, bronchospasm, hypotension, fatigue, lightheadedness, sexual dysfunction, depression	First line therapy	First line therapy	Other β blockers such as nadolol, sotalol, and arotinolol have second line recommendations; patients who do not respond to one β blocker will not respond to any
Primidone: metabolized to phenylethylmalonamide and phenobarbital; effect is independent of its phenobarbital metabolite[100 101]	Start 25 mg orally nightly; can titrate into divided doses up to 750 mg daily	Dizziness, fatigue, malaise	First line therapy	First line therapy	Side effects often dissipate early
Topiramate: stimulation of GABA activity; inhibition of carbonic anhydrase; antagonizes AMPA/kainite receptors; blockade of voltage dependent calcium and sodium channels	Start 25 mg BID; can increase up to 150-400 mg/day	Paresthesias, impaired attention, decreased appetite, nausea, fatigue, memory difficulties	Second line therapy; "probably effective"	First line therapy	Side effect profile often cause for cessation
Gabapentin: interacts with auxiliary subunit of voltage sensitive calcium channels[102]	Start 100-300 mg TID; can titrate up to 3600 mg daily	Lethargy/drowsiness, fatigue, decreased libido, dizziness, increased anxiety, shortness of breath	Second line therapy; "probably effective" as monotherapy	Second line therapy	Higher dosing does not increase side effect profile
Alprazolam: positive allosteric modulators on GABA-A receptor	Start 0.25 mg daily or 0.125 mg daily in elderly; average dose 0.125-3 mg/day	Sedation, cognitive impairment	Second line therapy	Second line therapy	Potential for misuse
Clonazepam: positive allosteric modulators on GABA-A receptor	Start 0.5 mg daily; average dose 1.5-2.0 mg daily	Sedation, cognitive impairment	Second line therapy	Not recommended	Potential for misuse
Zonisamide: inhibits T type calcium channels; weak inhibitor of carbonic anhydrase	Start 100 mg daily; average dose 225 mg in divided doses	Headache, nausea, fatigue/sleepiness, diarrhea	Not recommended	Second line therapy	-
Olanzapine: DA receptor blocker	Start 5 mg daily; average dose 10-20 mg/day	Weight gain, somnolence, extrapyramidal symptoms	Not recommended	Second line therapy	-
Clozapine: DA receptor blocker	Start 25 mg once a day; 12.5 mg in elderly; average dose 25-75 mg/day	Sedation, QT prolongation, orthostatic hypotension	Third line therapy; "possibly effective"	Second line therapy	Must monitor for agranulocytosis
Nimodipine: calcium channel blocker	Start 30 mg once a day; average dose 120 mg/day	Hypotension, diarrhea, dyspepsia	Third line therapy; "possibly effective"	Not recommended	-
Chemodenervation					
Botulinum toxin	Depends on muscle location	Weakness, dysphagia (neck injections), breathing difficulties (neck injections)	Recommended in medically refractory cases	Recommended in medically refractory cases	-
Surgical interventions					
Thalamatomy	Thalamus-ViM	Weakness, numbness	Case based decision	Not recommended	Delayed effect; may have progressive extension of lesion
Deep brain stimulation	ViM (unilateral preferred > bilateral); CzI	Limb paresthesia (usually improves with programming adjustments), dysarthria, disequilibrium, skin infections/breakdown	ViM recommended in medically refractory cases; no recommendations for CzI	ViM recommended in medically refractory cases; no recommendations for CzI	Bilateral ViM increases risk of dysarthria and disequilibrium
MRI guided focused ultrasound[103 104]	ViM (unilateral)	Dizziness (early), nausea/vomiting (early), headache (early), flushing (early), ataxia (late), paresthesias (late)	Recommended in medically refractory cases	Recommended in medically refractory cases	Rare cases with significant ataxia requiring walkers

AAN=American Academy of Neurology; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BID=twice daily; CzI=caudal zona incerta; DA=dopamine; GABA=γ amino butyric acid; IMDA=Italian Movement Disorders Association; LA=long acting; MRI=magnetic resonance imaging; TID=three times daily; ViM=ventral intermediate nucleus.

of patients taking propranolol showed a continued but sometimes reduced response to treatment; some patients needed dose increases.[117 118]

