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**REVIEW**

# Essential tremor—the most common movement disorder in older people

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## Abstract

Essential tremor (ET) affects ~4% of the population above 65 years of age. The traditional view that ET is a familial monosymptomatic disorder with a benign prognosis has recently been challenged, as it is now known to be a progressive and clinically heterogeneous condition with sporadic and familial forms. The pathogenesis of ET is not fully understood, though a disordered central mechanism is the most likely site of origin with possible modulation by muscle adrenoreceptors. The limited post-mortem studies have not shown consistent abnormalities in the brains of ET patients. ET is often misdiagnosed as Parkinson's disease, particularly in the older population. Tremor amplitude increases with age, accounting for substantial disability in older people. Current therapy (drugs and neurosurgery) has significant limitations in older people. A better understanding of its pathophysiology in the future will help in developing more effective therapy, including neuroprotective strategies.

**Keywords:** *essential tremor, older people, disability, elderly*

## Introduction

Descriptions of kinetic tremor can be found in Ancient Indian and Greek texts, but the first detailed description of essential tremor (ET) was provided in the 19th century by Dana [1]. ET was considered a benign condition of unknown cause associated with no significant disability or shortening of life span, and hence the original term 'benign essential tremor'. The clinical spectrum of ET is wide, ranging from a trivial condition in some patients to a greatly disabling condition in others. Despite significant progress in our understanding of this condition in recent years, there are still large gaps in our knowledge.

## Definitions

*Tremor*, an involuntary oscillation of a body part, can be classified into several types:

*Rest tremors* occur in a body part that is fully supported. Parkinson's disease (PD) is a classic example.

*Postural tremors* occur in a body part that is held in a posture against gravity. Physiological tremors and ET are examples of postural tremors.

*Kinetic tremors* occur during a voluntary movement. ET can be a mixture of postural and kinetic tremors. Kinetic tremors may worsen significantly on approaching a target, the so-called intention tremors of cerebellar origin.

*ET* is characterised by postural and kinetic tremor of the body parts (most commonly forearms and hands), in the absence of endogenous or exogenous triggers or other neurological signs [**2**].

## Classification of and diagnostic criteria for ET

There are no diagnostic pathological or biochemical markers to make a confident diagnosis of ET. Several diagnostic criteria have been proposed to improve diagnostic accuracy, e.g. those by the Tremor Investigation Group (TRIG) [3], National Institute of Health (NIH) Collaborative team [4] and Consensus Statement on Tremor by the Movement Disorder Society (MDS) [5]. Elble [**6**] proposed a scheme derived by combining TRIG and MDS criteria (see Appendix 1 in the supplementary data on the journal website)

## Epidemiology and risk factors

Accurate prevalence rates are difficult to ascertain as there are no diagnostic criteria and ET can be a very mild illness in some patients. The rates vary widely depending on the diagnostic criteria used [7], age, methodology of case ascertainment

and severity of ET. The studies based on clinical records grossly underestimate true prevalence, as nearly 90% of ET patients do not seek medical attention [8,**9**]. The community-based studies employing two-stage screening (questionnaire followed by examination by a neurologist/specialist) provide the most acceptable data on true prevalence. The prevalence of ET increases with age. A prevalence rate of ~40/1,000 has been reported in the population above 65 years of age [**10**]. It is more prevalent in whites than African-American men, and the rates for Hispanic Americans are intermediate [**10**]. No gender differences are reported. A recent population-based screening showed an incidence rate of 616/100,000 in older (>65 years) people [**9**]. Interestingly, >70% of cases were previously undiagnosed and were picked up by screening.

The familial nature of ET has been recognised from its early description. A positive family history has been reported in 17–100% of patients [**11**,12,**13,14**]. Genetic linkage studies have identified two susceptibility loci for ET on chromosomes 3q13 (*ETM1*) and 2p24.1 (*ETM2*) [**15**]. As many families do not show evidence for linkage to any of these loci, there are possibly as yet undiscovered genes for ET. In familial ET, an autosomal dominant mode of inheritance is probably the most common pattern, with a complete penetrence by the age of 65 years [**15**]. It is not known how genetic mutations cause ET.

