Essential Tremor: Diagnosis and Treatment

Jack J. Chen, Pharm.D., and David M. Swope, M.D.

Essential tremor is a common movement disorder in adults that interferes with the performance of functional and social activities. Differentiation of essential tremor from other tremor syndromes is important in order to provide appropriate patient education and therapy. The mainstays of pharmacotherapy are propranolol and primidone; however, in selected patients, agents such as alcohol, benzodiazepines, botulinum toxin, and gabapentin may provide symptomatic benefits. Advances in surgical interventions, such as stereotactic thalamotomy and thalamic deep brain stimulation, offer patients an alternative treatment modality when pharmacotherapy is inadequate. A treatment algorithm is provided to guide clinicians in the management of patients with essential tremor.

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Summary

In 1817, James Parkinson differentiated essential tremor from that of other tremors, including parkinsonian tremor (Table 1).1-6 As the most common movement disorder in the United States, essential tremor occurs across the adult age spectrum, with an overall estimated prevalence similar to that of angina, chronic heart failure, and stroke.7, 8 Surprisingly little is known about the etiology and pathophysiology of essential tremor, which is characterized by pathologic tremor affecting mainly the upper extremities followed by the head and voice. Mortality remains unaffected, and functional and psychosocial disability ranges from minimal to severe.9 In the elderly, essential tremor may be inaccurately attributed to parkinsonism or dismissed as an insignificant clinical finding. Appropriate diagnosis is paramount to manage symptoms and improve quality of life. Terms such as “benign essential tremor” and “senile tremor” have trivialized the clinical significance
General Definition of Tremor

Tremor is defined as an involuntary, rhythmic oscillation of a body part within a fixed plane, involving alternating or simultaneous contractions of agonist and antagonist muscles entrained by a signal pattern originating from a central oscillator. Other rhythmic hyperkinetic disorders such as segmental myoclonus, epilepsy continua, tardive dyskinesia (tardive stereotypy), and myoclonus are excluded.

Physiologic tremor is an asymptomatic, small-amplitude, 9- to 12-Hz tremor that is present in all individuals. A growing body of evidence suggests that it originates from spontaneous oscillatory activity within the olivocerebellar system and is influenced by peripheral factors such as body vibration induced by myocardial contractions (ballistocardiogram), resonance properties of the musculoskeletal system, motor neuron firing, state of muscle β-receptor activation, and stretch reflex and muscle spindle feedback. Under certain circumstances, physiologic tremor can be enhanced. Examples include exercise, emotional stress, metabolic abnormalities (e.g., thyrotoxicosis, hyperparathyroidism, hypoglycemia, pheochromocytoma), and drugs (e.g., sympathomimetic agents, lithium, valproate).

Table 2. Tremor Activation Behaviors

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>Tremor occurring in absence of voluntary muscle contraction in affected body part. Tremulous body part must be completely supported against gravity (e.g., hands in lap).</td>
</tr>
<tr>
<td>Action</td>
<td>Tremor occurring during voluntary muscular contraction; includes postural, kinetic, and isometric tremors.</td>
</tr>
<tr>
<td>Postural</td>
<td>Action tremor present while voluntarily maintaining a posture against gravity (e.g., hands and arms outstretched).</td>
</tr>
<tr>
<td>Kinetic</td>
<td>Action tremor present during movement (e.g., writing, bringing a drinking cup to mouth, inserting a key); also includes intention and task-specific tremors.</td>
</tr>
<tr>
<td>Isometric</td>
<td>Action tremor occurring as a result of muscular contraction against a rigid stationary object (e.g., making a fist).</td>
</tr>
</tbody>
</table>

Tremor Classification by Clinical Phenomenology

In the clinical setting, tremor most commonly is classified by phenomenology (behaviors that activate tremor, such as rest, sustained posture, and movements; Table 2) and etiology (Figure 1). Any tremor lower than 4 Hz or greater than 12 Hz can be considered pathologic because these frequencies rarely are encountered in healthy individuals. Classification and definitions of tremor were systematically described, summarized, and disseminated by the tremor investigation group of the International Tremor Foundation and the Movement Disorder Society in 1995 and 1998, respectively.

A simple physical examination is all that is required to determine conditions that activate tremor. Resting tremor is present when a body part is fully supported against gravity in a manner not necessitating voluntary activation of skeletal muscles. In the upper extremities, it can be observed with the patient sitting with hands resting in the lap. By definition, resting tremor is suppressed by voluntary movement of the affected body part. Action tremor occurs with voluntary muscle contraction and includes postural, kinetic, and isometric tremors. A postural tremor can be triggered by voluntarily attempting to maintain a position against the force of gravity. For example, it can be detected by having the patient extend the arms forward with fingers extended.

Kinetic tremor occurs during voluntary movement and can be elicited by having patients perform a finger-to-nose test, sign their name, write a sentence, draw freehand spirals, or drink water from a cup. Since kinetic tremor is associated with greater disability than postural tremor, a more detailed assessment of the patient should be performed to determine the presence and severity of functional disability. The examination should include having the patient pour water from one cup to another, drink water from a cup three-quarters full and raised from lap level to mouth, and use a spoon to drink water. These tests should be performed with dominant...
and nondominant arms.