Propranolol is contraindicated in patients with bronchial asthma and allergic rhinitis; selective β blockers might be considered in these cases. The AAN guidelines recommend the selective β blocker atenolol (100 mg daily) as "probably effective."[119]

Propranolol should be used with caution in patients with diabetes mellitus, as the adrenergic signs and symptoms of hypoglycemia can be masked. In the absence of contraindications, patients with stable heart failure due to left ventricular systolic dysfunction may take propranolol.[120]

Patients who do not respond to propranolol do not respond to other β receptor blocking drugs. If a patient cannot take propranolol for some reason but could take an alternate non-selective β receptor blocker, three other non-selective β blockers have indications for use as second line therapy. One multicenter crossover trial (n=145 completed study) reported that the response of tremor to arotinolol was significantly better than that to propranolol (30 mg daily arotinolol *v* 160 mg daily propranolol; P=0.002) on motor task assessment.[121] A randomized, double blind, placebo controlled trial in 24 patients found that sotalol (80 mg twice daily) was significantly better than placebo for the treatment of essential tremor (P<0.01); its effects were not compared directly with response to propranolol.[122] Nadolol was compared with placebo in a 10 person double blind crossover trial and shown to have efficacy at 120 mg and 240 mg daily dosing. The higher dose had no additional benefit.[123]

Anticonvulsants

Primidone is also a recommended first line treatment for essential tremor. Primidone is as effective as propranolol and may be more likely to completely suppress limb tremor.[100 109 124] A double blind comparative study (n=113) showed that all doses of primidone improved limb tremor. Lower doses of 250 mg were as good as or better than higher doses of 750 mg.[125] Reduction of tremor does not necessarily translate to improved function. An observational study of 11 patients initially responsive to primidone reported loss of efficacy and discontinuation (n=3) of the drug. The reduction in magnitude of tremor was 45% (SD 41%) at four weeks on accelerometric evaluation, and it was 41% (34%) at 12 months in the patients remaining on the drug.[126] A retrospective chart review (n=30) reported that approximately 50% (n=14) of patients taking primidone had improvement in vocal tremor. Head tremor does not consistently respond to primidone.[127-129]

Topiramate is recommended as first line treatment for essential limb tremor by the IMDA and as a second line treatment by the AAN. In a large multicenter,

Table 3 | Sample of level 1 evidence (randomized controlled trials) for propranolol in limb tremor. Shows small size, short duration, variability in definition of essential tremor, and dropout/side effect profile for propranolol

Trial	Dropout	Definition of essential tremor	Dosing	Study length	Side effects of propranolol
Propranolol *v* placebo (n=33)[105]	n=3: 1 syncope; 2 related to "other disease"	Not defined	Up to 40 mg TID	4 months	1 patient at month 4 stopped due to AV block; 24 reports of SE (insomnia and headache most common)
Propranolol *v* metoprolol (n=16)[106]	None	Not defined	Propranolol 120 mg, 240 mg daily	10 weeks; 2 weeks on each arm (low dose week always before high dose)	2/16 could not be increased to higher doses owing to SE on lower dose
Propranolol *v* phenobarbital *v* placebo (n=17)[107]	n=5 (not detailed)	Not defined	Propranolol 1.7 (SD 0.10) mg/kg	1 month on each treatment	Propranolol: lower BP and pulse (number not provided)
Propranolol *v* metoprolol (n=23)[108]	n=33 dropped out due to asthma exacerbations	Postural tremor affecting upper extremities and neck	Propranolol 120 mg, 240 mg (divided dose)	11 weeks (2 weeks each arm and 1 week washout in between)	Both drugs: headache, dizziness; propranolol: dizziness, rash, impotence (numbers not given)
Propranolol *v* primidone *v* placebo (n=19)[109]	n=5: 1 propranolol "subtherapeutic"; 1 SE propranolol; 4 SE primidone	Not defined	Propranolol 40 mg TID	10 days on maximum dose of each drug	Propranolol SEs not addressed
Propranolol *v* propranolol LA (n=23)[110]	n=8: 1 SE; 1 worse tremor; 6 personal reasons	Posture and action tremor in hands in absence of other neurologic signs	80 mg TID, 160 mg LA, 240 mg LA, 320 mg LA, (placebo)	15 weeks (3 weeks each arm)	80 mg: n=2; 160 mg LA: n=4; 240 mg LA: n=5; 320 mg LA: n=5
Propranolol *v* theophylline *v* placebo (n=10)[111]	None	Tremor absent at rest; tremor apparent in posture; tremor not exacerbated by movement; no signs of PD or cerebellar disease	80 mg propranolol	1 month on each treatment	Propranolol (n=3): anxiety, sleep disturbance, dizziness; theophylline: no SE
Propranolol *v* gabapentin *v* placebo (n=16)[112]	None	Chronic persistent postural tremor with or without kinetic tremor	Propranolol 40 mg TID	13 day treatment, then 1 day of washout	Propranolol: 5 events (3 instability (1 disabling), 1 depressive symptoms, 1 abdominal cramping)
Propranolol *v* olanzapine (n=38)[113]	None	Definition based on Tremor Research Group Criteria	Propranolol 120 mg/day	1 month on each drug	Propranolol: 27 events: fatigue, nausea, impotence most common