The non-familial, sporadic form of ET is well recognised, and environmental factors may play a role in the aetiology of ET. Toxins have been suggested as a potential cause of ET [16]. In a case–control study, no association was found between ET and lifetime occupational exposures to manganese or organic solvents [**17**]. The role of β-carboline will be discussed later.

## Pathophysiology of ET

It is generally agreed that ET is caused by a disordered activity in a central neuronal structure. The evidence for this theory comes mainly from animal studies, with only limited data from ET patients. Harmine, a β-carboline, can produce kinetic tremors in humans [18], and blood harmane concentrations have been reported to be higher in patients with ET than in controls [**19**]. In experimental animals, tremors similar to ET can be produced by a related agent, called harmaline [**20**]. They can be reduced by alcohol, diazepam and barbiturates [21]. It has been shown that harmaline induces a synchronised rhythmic discharge of neurones in the inferior olive (IO). This activity persists after transactions of brain structures at several levels, indicating that it is the IO and not its connections that acts as the pacemaker for tremors [**22**]. Transmission of this rhythmic activity by cerebellar pathways to spinal motor neurones produces tremor. A similar mechanism is possibly active in humans. It is possible that ET results from a disturbance in the function of the IO with no obvious structural change. Tremor induction by harmaline has been attributed to inhibition of γ-aminobutyric acid$_A$ (GABA$_A$) receptors, resulting in enhanced electrical coupling of cerebellar afferents in the IO [23].

Electrophysiological studies also lend support to the theory that ET is caused by a central pacemaker that is influenced by somatosensory feedback loops [**24**]. Though positron emission tomography (PET) studies show increased cerebellar blood flow in ET patients, this is not a specific finding as similar observations have been reported in tremors due to PD, writing tremor and orthostatic tremors [**25**].

## Pathology of ET

The pathology of ET remains unknown, as there have not been detailed pathological studies in modern times. It is difficult to infer from the post-mortem studies conducted a long time ago that showed no consistent abnormalities as they were not detailed and immunohistochemistry techniques were not available. Recently, an Essential Tremor Centralised Brain Repository was established in the USA for the systematic study of post-mortem brain tissues from ET patients. One such study showed localised multiple Lewy bodies (LBs) in the locus coeruleus, and none were found in the substantia nigra, dorsal vagal nuclei, thalamus, substantia innominata, inferior olivary nucleus or cerebellum [26]. Immunochemical staining using antibodies directed against α-synuclein confirmed the presence of many LBs in the locus coeruleus and showed rare LBs in the substantia innominata and dorsal vagal nuclein, but none in the substantia nigra. The authors suggest a possible link between essential tremor and LB disease.

## Clinical features of ET

ET can occur at any age, with bimodal peaks in the second and sixth decades [13]. There is typically a symmetrical postural and kinetic tremor most commonly affecting forearms and hands. Muscle tone is normal and there is no significant bradykinesia or ataxia. Postural tremors become obvious when the patient is asked to hold a body part motionless against the force of gravity, e.g. extending the upper limbs horizontally, or protruding the tongue. Their frequency in upper limbs is 4–12 Hz, though head tremors have a lower frequency of 2–8 Hz [27]. Older people often have lower frequency of tremor, leading to the condition being confused with PD. Kinetic tremors occur during a voluntary movement, e.g. drinking from a cup, finger–nose testing, writing, etc. Upper limbs are most commonly affected (~95% of cases), but ET can affect the head (~34%), voice (~12%), face (~5%) and legs (~20%) [**6**]. Family history of tremor is commonly noted. Head tremor is milder than limb tremor and usually is of the side-to-side ('no–no') type.

ET develops insidiously and progresses slowly over several years. It is not known what factors lead to the progression of ET. Although tremor frequency decreases with age, the amplitude tends to increase [28]. The kinetic tremor is higher in amplitude than postural tremor. These factors lead to difficulties with eating, drinking, writing, dressing and various other activities of daily living.