Intention tremor may be described as a type of kinetic tremor characterized by worsening (increasing tremor amplitude) during the terminal portion of goal-directed actions (as the finger nears the nose). It also can be seen in patients with multiple sclerosis and alcoholic cerebellar degeneration as well as essential tremor. Task-specific tremor is a type of action tremor and occurs only during specific highly skilled tasks (writing, playing the violin). Isometric tremors are present during voluntary muscle contraction against a rigid stationary object (making a fist, flexing the wrist against a flat surface, squeezing the examiner's fingers).

Once tremor is recognized and classified by activation condition, the next step is to investigate its etiology. Information obtained from medical history and neurologic examination are applied to delineate among various possible etiologies. The most common etiologies are essential tremor, parkinsonism, and tremorogenic drugs.

**Clinical Features and Diagnosis of Essential Tremor**

Appropriate diagnosis of essential tremor is made by clinical examination, medical history, and family history for tremor or other neurologic disorders. A thorough drug history is very important, as the following agents can produce tremor:

- Alcohol (chronic use)
- Antiarrhythmics (amiodarone, mexiletine, procainamide)
- Carbamazepine (especially when combined with a neuroleptic and lithium)
- Corticosteroids
- Cyclosporine

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**Figure 1.** Tremor classifications.

- **Tremor**
  - **Resting**
    - Common etiologies:
      - Drugs (neuroleptics)
      - Parkinsonism
  - Uncommon etiologies:
    - Cerebellar (e.g., multiple sclerosis, alcoholic degeneration, infarct)
    - Midbrain lesion
    - Neuropathic
    - Psychogenic

- **Action**
  - **Postural**
  - **Kinetic**
  - **Isometric**
    - Orthostatic (“shaky leg syndrome”)

- **Common etiologies:**
  - Essential tremor
  - Drugs (e.g., lithium, valproate)
  - Exaggerated physiologic condition (e.g., thyrotoxicosis, hypoglycemia, pheochromocytoma, drug withdrawal)

- **Uncommon etiologies:**
  - Cerebellar (e.g., multiple sclerosis, alcoholic degeneration, infarct)
  - Dystonic (e.g., cervical dystonia)
  - Midbrain lesion
  - Neuropathic
  - Parkinsonism
  - Psychogenic
  - Wilson's disease
heavy metals (arsenic, lead, manganese, mercury)
• Lithium (especially when combined with a selective serotonin reuptake inhibitor or tricyclic antidepressant)
• Metoclopramide
• Methylxanthines (caffeine, theophylline)
• Neuroleptics
• Nicotine
• Phenytoin
• Reserpine
• Sympathomimetics (e.g., albuterol, salmeterol, amphetamine, cocaine, ephedrine, methylphenidate, pseudoephedrine)
• Selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline)
• Thyroid preparations
• Tricyclic antidepressants (e.g., amitriptyline, imipramine)
• Valproate

Inquiring about time since onset of symptoms and factors that exacerbate or alleviate the tremor is helpful. Physical examination for other neurologic signs should be performed, and tremor-inducing behaviors (rest, postural, kinetic), approximate tremor frequency, and distribution and symmetry should be noted. Routine neuroimaging studies, such as computed tomography and magnetic resonance imaging, are not useful for diagnosing essential tremor. Certain laboratory tests will exclude treatable medical conditions associated with tremor; for example, an initial screen for hyperthyroidism and Wilson’s disease (for patients aged < 50 yrs). Core and supporting criteria for probable essential tremor are listed in Table 3. In the presence of one or more secondary criteria, the diagnosis is strengthened. It is important to note that clinical diagnostic criteria cannot be validated for accuracy until a genetic or histopathologic marker for essential tremor has been identified.

The hallmark symptom of essential tremor is a bilateral postural or kinetic tremor affecting the distal upper extremities characterized by insidious onset. Tremor at rest is not uncommon and observed in approximately 20% of patients. Tremor ranges from 4–12 Hz, and although it tends to decrease as the disease advances, amplitude generally increases and the ability to perform basic manual tasks becomes impaired. The second most frequent body part affected is the head, and although head tremor in the absence of hand tremor is not uncommon, it usually develops after hand tremor. Generally if head tremor is isolated, it may be a sign of dystonic tremor associated with cervical dystonia (spasmodic torticollis), especially if neck pain is also present. Essential tremor of the head is characterized by a horizontal “no-no” tremor pattern (tremblement negatif) or a vertical “yes-yes” pattern (tremblement affirmatif). Other body parts such as the legs, chin, trunk, tongue, soft palate, and rarely the lips and eyebrows may be affected (Table 4). If voice, tongue, and/or palatal tremors are present, the patient may develop dysarthric speech. In the small group of patients with essential palatal tremor (also known as essential palatal myoclonus), involvement of eustachian tubes and tensor veli palatini (muscle of the soft palate) results in a characteristic clicking within the ears. This chronic clicking can be distressing to patients and is audible to persons nearby.

