A TREMOR is an involuntary rhythmic movement characteristically affecting projecting parts of the body, including the hands, head, lips and tongue. Even the eyelids can be involved.

A fine degree of tremor is normal in healthy people; this physiological tremor is rarely visible, does not interfere with activities and is not thought to be related to disease. It occurs in all voluntary muscle groups and can be detected if a person is asked to extend his or her arms and a piece of paper is placed on top of the hands. Physiological tremor can become more pronounced as a result of fear, anxiety or exhaustion. Tremor can also be caused by conditions such as hypoglycaemia, as well as by diseases such as hyperthyroidism.

Tremors can be described in many ways but can generally be divided into those occurring at rest (when the muscle is relaxed; resting tremor), those demonstrated on posture (e.g., when sitting), and those occurring on movement (intention or action tremor). A resting tremor is often distal. It can be seen in Parkinson’s disease and can affect the left or right side of the body only, with motion being asymmetrical in one or more planes. It is differentiated from the other forms of tremor in that it is slow and its effect is diminished or eliminated by movement.

Intention tremor is predominantly peripheral with its motion being along one plane. It is faster than resting tremor and is evident throughout the range of movements a patient is asked to make when tremor is investigated. Intention tremor is sometimes seen in people with cerebellar disease (the cerebellum is involved in movement and its co-ordination). However, in these patients, the tremor is irregular, both proximal and distal, in different planes, and slow and exaggerated on activity.

The onset of a tremor can arouse concern of a central nervous system lesion, such as a tumour, or other serious disease process and investigation is needed. Initial investigations can include a physical examination (which will include observing tremor symmetry, and checking for any sensory loss, muscle weakness and

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**Reflect on knowledge gaps**

1. You conduct a medicines use review with a man in his 30s with asthma. He mentions that he is embarrassed because he cannot lift a pint in the pub without his hands shaking. What questions do you ask and what advice do you give?

2. What treatments are used for essential tremor?

3. What practical advice can you give to people suffering with tremor?

Before reading on, think about how this article may help you to do your job better.
Tremor — resting, postural or intention — can be induced by drugs. For example, pharmacists will know that antipsychotics can cause extrapyramidal side effects, including tremor. Other examples are given in Panel 1.

### Panel 1: Drugs associated with tremor
A common example of a drug associated with tremor is salbutamol (and other bronchodilators), which stimulates beta2 adrenoceptors on skeletal muscle to cause a fine tremor, especially in the hands. (Hence beta-blockers can be used for symptom control [see main text]). Dopamine receptor blocking drugs, such as metoclopramide, can also induce tremor, and it is noted that tremor emerges in patients with Alzheimer's disease who are treated with cholinesterase inhibitors, (reinforcing that anticholinergics are effective in the treatment of Parkinson's disease tremor).

Amiodarone is structurally similar to thyroxine so its binding to the nuclear thyroid receptors could be linked to its side effects of hypothyroidism, the latter being a state in which tremor may manifest.

Fine tremor can also be a side effect of lithium therapy but a coarse tremor is a sign of toxic doses, as pointed out in information for patients, recently published by the National Patient Safety Agency. The mechanism of action remains somewhat unclear, but lithium appears to substitute sodium and potassium in cellular transport processes. It also has an effect on the release of monoamine neurotransmitters, by way of altering ion concentrations and flux across cell membranes. Lithium also plays a role in the regulation of second messenger systems relating to beta adrenoceptors and muscarinic receptors.

Examples of other drugs that induce tremor include pseudoephedrine, theophylline, tricyclic antidepressants, selective serotonin reuptake inhibitors, nifedipine and valproate.

Withdrawal of some drugs, such as benzodiazepines, can induce tremor. Alcohol withdrawal can also bring about tremor. Conversely, small amounts of alcohol may help to decrease essential tremor (see main text) but the mechanism behind this remains unclear.

### Panel 2: Main differences between essential tremor and Parkinson's disease tremor

<table>
<thead>
<tr>
<th>Essential tremor</th>
<th>Parkinson’s disease tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noticed on action</td>
<td>Noticed at rest (also known as “pill-rolling tremor”)</td>
</tr>
<tr>
<td>Generally not associated with other symptoms or conditions, although anxiety can co-exist</td>
<td>Associated with bradykinesia (slow movement), rigidity, akinesia (absence of movement) and depression</td>
</tr>
<tr>
<td>Does not usually respond to anti-Parkinsonian drugs</td>
<td>Does not usually respond to treatments for essential tremor</td>
</tr>
</tbody>
</table>

### Essential tremor symptoms
Aside from enhanced physiological tremor (ie, natural tremor that is observed during a stressful encounter) essential tremor is the most common type of tremor. However, pharmacists will probably be more familiar with the tremor of Parkinson’s disease and the differences between this and essential tremor are summarised in the Panel 2. (It should be noted that it is possible for essential tremor to co-exist with other conditions causing tremor.)