AV=atrioventricular; BP=blood pressure; LA=long acting; PD=Parkinson's disease; SE=side effects; TID=three times daily.

double blind, placebo controlled, parallel design study (n=108 topiramate, 100 placebo) use of topiramate improved scores on the Fahn-Tolosa-Marin Tremor Rating Scale by approximately 30%. Improvements in function and disability were seen (P<0.001).[130] A meta-analysis of randomized controlled trials reported improvement in motor skills and functional disability as well.[131] The side effect profile contributes to a high rate of drug cessation.[130 132]

Gabapentin is a second line treatment in both guidelines. AAN recommendations were based on a comparative, double blind, placebo controlled trial in which 16 patients received 400 mg gabapentin three times daily in the treatment arm. After 15 days of treatment, a mild to moderate reduction of tremor was seen, which was not significantly different from that seen with propranolol 120 mg daily.[112] A double blind, placebo controlled, crossover trial reported modest improvements in limb tremor at 1800 mg and 2700 mg gabapentin daily in divided doses, with no significant difference in efficacy between the two doses in the 20/25 patients who completed the trial.[102]

Benzodiazepines—Two benzodiazepines, alprazolam and clonazepam, are recommended as second line treatments. A double blind, placebo controlled parallel study (n=24) reported clinical improvement in patients taking alprazolam (P<0.01).[133] Rating scales and psychomotor tests were used for assessment, not accelerometry. Another double blind, placebo controlled trial (n=22) reported that the functional ability and global functioning subsets of a "tremor intensity" rating scale improved (P=0.03) in patients treated with alprazolam.[134] A double blind, placebo controlled trial of clonazepam showed benefit in patients (n=15) receiving up to 4 mg of clonazepam daily (P<0.001).[135] A later study of 14 patients with severe kinetic tremor reported a mean tremor reduction of 71% on accelerometry; the mean clonazepam dose was 2.2 mg.[136]

Zonisamide—Weak evidence supports the use of zonisamide in essential tremor. A 2017 Cochrane review found insufficient evidence to support the efficacy and safety of its use.[137] However, the IMDA recognizes zonisamide as a second line treatment. A double blind, placebo controlled trial (n=20) reported improvement in tremor accelerometry.[138] An evaluator blinded open treatment trial (n=25) found that approximately a third of patients had at least moderate improvement.[139]

Antipsychotics

Antipsychotics have some benefit in essential limb tremor. In an open label prospective trial, 37 patients received olanzapine, most taking 10-20 mg daily in divided doses.[140] Tremor significantly improved, and the effect was maintained over six months. Sedative side effects lessened one week after the start of treatment. A randomized, double blind, crossover study compared the efficacy of olanzapine (20 mg/day) and propranolol (120 mg/day) in a group of 38 patients who had previously not responded to at least one other drug for essential tremor.[113] Both drugs significantly improved tremor, and no significant difference in the efficacy of the two drugs was seen after 30 days of treatment. Almost 40% of patients taking olanzapine reported that their tremor completely disappeared, and around 58% had a slight/barely noticeable tremor. Patients in this study did not have any significant side effects.