ET may temporarily disappear after alcohol intake in up to 75% of patients [**29**] and this may provide an important

clue to the diagnosis. However, tremor tends to reappear with a vengeance after the effect of alcohol wears off.

## Associated disorders and atypical ET

Several conditions have been reported with ET. In a study of 678 patients with ET, Koller *et al.* [**29**] reported concomitant PD and dystonia in 6.1 and 6.9%, respectively. They infer that the frequency of PD in ET is higher than in the general population. Previous studies also showed a higher prevalence of PD in ET patients [30]. A recent clinicopathological study, however, showed the risk of PD in ET to be comparable with that of the general population [**31**]. Postural tremor is often seen in PD. This is mostly a re-emergent rest tremor that appears after a latency of several seconds, in contrast to the immediate appearance of ET on outstretching the arms [32]. A recent paper suggests excercising caution in diagnosing ET in patients presenting with late onset asymmetrical postural tremor even in the absence of rest tremor, as this could represent PD [33]. However, the subject of the relationship between ET and PD is rather complex, and PD could represent a spectrum, from mild tremor at one end to the severe akinetic rigid state at the other. It is uncertain whether orthostatic tremor and some of the task-specific tremors (e.g. primary writing tremor) are variants of ET. Mild cognitive impairment and olfactory dysfunctions have been reported in ET [34]. A possible link between LB disease and ET has already been discussed. A syndrome of sensorineural hearing loss, early greying of scalp hair and adult-onset essential tremor has been described [35]. ET patients have a lower body mass index (BMI) than controls despite a similar caloric intake [**36**].

## Assessment of tremor

Tremor can be measured by different methods [**37**], e.g. physiological methods including accelerometry and electromyography (EMG), functional performance tests including the amount of water spilled from a cup and nine-hole pegboard test, tremor rating in drawing spirals or handwriting and by measuring the impact of tremor on patient's life, e.g. disability and handicap. Accelerometry and EMG can be objectively used to measure the frequency and magnitude of tremor. However, they are expensive and time consuming. The most commonly employed methods for tremor assessment, spiral drawing (Figure 1) and handwriting, have been shown to be useful in clinical practice [**38**]. Functional performance tests are simple and objective, and test tremor in real life situations. However, mild tremors may be missed, and the nine-hole peg test can be affected by conditions other than tremor. Generic and ET-specific questionnaires can be used to assess the impact of tremor on a patient's life.

Figure 1. Drawing of an Archimedes spiral by a patient with ET.

## Diagnosis and differential diagnosis of ET

In the absence of diagnostic markers, ET remains a clinical diagnosis. It can be confused with other conditions, e.g. PD, enhanced physiological tremor, dystonic tremor and cerebellar tremor. In old people, PD can be a difficult differential diagnosis. Table 1 summarises the important differences between ET and PD.

Dystonic tremors could be differentiated from ET by their irregular and jerky nature, presence of dystonic postures or movements, hypertrophy of the involved muscles, null point (the limb position that the patient finds for temporary resolution of tremors) and a sensory trick (method of touching tremulous part to lessen the tremor) [39]. Exaggerated physiological tremor (e.g. caused by drugs, caffeine, smoking and hyperthyroidism) can mimic ET and need to be ruled out by a detailed history, physical examination and appropriate investigations.

## Role of dopamine transporter (DAT) scan

Recently, functional imaging using specific single positron emission computerised tomography (SPECT) ligands for DAT has been introduced. It provides a marker for presynaptic neuronal degeneration [**40**]. It is mainly used to differentiate ET from PD in difficult or uncertain types of parkinsonism. The DAT scan is normal in ET (and drug-induced tremors) whereas it is abnormal in PD. However, it cannot differentiate PD from other presynaptic degenerations, e.g. multiple system atrophy and progressive supranuclear palsy, that are also associated with abnormal DAT scans.

## Treatment of ET

Mild non-disabling tremors do not warrant therapy. Current therapy is ineffective in controlling tremor in some patients and is not uniformly effective against tremors of all body parts. The adverse effects of therapy can limit clinical effectiveness in some patients. Neurosurgery may be considered in patients who are intolerant or resistant to the drugs.