Essential tremor is a neurological condition that most recognisably causes the hands, head, legs and trunk to shake on voluntary movement. The voice can also be affected. The condition can be progressive. The general pattern is of a tremor starting in the arms and then progressing to other parts of the body. Some patients develop problems with their gait and balance that are beyond those caused by normal ageing.

The overall prevalence of essential tremor is thought to be 300 to 400 per 100,000. Although incidence increases with age, essential tremor is not a condition confined to the elderly. If present in childhood, symptoms can be worse around puberty.

Although the mechanism is not clearly understood, essential tremor is believed to be generated within the central nervous system by way of olivo-cerebellar oscillation.

Essential tremor, which is sometimes called familial tremor, can be described in genetic terms as having an autosomal dominant trait with variable penetrance, mapping to chromosome 2p 2-25. Essential tremor is also sometimes called benign tremor and for those with mild symptoms, psychological measures, such as biofeedback and relaxation techniques, may be helpful. However, the condition can be challenging, affecting daily activities such as writing, typing, dressing, personal grooming and eating. Such problems can lead to frustration, cause stress and temporarily worsen symptoms, and sufferers describe their experiences as ranging from trivial to disabling. Some patients are afraid that people assume they have drug or alcohol problems. For people with more severe symptoms or those unresolved by psychological measures, pharmacological approaches may be needed.

### Pharmacological treatment
At present there is no medicine created specifically to treat essential tremor — all those used have other indications — but some prove beneficial for sufferers. These drugs can either be used alone or in combination. It is worth reminding patients that although a medicine may work well for one person it might not for another. Deciding on the best treatment is a trial-and-error process that requires time and patience.

Medicines prescribed for essential tremor mainly include propranolol, primidone and other antiepileptic drugs, and benzodiazepines.

**Propranolol** Propranolol is generally the drug of choice because it has been...
Gabapentin and topiramate are emerging as treatment options for essential tremor. Gabapentin has been evaluated in several randomised controlled trials for its efficacy and safety. Its mechanism of action remains unclear but it is believed to work by enhancing central gamma-aminobutyric acid (GABA) agonist activity and hence ion channel tone. These trials suggest that short-term treatment at doses of 1,200–1,800mg/day is tolerated well, serving as a viable option as monotherapy for essential hand tremor. Gabapentin is generally well tolerated in both young and old, despite possible side effects of ataxia, irritability, sedation and weight gain. With its comparably safe profile and relative ease of use, gabapentin serves as a useful alternative as a second-line agent and also as an adjunct when symptom relief is insufficient.

**Essential tremor can be disabling and those affected often suffer in silence**

Topiramate works by blocking sodium channels. Its reduction of essential tremor has been observed at doses lower than those required in the management of epilepsy. Most of its side effects are usually minimal and reversible, but can include cognitive slowing, anhidrosis, acute glaucoma and renal stones. Literature suggests starting at 25 or 50mg at night for the first week and increasing by 25mg or 50mg each week, with titration based on side effects and tolerance, to a maximum daily dose of 400mg daily. Although topiramate is seen as a possible option for the treatment of essential tremor, especially where other therapies prove ineffective, further research is needed.

**Benzodiazepines** Benzodiazepines, such as clonazepam, diazepam, lorazepam and alprazolam, may be useful in patients who do not respond to propranolol or primidone, or in those who have associated anxiety. The mechanism of action is unknown but may be related to GABA agonist augmentation by its action at the benzodiazepine receptor-GABA receptor channel complex for passage of chloride ions.

Side effects of drowsiness, depression, fatigue, loss of co-ordination, memory loss and confusion, mean caution should be exercised, particularly in the elderly. Moreover, these drugs must be prescribed judiciously because of their potential to cause dependence.

Benzodiazepines are generally less effective than primidone and propranolol and have a more concerning side effect profile. Lorazepam may be preferred because of its milder sedative profile at doses of 0.25–0.5mg but no dose is specifically advised in the British National Formulary. Caution is needed in not exceeding the maximum daily dose of 4mg in adults. (In the elderly or debilitated half this maximum dose would be wise.)

**Other therapies** Other pharmacological therapies that have been used for essential tremor include mirtazapine and botulinum toxin.

**Mirtazapine** Mirtazapine is a presynaptic alpha2 adrenoceptor antagonist, which increases central noradrenergic and serotonergic transmission. Although it is indicated as an antidepressant, it is sometimes used for essential tremor. However, due to its lack of reported effectiveness for many patients and its significant side effects, it is not routinely recommended for this condition. Some of its adverse effects include dry mouth, confusion, urinary frequency, weight gain, disorder of gait, nausea and blurred vision. No recognised doses have been recorded but the lowest tolerable dose, within its limits of the maximum daily dose used for mood disorders, would be sensible.