In an open label trial, 12 patients with essential tremor were in a group receiving clozapine, with doses ranging from 18 mg to 36 mg.[141] Seven had a marked improvement in tremor, two had mild improvement, and three had no benefit. In a randomized, double blind, crossover study, 15 patients who had side effects or were resistant to propranolol or primidone were given 12.5 mg of clozapine.[142] Those who had a greater than 50% tremor response were asked to stay in an open label arm of the trial and allow examiners to follow their response. Patients were treated with up to 50 mg/day and were followed for between one and two years. Thirteen patients agreed to enter this arm, and all patients continued to have clinical response throughout the study. No signs of tolerance were seen, and most patients with sedation found that this significantly diminished after a six to seven week period.

Other drugs

AAN guidelines state that nimodipine may be effective in treating essential tremor. In a small double blind, placebo controlled trial, nimodipine was dosed at 30 mg four times daily to 16 patients with essential tremor. Of the 15 patients who completed the trial, tremor improved in eight after they had been taking the drug for two weeks.

Chemodenervation

The IMDA and the 2005 AAN practice parameters recommend botulinum toxin injections in medically refractory cases of essential tremor. In 1996 the first randomized, double blind, placebo controlled trial (n=25, 13 in treatment arm) reported modest outcomes in patients with essential tremor treated with onabotulinum toxin.[143] Patients in the treatment arm received 50 units of toxin (15 units flexor carpi radialis, 15 units flexor carpi ulnaris, 10 units extensor carpi radialis, 10 units extensor carpi ulnaris). Another set of injections was administered four weeks later in doubled doses in the case of no clinical response and no weakness. Patients reported modest improvements, but no significant improvement in function was seen.

In 2001 a randomized controlled trial compared the effect of low versus high doses of onabotulinum toxin on limb tremor in essential tremor. Patients were randomized to one of three interventions targeting the same muscles as the previous trial: injections totaling 50 units, 100 units, or placebo.[144] Patients reported subjective improvement with low dose and high dose toxin injections (75% treatment *v* 27% placebo; P<0.05). The postural component of the tremor showed sustained benefit over the course of treatment in both treatment arms. However, kinetic tremor improved significantly only six weeks

after injection. Approximately 30% of the patients in the low dose group and 70% of those in the high dose group experienced weakness.

Criticism of these initial studies included the uniform selection of muscles for injection despite the variability in muscle involvement and directionality of essential limb tremor. Additionally, the complexity and variability of essential limb tremor is challenging, with clinicians' visual assessment in agreement with kinematic assessment only 36% of the time.[145] To improve outcomes, later studies sought methods to individualize injections. An open label study of 20 patients studied the effects of abobotulinum toxin injections up to six months after a single treatment.[146] Injectors identified the involved muscles through use of accelerometry and electromyography. When possible, extensor carpi muscles were avoided owing to an increased risk of weakness of finger extension in the third digit. Electromyography guidance was not used. Significant improvement on the Activities of Daily Living Self-Questionnaire was seen at one month (33.1 (SD 14.83) *v* 19.1 (9.55); P<0.05) and three months (33.1 (17.70); P<0.001) after injections.

The open label study of patients receiving botulinum toxin A with the longest reported follow-up followed 10 patients receiving incobotulinum toxin injections every four months.[147] Dosing patterns were determined through kinematic tremor assessment using motion sensors. In this manner, injections were tailored to the muscles associated with a patient's tremor (wrist flexion/extension, pronation/supination, proximal arm flexion/extension) rather than using a predetermined dosing at a predetermined location. Patients had a significant improvement in function and tremor over the 96 weeks of the study. The main side effect, weakness, improved with dose reduction.

A randomized, double blind, placebo controlled, crossover trial published in 2018 reported benefit of customizing injections of incobotulinum toxin with electromyography guidance for patients with essential tremor.[148] Statistically significant improvement in tremor severity as measured on the Fahn-Tolosa-Marin Tremor Score was reported at four weeks (2 *v* 3; P=0.003) and eight weeks (2 *v* 3; P<0.001) Minimal hand weakness (~4%) was reported. The success of treatment was attributed to avoidance of the extensor muscles, the use of low dose injections into flexor muscles (often 10 units), and customization of the injections. Patients rarely received more than 100 units of toxin. Benefits were seen at four and eight week assessments after injections.

One double blind, placebo controlled trial has looked at botulinum toxin for neck tremor.[149] Three of the 10 patients in the trial did not have hand tremor and would not meet criteria for the current definition of essential tremor. Half of the study patients had a moderate to marked response to injections: bilateral sternocleidomastoid muscles (40 U/muscle) and splenius capitus muscles (60 U/muscle).