### Pharmacotherapy

*β-Adrenergic blockers*

Propranolol is the most studied agent in this class of drugs. It reduces tremor amplitude but not frequency. Its efficacy has been shown in several studies [41,**42,43**]. About 40–50% of patients derive symptomatic benefit. The response rate is lower in head and voice tremor. It should be started at a low dosage in older patients, e.g. 40 mg three times a day, with gradual dose increments based on benefit and side effects. The optimal dose varies amongst patients, but doses >320 mg/day usually do not provide additional benefit. The once-daily slow-release preparation of propranolol has the advantage

Table 1. Important differences between essential tremor and Parkinson's disease

| Characteristic | Parkinson's disease | Essential tremor |
|---|---|---|
| Age of onset | Usually >50 years | Any age; bimodal peaks in second and sixth decades |
| Family history of tremor | Less common | Common |
| Body parts affected | Upper limbs, legs, chin, tongue | Hands, head and voice |
| Type of tremor | Rest, postural tremor usually re-emergent type | Postural and kinetic |
| Frequency of tremor | 4–6 Hz | 4–12 Hz |
| Associated rigidity and bradykinesia | Characteristic | Typically none |
| Asymmetry | Typically asymmetric | Typically symmetric |
| Effect of alcohol on tremor | Usually none | Often significantly reduced |
| Dopamine transporter (DAT) scan | Abnormal | Normal |
| Treatment | Dopaminergic agents, anticholinergic drugs, surgery | Propranolol, primidone |

of convenience with no loss of efficacy. Metoprolol [44] and atenolol [45] have also been shown to be effective against ET.

The mechanism of action of β-adrenergic blockers in ET is not known. A peripheral mechanism of action is supported by the fact that β-blockers with poor or no penetration of the blood–brain barrier are also effective in ET [**46**]. The side effects include bradyarrhythmias, tiredness, cold extremities and impotence. High degree atrioventricular blocks and bronchial asthma are the main contraindications.

### *Primidone*

Several open-label and double-blind, placebo-controlled studies have confirmed the efficacy of primidone in ET [41,42]. Due to the common occurrence of acute side effects (e.g. sedation, tiredness, dizziness, nausea and vomiting), primidone is started at a low dose of 25 mg taken at night time. The dose can be gradually increased and the usual effective dose is 50–250 mg/day. The side effects tend to wear off in several days.

Like propranolol, primidone also decreases the amplitude of tremor. Its mechanism of action in ET is unknown. Primidone is converted into two active metabolites—phenyethylmalonamide (PEMA) and phenobarbital. These metabolites, when given individually, have no significant effect on ET. It is likely that either primidone itself, or its unknown metabolite, has an antitremor effect.

### *Botulinum toxin-A (BTX-A)*

A modest beneficial effect of BTX-A on ET was reported in earlier open-label studies. In a randomised, double-blind, placebo-controlled study, 75% of BTX-A-treated patients showed mild to moderate reduction in tremor severity on clinical rating scales and accelerometry as compared with 27% of placebo-treated patients [**47**]. However, these results have not been confirmed by subsequent studies. Moreover, any functional gain is limited by BTX-A-induced muscle weakness. Some authors have reported excellent results in vocal ET [48].

### *Alcohol*

A significant majority of patients with ET derive beneficial effect, albeit temporarily, from alcohol ingestion. However, the usefulness of this therapy is limited by its brief duration of action and the risk of dependence. The prevalence of alcohol abuse in ET is unknown, but a prospective study did not show it to be greater in patients with ET than in any other chronic neurological disorder [49].

The mechanism of action of alcohol in ET is not known. A central mechanism has been supported by PET studies that showed attenuation of increased blood flow in the IO after alcohol ingestion [25].

### *Benzodiazepines*

Alprazolam significantly reduced tremor in ~50% of patients in a double-blind, placebo-controlled trial [50]. Though benzodiazepines can increase GABAergic transmission in brain, the beneficial effect could largely be due to sedative and anxiolytic actions. Because of their side effects, benzodiazepines should be used cautiously in older people.