**Botulinum toxin** Botulinum toxin has been used in some hyperkinetic movement disorders. Botulinum toxins are derived from *Clostridium botulinum* and seven serologically distinct neurotoxins. They are composed of two chains, heavy and light, each differing in their mechanism of action. Type A botulinum toxins includes four subtypes — A to G — have been isolated, each differing in their mechanism of action.
light, connected via a disulphide bond, is used in the management of essential tremor. Treatment involves multiple point injections into the affected muscle groups, repeated every three to four months.

The mechanism of action can be described in three steps. The first step involves the binding of the heavy chain to a specific membrane acceptor situated on the presynaptic cholinergic terminal of the neuromuscular junction. The light chain of the toxin is then endocytosed and targets and cleaves the synaptosome-associated protein (IETF), drugs being investigated for essential tremor include: 1-octanol (an alcohol that naturally occurs in citrus oils), sodium oxybate (a central nervous system depressant used for cataplexy but with abuse potential), T2000 (a barbiturate) and carisbamate (a new anticonvulsant).

**Non-pharmacological strategies**
The medicines available can effectively treat only about half of affected individuals with disabling tremor. In addition, with long-term propranolol and primidone treatment, tolerance can develop. The advent of new surgical techniques, such as thalamotomy and thalamic deep brain stimulation, has, therefore, proved a valuable option for those with a disabling tremor who have not had adequate control from pharmacotherapy.

**Surgery**
Surgery for tremor disorders was first attempted some 100 years ago. It involved the destruction of large parts of the brain so weakness and paralysis were possible complications. In 1947, surgical advances allowed for selective destruction, sparing surrounding areas of the brain, and the ventralis intermedius (VIM) nucleus of the thalamus became recognised as the most effective target. The thalamus is a collection of cells deep in the brain involved in relaying motor and sensory signals. The VIM is a collection of neurons and it is now understood that creating a lesion here disrupts the cerebellar-thalamic circuit from generating a tremor.

**Thalamotomy**
Thalamotomies are generally unilateral and performed on the side of the brain contralateral to the dominant or most affected limb. Bilateral procedures are generally avoided due to the increased risk of severe permanent dysarthria or even mutism. The procedure is carried out under local anaesthesia because the brain is devoid of pain sensation and also allows the subject to participate in physiological tests to ensure a satisfactory result. It is reported that more than 80 per cent of patients who have had this procedure experience long-lasting and complete (or near complete) resolution of their disabling tremor. Concomitant midline head and voice tremors can respond to this surgical intervention. In some circumstances the procedure may be repeated should there be incomplete resolution or if the tremor re-emerges.
Deep brain stimulation (DBS) of the thalamus is another option for patients with disabling tremor that has not been adequately treated with pharmacotherapy. Surgery is used to place a wire in the VIM nucleus of the thalamus and this is connected, under the skin, to a device that provides electrical currents to control symptoms. DBS is non-ablative and adjustable (it is reversible and impulse settings can be changed to minimize side effects and ensure optimum efficacy). Bilateral DBS has a reduced risk of permanent morbidity compared with bilateral thalamotomy.

The mechanism of action remains unknown but current lines of thought describe the device as providing a chronic artificial “neural noise” that disrupts the cyclical activity within the motor circuits. The efficacy of DBS is at minimum on a par with thalamotomy but it is a relatively expensive option with respect to the cost of the device and maintenance required.

Lifestyle

Although essential tremor does not alter mortality, it can be progressive and disabling. Many sufferers will have altered their lifestyles and avoided events they previously enjoyed and some even feel they cannot leave their homes. Patients affected by tremor may suffer in silence and seek independent means, such as increased alcohol consumption, for managing the condition. The IETF has prepared a list of suggestions to help those with tremor continue with activities of daily life (see Panel 3, p39). It also gives advice covering situations such as visiting the dentist (especially for those who suffer altered speech), using suitable devices and equipment, and avoiding events such as voice-activated equipment or alcohol and going through airport security and the dentist (especially for those who suffer altered speech). It also gives advice covering situations such as visiting the dentist (especially for those who suffer altered speech), using suitable devices and equipment, and avoiding events such as voice-activated equipment or alcohol and going through airport security and the dentist (especially for those who suffer altered speech).

Other lifestyle adjustments include3

- Ensuring the seclusion and independence of patients.
- Ensuring availability of easy-to-use dosage systems.
- Ensuring the management of essential tremor.
- Ensuring the availability of medicines. Pharmacists can also help sufferers by providing medicines in easy-to-use dosage systems.
- Ensuring a full assessment by a GP is a sensible starting point for people presenting with a tremor and pharmacists are ideally placed to point patients in the right direction. They can also signpost to organisations such as the National Tremor Foundation (see Signposting).

Signposting

- The International Essential Tremor Foundation also offers excellent advice and suggestions for the management of essential tremor (www.essentialtremor.org).
- The National Tremor Foundation is a UK-based charity providing help, support and advice to those living with all forms of tremor irrespective of age. It also assists healthcare professionals (www.tremor.org.uk).

References


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