Although not confirmatory, determining the effect of alcohol on tremor symptoms is helpful in strengthening the diagnosis of essential tremor. In many patients, consuming small quantities of alcohol often results in transient

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**Table 3. Criteria for Diagnosing Essential Tremor**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>Bilateral postural tremor (with or without kinetic tremor) of hands or forearms; predominantly symmetric; tremor visible</td>
</tr>
<tr>
<td>Core</td>
<td>May have isolated head tremor (with no abnormal posturing)</td>
</tr>
<tr>
<td>Core</td>
<td>Absence of other neurologic signs (except Froment’s sign)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Duration greater than 3 yrs</td>
</tr>
<tr>
<td>Secondary</td>
<td>Positive family history</td>
</tr>
<tr>
<td>Secondary</td>
<td>Positive response to alcohol</td>
</tr>
<tr>
<td>Red flags</td>
<td>Sudden onset; presence of tremorogenic drugs, or states of drug withdrawal, tremor at rest, bradykinesia, rigidity, unilateral tremor, dystonia, leg tremor, significant gait disturbance</td>
</tr>
</tbody>
</table>

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**Table 4. Anatomic Distribution of Tremor in Essential Tremor**

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hands</td>
<td>85–95</td>
</tr>
<tr>
<td>Head</td>
<td>35–45</td>
</tr>
<tr>
<td>Voice</td>
<td>15–20</td>
</tr>
<tr>
<td>Leg</td>
<td>10–15</td>
</tr>
<tr>
<td>Chin or jaw</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Trunk</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Tongue</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>
Only rarely are other forms of pathologic tremor attenuated with alcohol ingestion. If tremor onset is abrupt or other neurologic symptoms are present, an alternative diagnosis should be suspected. For example, patients with a history of heavy alcohol consumption may have an alcohol withdrawal tremor. It is very similar to an essential hand tremor except that onset is sudden and duration is transient. Parkinsonism should be suspected in the presence of rigidity, bradykinesia, shuffling gait, or reduced arm swing; and dystonic tremor suspected if focal, segmental, or generalized dystonia is noted.

Although essential tremor has been defined as a monosymptomatic disorder (occurring in the absence of other neurologic abnormalities), many patients may have subtle signs of ataxia or cognitive impairment, especially with advanced disease. Migraine headache and olfactory or hearing impairment are more frequent in patients with essential tremor than would be expected, although their absence or presence is not diagnostically specific or sensitive.

## Essential Tremor versus Tremor of Parkinsonism

Up to 20% of patients with essential tremor may develop parkinsonism, and 10% report a family history of parkinsonism. However, whether essential tremor is a risk factor for parkinsonism remains an unresolved and somewhat controversial issue. Although some studies suggest that the risk of parkinsonism in patients with essential tremor is greater than expected, others found no association between them. Pathologic studies reveal a normal substantia nigra and absence of Lewy bodies. At present, clinicians can be assured that most patients do not develop parkinsonism.

Because essential tremor and parkinsonian tremor are two common and chronic forms of pathologic tremor, it is important to be able to differentiate them (Table 5). In many patients with essential tremor, a palpable, cogwheel-like, upper limb tremor may be detected, especially with voluntary, repetitive motion of the contralateral limb. This phenomenon (Froment sign) should not be mistaken for the cogwheel-like rigidity of parkinsonism.

In parkinsonism, a “pill-rolling,” resting tremor of the hand is common, but it is less frequent in essential tremor. The presence of other parkinsonian features, such as rigidity, bradykinesia, and shuffling gait, is confirmatory for parkinsonism and excludes essential tremor. Of note, in patients with parkinsonism, a resting tremor often coexists with a postural tremor. This postural tremor can be divided into two

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Essential Tremor</th>
<th>Parkinsonian Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor type</td>
<td>Postural, kinetic; postural tremor</td>
<td>Resting and postural (reemergent); postural tremor</td>
</tr>
<tr>
<td></td>
<td>immediately observable; resting tremor less common</td>
<td>observable after mean latency of 5 sec; rarely kinetic</td>
</tr>
<tr>
<td>Age of onset (yrs)</td>
<td>Bimodal 15–20; 50–70</td>
<td>55–65</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Bilateral</td>
<td>Unilateral or bilateral</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>4–10</td>
<td>4–6 resting, 4–10 postural</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>50</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Response to alcohol</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Response to anticholinergics</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Response to levodopa</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Response to pramidone</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Response to propranolol</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Worsened by emotional stress</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Body part affected</td>
<td>Hands &gt; head &gt; voice, rarely legs</td>
<td>Hands &gt; legs, rarely head or voice</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

0 = not effective; + = mildly beneficial; ++ = moderately beneficial; +++ = most beneficial.
types. Reemergent postural tremor of parkinsonism has a frequency identical to that of the resting tremor (4–6 Hz). It is reemergent because, on arm extension, a mean latency of 5 seconds occurs before the tremor expresses itself. This contrasts with the postural tremor of essential tremor, which manifests immediately (< 1 sec) on extending the arm. The second type of postural tremor in parkinsonism is identical to essential tremor. Treatment of parkinsonian tremor is much different from that of essential tremor, with the best response associated with carbidopa-levodopa or dopamine agonists, and modest response with anticholinergic agents and propranolol.23

Epidemiology

The peak age for essential tremor shows a bimodal distribution pattern with onset occurring between ages of 15–20 years and 50–70 years.20 Both the frequency and prevalence of essential tremor increase with advancing age, and mortality is not adversely affected.

Prevalence data on essential tremor are surprisingly difficult to interpret, with estimates between 0.08–220 cases/1000 persons, a variation of 2750-fold.7 The disparity in epidemiologic data arises largely from inconsistent definitions of essential tremor and contamination of the patient population (inclusion of patients with dystonia or parkinsonism, use of hospital- or clinic-based medical records). Ideally, a population-based epidemiologic study should meet four basic criteria: a clear definition of essential tremor that excludes physiologic tremor, community-based design, inclusion of familial and sporadic cases, and confirmation of essential tremor by clinical examination. Based on epidemiologic data from the Sicilian municipality of Terrasina, the estimated prevalence of essential tremor was 625.8/100,000 individuals over 19 years of age and 3535.4/100,000 persons aged 70 years or older.24 The latter estimate is consistent with epidemiologic data collected from a northern Manhattan community, which reported an age-adjusted prevalence of 4020/100,000 individuals aged 65 years or greater.25 Extrapolation of that prevalence estimate to the United States elderly population (based on 2000 U.S. Census Bureau data) would yield an estimated 1.4 million individuals aged 65 years and over with essential tremor. If individuals younger than 65 years of age were included, this estimate would fall into the range of 5–10 million.