Open label trials have shown benefit of botulinum toxin injections for voice tremor in essential tremor.[150 151] The main side effect was local muscle weakness causing impaired phonation and breathy voice. A retrospective study of patients with vocal tremor in essential tremor provides guidelines for muscle selection and reports a consistent clinical response with repeated injections.[152] Notably, many of these patients would now be "essential tremor plus," as half of the study patients had comorbid dystonia. A randomized, prospective, crossover study comparing botulinum toxin with injection augmentation of the vocal cords (n=7) found no advantage with augmentation.[153]

Surgical interventions

Deep brain stimulation

Before the 1990s, the main surgical intervention for essential tremor was thalamic lesioning. However, this approach fell out of favor with the development of deep brain stimulation (DBS). DBS can be done with or without general anesthesia. A frontal burr hole is drilled and then electrodes are implanted. Microelectrode and macroelectrode recordings can be used to assist in location of leads. The intracranial electrodes are ultimately connected to an implanted pulse generator.

Although alternative lead locations are under assessment, the approach for most surgeries in essential tremor is to target unilateral or bilateral lead placement in the thalamic ventral intermediate nucleus (ViM).[154-156] Improvement of tremor is thought to be due to the disruption of the synchronous firing in the ViM. Patients undergoing DBS in the ViM report improvement in severity of limb tremor and activities of daily living, as well as non-motor symptoms such as "tense feelings."[157 158] A retrospective analysis of a patient cohort who had ViM DBS, including 28 patients with essential tremor, found sustained reduction in limb tremor 10 years after surgery, although some loss in efficacy was seen over time—66% improvement from baseline in year one and 48% improvement from baseline in year 10.[159] Head tremor often improves with both unilateral and bilateral ViM placement. Studies have shown inconsistent improvement in voice tremor.[160-162] Common side effects are listed in table 2.

Implantation in the caudal zona incerta (cZI) is an alternative to ViM lead placement. A retrospective study comparing ViM (n=17) with cZI targeting (n=19) suggested that cZI was a superior target.[163] A study of 15 consecutively recruited patients with essential tremor who had bilateral cZI DBS showed significant improvements in action tremor, proximal tremor, and activities of daily living. Benefits were sustained for up to seven years.[164]

Focused ultrasound

MRI guided high intensity focused ultrasound (MRIgFUS) is a lesional surgery that is less invasive than DBS. The current procedure allows penetration

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of the skull without heating of the bone. The thalamic ViM nucleus is the typical lesion location.

In an open label uncontrolled pilot study, 15 patients with severe, drug refractory essential tremor underwent MRIgFUS lesioning of the ViM nucleus.[165] Significant improvements were seen in tremor, disability, and quality of life scores. Two additional open label trials in the following year reported sustained improvement of tremor (three to six months) with minimal side effects.[166 167]

Subsequently, a double blind trial (n=76) randomized medically refractory essential tremor patients to unilateral ablation versus sham surgery in a three to one ratio. Assessments were done one, three, six, and 12 months after surgery, using the Clinical Rating Scale for Tremor to measure tremor severity.[168] Three months after surgery, a 47% improvement of hand tremor was seen in the interventional arm compared with 0.1% in the sham procedure group. The between group difference was 8.3 (95% confidence interval 5.9 to 10.7) points. Continued benefit was seen at 12 months, with 40% improvement from baseline in tremor on the treated side, a difference of 7.2 (6.1 to 8.3; P<0.001) points from baseline. No significant improvement in tremor was seen on the untreated side. The study also found sustained improvement in quality of life and functional ability scores. Objective ataxia (20% of patients) and subjective balance difficulties (16% of patients) were reported after surgery and persisted in a few patients (4-5%).

As of the date of this literature search, the longest reported duration of follow-up for MRIgFUS was two years. A study of 37 patients with FUS surgery between 2012 and 2016 at two clinical sites reported persistent benefits on tremor, with 75% of patients having at least partial tremor reduction.[169] In this trial, sustained benefit was seen at two years, but with diminishing efficacy. Almost 46% of patients had significant reduction in tremor at year one; at year two, a 35% reduction was seen. The authors hypothesized that the causes of the diminishing effect may be multifactorial, including diminishing lesion size, reduction in perilesional edema, or inaccurate targeting. A prospective, multicenter, randomized trial also reported sustained benefit at two year follow-up, with 62% of patients showing a 50% improvement in tremor rating. Two patients were tremor-free. Mild progression of tremor and disability scores was seen between years one and two.[170] Adverse reactions are summarized in table 2.