### *Carbonic anhydrase inhibitors (CAIs)*

In an open trial, methazolamide, a CAI, produced marked reduction of tremor, particularly that of the head and voice, in ~40% of patients [51]. However, a subsequent placebo-controlled, double-blind trial failed to show its superiority over placebo [52].

Zonisamide (ZNS), a CAI with antiepileptic activity, was reported to have a beneficial effect on ET in a cross-over, pilot study [**53**]. Patients were randomly selected to start either ZNS or arotinolol (an α-β adrenergic blocker) treatment for 2 weeks. After a washout period, the patients were switched to an alternative drug. Both agents produced similar improvements in tremor, though ZNS was more effective for head and voice tremors.

### *Other drugs*

Levetiracetam, an agent used in epilepsy, was recently evaluated in ET in a 4-week, open-label trial [54]. It failed to show a consistent beneficial effect.

## Neurosurgical treatment of ET

ET patients who do not respond to medical treatment and are disabled by their tremor should be considered for surgery. Neurosurgery has been in use to treat ET for more

than half a century, with different areas of the brain targeted by different workers. The ventralis intermedius (VIM) nucleus of the thalamus was eventually found to be the optimal site. The lesions in VIM and subthalamic nucleus improved contralateral tremor in 14 out of 15 patients [**55**]. The benefits tend to last for a long time in most patients [56]. Complications occur in <10% of patients and include dysarthria, dysequilibrium, weakness and cognitive impairment. Bilateral thalamotomy is associated with significantly higher morbidity.

An alternative approach to thalamotomy is chronic stimulation of the VIM. This is a safe and effective method to control ET. It results in a significant reduction in tremor severity and global disability [**57**]. Activities of daily living including writing, pouring liquids, drawing spirals and ability to bring a drink to the mouth improve. Stimulation therapy is preferred over destructive treatment due to its reversibility, ability to adjust the stimulation parameters to optimise benefits and side effects, and the feasibility of performing bilateral procedures with no permanent complications. The drawbacks include complications of a foreign body, expense and finite battery life.

Appropriate patient selection is crucial for deriving maximal benefits from neurosurgery. Patients with significant cognitive impairment and extensive co-morbidities are unsuitable for these procedures.

## Disability in ET

ET is associated with considerable disability. In a study to ascertain correlates of functional disability and the extent of functional disability in community-dwelling ET cases, approximately three-quarters reported disability [**58**]. Depression, anxiety and age, independent of the severity of tremor, were associated with greater functional disability in ET. Functional disability is common with upper limb tremor [31]. Incapacitating tremors result in premature retirement and employment problems in a large number of patients [**59**]. An ET-specific quality of life (QOL) questionnaire has recently been developed and validated in older people [**60**]. This 30-item scale measures the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health and overall QOL.

## Conclusion

ET is a progressive condition with significant clinical, aetiological and pathophysiological heterogeneity. It is associated with considerable physical and psychosocial disability, particularly in older people. There has been increased interest in recent times in this entity, and it is hoped to provide better understanding of its aetiopathogenesis, eventually leading to development of more effective therapy.

## Key points

- ET is the most common movement disorder in older people.
- It is typically characterised by symmetrical postural and kinetic tremors of the body parts affected. ET has a great clinical heterogeneity.
- Family history of tremor and responsiveness of tremor to a small amount of alcohol may be important clues to the diagnosis.
- The aetiopathogenesis of ET is unknown, though a disorder of central structure(s) appears to be a likely mechanism.
- ET is a clinical diagnosis as there are no diagnostic biochemical, pathological or genetic markers.
- ET is commonly misdiagnosed as PD, particularly in older people.
- There is no cure for ET, and current symptomatic therapy has significant limitations in older people.
- ET can cause considerable personal and social handicap.

## References

PLEASE NOTE: The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website http://www.ageing.oxfordjournals.org/ as Appendix 2.

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