Only one study has attempted to quantify the frequency of essential tremor. Conducted in Rochester, Minnesota, it reported an age-adjusted annual incidence of 18.3/100,000 men and 17.1/100,000 women.9 Age- and gender-adjusted prevalence was estimated at 305.6/100,000 caucasians in the United States, which is consistent with the Italian figure. To capture the epidemiology of essential tremor in the general population more accurately, additional prospective, community-based investigations that use uniform diagnostic criteria are required.

Pathophysiology

A specific structural lesion has not been identified in the brains of patients with essential tremor, and underlying pathophysiologic mechanisms remain elusive. Data from metabolic neuroimaging studies suggest the presence of cerebellar neuronal damage.26 Animal models of harmaline-induced tremor and data from functional neuroimaging studies in humans implicate the inferior olivary nucleus and cerebellum as brain structures involved in the generation and propagation of abnormal oscillatory activity that is expressed peripherally as pathologic tremor.10, 27

Altered central and peripheral concentrations of biochemical markers are observed in patients with essential tremor. Compared with healthy controls, patients had reduced cerebrospinal fluid concentrations of γ-aminobutyric acid (GABA), glycine, and serine, together with a slight increase in glutamate.28 Neuroimaging studies also revealed abnormalities in thalamic GABA A receptors.27 These observations are consistent with tremor-relieving properties of agents with GABA-enhancing activity (e.g., alcohol, benzodiazepines, gabapentin). Increased concentrations of norepinephrine are also found in specific regions of the brain in patients with essential tremor compared with normal controls: locus ceruleus 5-fold, dentate nucleus 130-fold, and cerebellar cortex 2-fold.29 This is consistent with the efficacy of β-blockers (propranolol) in treating essential tremor and the ability of β-receptor agonists (albuterol) to exacerbate tremor.

Elevated blood concentrations of harmamine and harmine were noted in essential tremor cases compared with non–essential tremor controls.30 Harmamine and harmine are lipophilic β-carboline alkaloids, a group of potent tremorgenic
substances that are found in plant-derived foods and beverages and also produced endogenously in humans. The reason for elevations of β-carboline alkaloids in patients with essential tremor is unknown but may be due to increased dietary intake of the substances, increased endogenous synthesis, or reduced metabolism.

Genetics

The term “essential” implies that essential tremor is an inherent or inherited condition. In general practice, approximately 50% of patients report a positive family history of tremor. Familial or hereditary essential tremor appears to follow an autosomal dominant mode of inheritance. Genes for familial essential tremor have been identified and linked to chromosomes 3q (FET1) and 2p (ETM). However, these gene mutations are rare and a common essential tremor genotype responsible for most familial essential tremor has yet to be identified. In addition, the two forms of essential tremor, familial and sporadic, are clinically indistinguishable. In families with a history of essential tremor, onset is generally in the second or third decade of life. This may account for the bimodal age distribution reported in epidemiologic studies, since the onset of sporadic essential tremor is commonly in the sixth or seventh decade of life.

Patients with a strong family history may be informed that their offspring are at high risk for developing essential tremor. Ideally, studies measuring the extent of genetic aggregation beyond that expected by chance should include a control group, a community-based population, and confirmation by clinical examination. These three methods were incorporated in a study to determine the risk of essential tremor in relatives of patients. Patients were identified from a northern Manhattan community, and after adjusting for age, gender, and ethnicity, the risk of essential tremor was approximately 5 times greater in first-degree relatives of a patient than in first-degree relatives of a control. In patients with onset at age 50 years or younger, the risk in first-degree relatives was approximately 10 times greater than in first-degree relatives of controls. This suggests a stronger genetic influence in persons with younger-onset essential tremor.

In families with a positive history, the chance of developing essential tremor declines with age. If offspring have not developed essential tremor by age 10 years, the risk of developing it at a later age is less than 39%; if the offspring remain unaffected by age 25 years, the risk falls to less than 20%, and if the offspring remains unaffected by the age of 50 years, the risk is less than 6%.

Further understanding of the extent of genetic influence and mode of inheritance is crucial for clinical counseling and for research aimed at localizing and identifying susceptibility genes.

Disability Associated with Essential Tremor: Clinical, Functional, and Psychosocial

Unlike parkinsonian resting tremor, which is the least disabling aspect of parkinsonism, the action tremor of essential tremor can be associated with severe disability. For example, it often becomes more pronounced as the hands near the face, making eating, drinking, and facial care very difficult and sometimes unsafe. If hand tremor is severe, patients may avoid eating, drinking, and writing in public. Voice tremor may be severe enough to inhibit talking and singing. Functional disability may interfere with on-the-job tasks, resulting in lack of promotion, job changes, or premature retirement. Patients rarely are able to continue occupations requiring fine hand movements.

Many patients, however, can partially compensate for functional disabilities. If the dominant arm is disabled, they may learn to use the nondominant arm as long as it is moderately unaffected. Drinking may be made easier by using straws and using the other hand (if less affected) or both hands to hold glasses and cups. Patients with difficulty tying shoelaces can wear laceless shoes and those who find it hard to type on a computer keyboard may use voice-activation software (if voice tremor is not pronounced).