As technology advances, the technique used for MRIgFUS improves. A retrospective cohort study used diffusion weighted MRI with tractography in 66 patients to assess the lesion location that provided the best clinical outcome in patients undergoing ViM lesioning with FUS.[171] The area straddling the border of the ViM and the ventro-caudalis nucleus was identified. This area was distinct from areas that caused side effects. Lesions larger than 170 mm^3 significantly increased the risk of side effects. Small prospective trials have shown benefit in using tractography to identify the location to lesion and shown the viability of using 1.5 T MRI for the procedure.[172-174]

Lifestyle management

Patients with essential tremor may have considerable challenges in writing, eating, and using household devices. Use of weighted devices (pens, computer mouse) can help to reduce the amplitude of tremor. Devices are available to help patients to button clothes, write, drink, and eat. A non-invasive handheld device, designed to stabilize tremor when eating, was shown to be beneficial in 11/15 patients in a small pilot study.[175]

Emerging therapies

New approaches to treatment are under investigation. As many patients report alcohol responsive tremors, one novel drug being explored is 1-octanol, a long chain alcohol. A phase I/II double blind, placebo controlled trial tested 4 mg/kg daily doses (rounded to the nearest 50 mg) of 1-octanol in 19 patients with essential tremor and reported significant improvement of tremor at 300 minutes (dominant hand, $F_{1,16}$=5.49, P=0.032 *v* placebo), with a trend to improvement 150 minutes after treatment.[176] Doses up to at least 128 mg can be tolerated.[177]

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that blocks glutamate activity in postsynaptic AMPA receptors, is another drug of interest. In a pilot study, all eight patients ultimately taking 4 mg of perampanel at night had improved tremor 56 days later and half of the patients had greater than 50% improvement on the Tremor Clinical Rating Scale (52.13 (SD 5.84) at baseline to 26.1 (9.46); P<0.001).[178] Results from a double blind, crossover, placebo controlled trial on the efficacy and tolerability of perampanel are pending.

Non-invasive neuromodulation through ulnar and radial nerve stimulation is a novel approach to treatment of essential tremor that is under investigation. A sham controlled pilot study (n=23) showed up to 60% reduction in tremor in the patients with the device (rating scores: stimulation 1.77 (SD 0.21) *v* sham 2.77 (0.22); P=0.01) Transient redness and pruritus were the most common side effects reported.[179] Transcranial magnetic stimulation is also being explored as a treatment option.

Guidelines

At the time of this review, the AAN and the IMDA had produced guidelines for the management of essential tremor.[96-98] The Quality Standards Subcommittee of the AAN initially published guidelines in 2005 and updated them in 2011. The IMDA guidelines were published in 2013. Whereas the AAN guidelines make no specific dosing recommendations, the Italian guidelines do. Both guidelines endorse propranolol

RESEARCH QUESTIONS

1. Can we improve phenotyping of essential tremor to achieve gene identification and improved treatment response?
2. How should we interpret the presence of dystonia in patients with essential tremor?
3. What are the long term responses to current interventions for essential tremor?

and primidone as first line treatment, and both recommend gabapentin and alprazolam as second line treatment. They make no recommendations for polytherapy. In medically refractory cases, botulinum toxin injections, ViM deep brain stimulation, and guided focused ultrasound of the ViM are endorsed in both guidelines. However, some discrepancies exist, and these are highlighted in table 2.

Conclusion

In the past decade, the variability of the symptoms, disease course, and response to treatment of essential tremor has led to the recognition of essential tremor as a syndrome. A new classification system has made a first attempt to characterize essential tremor better. Challenges remain with this new classification, as "soft" signs are not clearly defined and confusion remains as to whether all "soft" signs should really be placed into an "essential tremor plus" category, and further revisions to this classification system will likely be needed. Although surgical approaches to the treatment of essential tremor have expanded, no oral drug has emerged that surpasses the efficacy of the first line treatments (propranolol and primidone) identified decades ago.

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Appendix
Patient video