Tremor-rating scales used in routine clinical practice and in most early clinical studies are crude and lack uniformity and performance validity. Most are based on a simplistic rating score in which hand and forearm tremors are rated as absent, mild, moderate, or severe (0, +1, +2, +3, respectively). The Unified Tremor Rating Assessment scale and Fain-Tolosa-Marin Tremor Rating Scale were used in several clinical trials; however, neither one has been validated. Investigators of the Washington Heights–Inswood Genetic Study of Essential Tremor (WHIGET) developed a tremor-rating scale, together with a teaching videotape, that was validated and found reliable among raters with various levels of medical experience (Table 6). This scale shows promise for future trials.
healthy individuals, especially the elderly, a mild, clinically detectable tremor is often present during posture or action (WHIGET score 1). Distinguishing this physiologic tremor from essential tremor may be difficult, although patients with essential tremor typically will have a +2 rating in sustained arm extension, pouring water, and drawing spirals. Very few healthy individuals have a +2 score in these three tests.

Once essential tremor is diagnosed, the clinician should focus on associated functional disability and the need for pharmacotherapy. Simple, objective, functional performance tests are inexpensive, user-friendly, and suited for evaluating the ability to perform common manual tasks. Fluctuation and magnitude of hand tremor often are assessed by having the person draw spirals or write sentences; generally, handwriting is shaky and relatively large. The patient can be asked to transfer water from one cup into another or to hold a cup of water for 60 seconds. The former assesses kinetic tremor severity and the latter postural tremor severity. The volume of water spilled can be quantified and documented; the greater the amplitude of the tremor, the more water is spilled.

Subjective evaluations are also effective. The Tremor Disability Questionnaire is a valid and reliable disability tool specific for patients with essential tremor that can be completed within 10 minutes and is applicable in clinical practice and research settings. The results are highly correlated with level of functional disability, and objective and subjective tests help determine the effectiveness of therapy. Selected tasks in the questionnaire are as follows: signing one's name, writing a letter or check, typing, placing a letter in an envelope, drinking from a glass, pouring milk or juice from a bottle, carrying a cup of coffee, using a spoon to drink soup, carrying a tray of food, inserting a coin into a vending machine, dialing a telephone, holding a telephone to the ear, buttoning buttons, tying shoelaces, zipping a zipper, putting on eyeglasses, putting in contact lenses, using eye drops, cutting, trimming, or filing nails, putting on a watch, brushing teeth, placing a bill in wallet or purse, reading a book or newspaper, unlocking door with a key, threading a needle, using a screwdriver, screwing in a light bulb, placing a plug into an electrical socket, tying a necktie (men) or putting on lipstick (women), and shaving (men) or putting on eyeliner (women).

Physiologic assessment techniques capture tremor-related measurements (amplitude, frequency) and include systems based on linear accelerometry; electromyography; optical, photosensory, and gyroscopic techniques; and computerized tracking and digitizing technology. In general, these are not widely used in clinical practice due to expense, complexity, and need for technical training. Most important, objective measurements obtained from physiologic techniques do not necessarily correlate with functional disability. Overall, physiologic techniques are not very helpful for routine clinical assessment and are better suited as research tools.

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absolutely no visible tremor</td>
</tr>
<tr>
<td>1</td>
<td>Mild tremor, intermittent or continuous; similar to normal or enhanced physiologic tremor</td>
</tr>
<tr>
<td>2</td>
<td>Obvious tremor that is expected in patients with essential tremor. Must meet all the following criteria:</td>
</tr>
<tr>
<td></td>
<td>• Moderate amplitude</td>
</tr>
<tr>
<td></td>
<td>• Usually present</td>
</tr>
<tr>
<td></td>
<td>• Clearly oscillatory (hand not just a little shaky or unsteady but clearly oscillates between two extremes)</td>
</tr>
<tr>
<td>3</td>
<td>Large-amplitude, jerky tremor. Examples include:</td>
</tr>
<tr>
<td></td>
<td>• When handling liquids (pouring, drinking, using a spoon), patient spills but is able to complete the task without spilling all the liquid.</td>
</tr>
<tr>
<td></td>
<td>• When touching finger to nose, patient has difficulty hitting examiner's finger and circles around it many times.</td>
</tr>
<tr>
<td></td>
<td>• When drawing a spiral, large-amplitude wavy tremor present, but patient able to draw spiral.</td>
</tr>
<tr>
<td>4</td>
<td>Extremely large-amplitude, jerky tremor. Examples include:</td>
</tr>
<tr>
<td></td>
<td>• When handling liquids (pouring, drinking, using a spoon), patient unable to attempt the task or to perform the task without spilling all the liquid.</td>
</tr>
<tr>
<td></td>
<td>• When touching finger to nose, patient has difficulty hitting examiner's finger and circles around it many times; patient reluctant to touch own face for fear of self-injury.</td>
</tr>
<tr>
<td></td>
<td>• When drawing a spiral, patient unable to make or maintain pen to paper contact; unable to draw a spiral.</td>
</tr>
</tbody>
</table>
For most patients, psychosocial disability is much more significant than functional disability. In those with head tremor, significant embarrassment is associated with social appearances, and because stress or anxiety exacerbates the tremor, patients may progressively withdraw from social activities. Since depression is common and social phobia is not uncommon in patients with essential tremor, proper identification and management of these psychiatric conditions are important. Although tremorlytic drugs tend to improve tasks such as writing, drinking, and eating, fine manipulations such as using a screwdriver and typing may not improve much. Head and voice tremor are less responsive to drug therapy, and psychosocial disability due to these highly noticeable tremors remains significant.

Management

In one community-based study, only 11% of patients with essential tremor had sought medical advice for tremor. Of those who do seek medical advice, approximately 15% do so only after significant functional disability has occurred.

The goal of treatment is to minimize functional disability, reduce social handicap, and improve quality of life. The selection of treatment options is based largely on the patient’s needs and history (tremor severity, coexistent disease, current drug therapy, response to previous therapy). Treatment may include physical therapy, behavioral and psychologic interventions, lifestyle changes, pharmacotherapy, and surgery. Drug therapy does not cure, prevent, or slow the rate of disease

![Figure 2. Treatment algorithm for essential tremor. Vim = ventralis intermedius nucleus of the thalamus; DBS = deep brain stimulation.](image-url)
progression and is considered symptomatic treatment. Treatment is not required if the patient does not have significant functional or psychosocial disability. Figure 2 is a treatment algorithm, and Table 7 provides dosages of common antitremor drugs.

Behavioral Techniques and Physical Therapy

Most patients with mild essential tremor are able to minimize functional disability, social embarrassment, and personal injury by learning adaptive techniques. Examples include learning to write with the least disabled hand, placing a napkin between cup and saucer to avoid rattling, avoiding difficult foods (e.g., soup, spaghetti), using blunt-tip safety scissors, wearing clip-on neckties, having autodial on a telephone or asking the operator to place calls, learning deep breathing and other relaxation techniques, avoiding awkward or uncomfortable situations, and explaining their condition to people. The number of adaptive techniques is numerous, and people can be very creative.

Physical and occupational therapists may offer suggestions regarding wrist weights, plate guards, and other adaptive devices. These devices can provide considerable benefit in activities of daily living. Additional sources of information for clinicians and patients can be found by contacting the International Tremor Foundation (7046 West 105th Street, Overland Park, KS 66212-1803; www.essentialtremor.org).

Pharmacotherapy

For patients with mild tremor, minimizing exposure to emotional stress, tremorogenic foods and drugs, and reassurance are all that is required. Intermittent administration of a β-blocker or small amounts of alcohol may be effective in special social situations.

When tremor significantly interferes with daily activities, long-term pharmacotherapy is indicated, with drug selection dictated by comorbid conditions and anticipated safety and efficacy. The primary goal is to minimize drug side effects while providing maximum improvement in function. Patients should be informed that although significant benefit may be derived, complete tremor eradication is not a realistic expectation.

Drugs reduce tremor amplitude and associated disability. Tremor frequency is not significantly affected and is generally not correlated with disability. Assessment techniques for drug effectiveness include tasks such as handwriting, pouring, and drinking. It is important to recognize that improvements in accelerometric measurements (tremor amplitude) may not translate into proportional improvements in function. In addition, patients may improve in certain tasks such as drinking from a cup or using food utensils, but tasks requiring fine hand manipulations may not improve.

Table 7. Common Antitremor Drugs for Essential Tremor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Initially 20 mg b.i.d.; may titrate up to 120–240 mg/day</td>
</tr>
<tr>
<td>Propranolol, sustained release</td>
<td>Initially, 120 mg q.d.; may titrate up to 240 mg once/day</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Initially 50 mg q.d.; may titrate up to 200 mg/day in divided doses</td>
</tr>
<tr>
<td>Metoprolol, extended release</td>
<td>Initially 50 mg q.d.; may titrate up to 200 mg once/day</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Initially 12.5 mg hs; may titrate up to 250 mg/day</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Initially 300 mg t.i.d.; may titrate up to 1800 mg/day^</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Initially 0.25 mg q.d.; may titrate up to 6 mg/day</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Initially 1 mg q.d.; may titrate up to 10 mg/day</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Initially 1 mg q.d.; may titrate up to 10 mg/day</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Varies by muscle injected; ≥ 1.25 U for voice tremor to ≤ 400 U for head tremor. Repeat injections every 3-4 mo.</td>
</tr>
</tbody>
</table>

^Adjust dosage for renal insufficiency.
essential tremor dates back over 40 years. Since then, the drug's efficacy was confirmed in several double-blind, placebo-controlled, crossover trials, supporting its status as one of the most widely administered agents for management of essential tremor symptoms. Propranolol is the only agent that has approved labeling for this indication.

Lipid solubility does not appear to be critical for tremorlytic activity, as water-soluble agents (e.g., nadolol) are also effective. Propranolol is the only agent that has approved labeling for this indication.

The exact tremorlytic mechanism of propranolol remains unknown but may involve blockade of peripheral \( \beta_2 \)-receptors within muscle fibers or muscle spindles. Approximately 50–60% of patients experience some improvement in functional disability due to a reduction in tremor amplitude, but total tremor suppression rarely is achieved. The greatest improvement is in hand tremor and the least in head and voice tremors. The duration of effect after each dose is approximately 4 hours, so two daily doses are required. Sustained-release propranolol may enhance adherence and therefore therapeutic outcomes. In 18 patients with essential tremor, sustained-release propranolol was compared with the regular-release formulation and was preferred by 67% for tremor suppression and by 87% for ease of administration.

The short- and long-term tolerability of propranolol were evaluated in a nonrandomized, comparative study of 25 patients who received long-acting propranolol 80–160 mg/day and 25 who received primidone 50–250 mg at bedtime. Patients were followed for 12 months. Tremor measurements included a clinical severity score based on observable tremor amplitude, ability to perform writing, drawing (spirals), and pouring tasks, and linear accelerometry. Of patients receiving propranolol, the mean age was 68.9 years and mean disease duration was 20.4 years. Approximately 1 in 10 of them experienced short-term side effects (bradycardia, syncope) and 1 in 5 experienced long-term side effects (bradycardia, fatigue, erectile dysfunction) that required discontinuation of therapy.

When taking propranolol, monitoring of heart rate and blood pressure is recommended, especially during dose titration. Side effects such as diminished exercise tolerance, fatigue, bronchospasm, depression, insomnia, and erectile dysfunction may not be tolerated by some patients. Those with underlying cardiovascular disease should not have long-term propranolol therapy discontinued abruptly due to possible rebound cardiovascular events. Relative contraindications include severe heart failure, cardiac conduction blocks, and bronchospastic conditions. Propranolol also can inhibit sympathetically mediated hypoglycemic response in patients with diabetes, and benefits of therapy should be weighed against risks.

Propranolol may be administered on an intermittent (as needed) or scheduled basis. When administered intermittently, 20-mg tablets are preferred, with instructions to take one-half to two tablets about 30 minutes to 1 hour before social activities or anxiety-provoking events that may increase tremor. If administered as long-term suppressive therapy, it should be started at 20 mg twice/day. Optimal tremor reduction usually is achieved at 120–240 mg/day. Higher dosages may be given, but dosages greater than 320 mg/day do not appear to provide additional benefits. For elderly and frail patients, treatment should be begun at 10 mg twice/day and gradually titrated to an average of 80–120 mg/day. If propranolol is effective and tolerated, the once-daily long-acting preparation may be substituted.

Generally, propranolol retains its antitremor effect during long-term therapy. However, after 1 year, approximately 10–15% of responders develop tolerance to the tremorlytic effect and may require dosage increases. \( \beta \)-Blockers should be considered as first-line therapy unless the patient has contraindications or history of \( \beta \)-blocker intolerance. Concomitant conditions that may benefit (e.g., hypertension, stable angina, mild-to-moderate chronic heart failure, migraine headache) would strengthen the selection of a \( \beta \)-blocker.

Primidone

Over 20 years ago, primidone, a structural analog of phenobarbital, was serendipitously discovered to have antitremor activity when it was given to a patient with epilepsy and essential tremor. Since then, its efficacy for essential...
tremor has been confirmed by several double-blind, placebo-controlled, crossover trials. The principal metabolites of primidone, phenobarbital and phenylethylmalonamide (PEMA), do not possess significant tremorlytic activity. Therefore, primidone or an unknown metabolite appears to be the active tremorlytic agent. The exact mechanism of action remains unknown, and serum concentrations of primidone, PEMA, and phenobarbital are not correlated with antitremor efficacy.

Primidone is similarly or slightly more efficacious than propranolol, with near complete tremor suppression achieved in a greater proportion of patients. However, as with propranolol, primidone is most beneficial for essential hand tremor, and efficacy against head and voice tremor is variable. The duration of effect after a single dose is approximately 24 hours. As with propranolol, after 1 year of therapy approximately 10–15% of responders may develop tolerance to the tremorlytic effect of primidone.

In the short term, primidone is less well tolerated than β-blockers. In the nonrandomized, comparative study of 50 patients who received either propranolol or primidone, of 25 patients receiving primidone, the mean age and tremor duration were 66.6 years and 20.4 years, respectively. Nearly one-third of patients experienced short-term side effects (nausea, ataxia, dizziness, sedation, confusion, malaise) that occurred the morning after the first nighttime dose and persisted for up to 4 days; however, only 12% discontinued therapy. All patients had been educated as to the potential for reactions and that they would abate rapidly. During long-term therapy, only 8% of patients complained of side effects (sedation) and none discontinued the drug due to side effects.

Primidone is contraindicated in pregnancy, breastfeeding, and porphyria, and caution should be exercised in debilitated patients and those with impaired hepatic or renal function. Serious complications are rare and include red cell hypoplasia or aplasia, agranulocytosis, and megaloblastic anemia. A complete blood count should be performed at baseline and every 6–12 months to screen for blood dyscrasias. Clinicians also must keep in mind the potential for drug interactions secondary to the phenobarbital metabolite.

Primidone is available as scored 50- and 250-mg tablets and as an oral suspension of 250 mg/5 ml. It typically is prescribed on a constant-use basis. Because it has a long duration of antitremor activity, dosing is once/day. Strategies to minimize short-term reactions include starting therapy at a subtherapeutic bedtime dose (12.5 mg). The suspension formulation is particularly helpful for administering small doses. The dosage should be titrated slowly upward for desired tremor control. Most patients achieve optimal benefit with dosages of 250 mg/day or less. If higher daily doses are required, administration in several daily doses is recommended. Strategies to promote adherence to primidone include educating patients on potential short-term side effects and reassuring them that these reactions will disappear after the first few doses, and attempting to achieve optimal symptomatic control with a single daily dose.

The role of primidone is as a second-line agent for monotherapy or first-line agent in patients who do not tolerate propranolol. Primidone also may be used as an add-on drug if symptomatic relief is insufficient despite maximally tolerated doses of existing monotherapy.

Gabapentin

The efficacy and safety of gabapentin for the management of essential tremor were evaluated in several randomized controlled trials. Although the drug's antitremor effect remains unknown, enhancement of central GABAergic tone may play a role.

The efficacy of gabapentin 1800 mg/day in divided doses for essential tremor was evaluated in a randomized, double-blind, placebo-controlled, crossover trial. Clinical tremor outcomes were measured by the Fahn-Tolosa-Marin Tremor Rating Scale and quality of life by the Sickness Impact Profile (SIP). Treatment duration was 2 weeks with a 5-day washout between active drug and placebo. All 20 patients had disabling essential hand tremor (mean age 66.5 yrs; mean tremor duration 33.4 yrs). Renal function parameters were not reported. At the conclusion of the study, subscales of the tremor-rating scale (tremor severity, motor task performance, activities of daily living) and SIP scores were no different from baseline in both groups. However, this study was not designed to assess the efficacy of gabapentin monotherapy, as 70% of patients were taking one or more tremorlytic agents (e.g., propranolol, primidone, clonazepam, methazolamide) during the study.

A randomized, double-blind, placebo-controlled, crossover study compared gabapentin and propranolol. Sixteen patients received
monotherapy with divided doses of gabapentin 1200 mg/day, propranolol 120 mg/day, and placebo for 14 days with a 1-week washout period between treatments. All patients (mean age 67.9 yrs; mean tremor duration 12.2 yrs) had postural and kinetic hand tremor. Although none of them was taking other antitremor agents, 10 (62.5%) had received propranolol or diazepam in the past. Renal function parameters were not reported. Tremor was evaluated by the Fahn-Tolosa-Marin Tremor Rating Scale and linear accelerometry. Compared with placebo, gabapentin and propranolol were associated with statistically significant improvements in all subscales of the tremor-rating scale and patients' subjective assessment. Although not statistically significant, tremor-rating scores were slightly better for propranolol than for gabapentin. When asked which treatment was more effective, however, 50% of patients indicated gabapentin, 38% propranolol, and 12% both. As would be expected, a number of patients (~38%) did not respond to either drug, and approximately 19% responded positively to placebo.

Electromyographic (EMG) recordings from the extensor and flexor forearm muscles also were obtained and suggest that pharmacologic response may correlate with various EMG patterns. In patients with simultaneous contractions in antagonist muscles, propranolol was more effective and in those with alternating contractions, gabapentin was more effective. Although EMG measurements may not be practical in routine office practice, confirmation of these results may yield insight into the pharmacodynamic mechanism of antitremor agents.

A randomized, double-blind, placebo-controlled, crossover, dose-escalation study assessed the efficacy of gabapentin 1800 mg/day and 3600 mg/day for control of essential hand tremor. Among 20 patients completing the study, mean age was 69.9 years and mean tremor duration 29.1 years. This study was not designed to assess the efficacy of gabapentin monotherapy because most patients also were taking one or more tremorlytic agents (primidone, propranolol, benzodiazepine). After a 1-week titration phase, patients were maintained with gabapentin 1800 mg/day or placebo in divided doses for 2 weeks and evaluated. Doses were titrated over another week to 3600 mg/day. After 2 weeks at 3600 mg/day or placebo, another evaluation was performed. After a 1-week washout period, patients receiving gabapentin were switched to placebo and vice versa, and the 6-week evaluation process was repeated. Tremor severity was measured by the Unified Tremor Rating Scale and triaxial accelerometry. No statistically significant difference in accelerometry measurements was seen between placebo and the two gabapentin dosages. However, not surprisingly, this did not correlate with functional disability scores, and gabapentin 1800 mg/day was associated with statistically significant improvements in scores for activities of daily living and pouring; however, improvements in spiral drawing were not significant. Similar, but not superior, results were associated with high-dose gabapentin.

Interpretation of the results of these trials suggests that short-term treatment with gabapentin 1200–1800 mg/day is well tolerated in elderly patients with essential tremor and that the drug is effective as monotherapy for essential hand tremor. As add-on therapy to standard antitremor agents, the benefits are less robust and variable. Gabapentin is associated with few drug interactions, and long-term therapy appears well tolerated in both young and elderly patients, although ataxia, irritability, sedation, and weight gain may occur. Additional clinical studies are required to determine the agent's true benefit; however, due to a favorable safety profile and ease of use, gabapentin may be considered an alternative second-line agent for management of essential tremor and also as an add-on agent if symptom relief is insufficient despite maximally tolerated dosages of concurrent antitremor therapy.

**Alcohol**

The tremorlytic activity of alcohol in essential tremor has long been recognized, with up to two thirds of patients reporting temporary relief. Studies of positron emission tomography reveal that alcohol reduces the cerebellar hyperactivity in essential tremor. Although not confirmed, this may be mediated by GABAergic mechanisms. A glass of wine or light cocktail is often enough to attenuate the tremor for up to an hour; however, a rebound exacerbation of tremor often occurs. Many patients have learned to self-medicate in a controlled manner, and although it was suggested that they have an increased risk of developing alcoholism, their pattern of alcohol use is the same as that of the general population. Although routine ingestion of alcohol for symptom control cannot be widely proscribed to patients with essential tremor, many do benefit
from the sparing and responsible ingestion of alcohol before selected tasks or social events.

**Benzodiazepines**

Benzodiazepines, such as alprazolam, clonazepam, diazepam, and lorazepam, may be considered adjunctive therapy for patients whose essential tremor is not well controlled with standard agents. The drugs' tremorlytic mechanism of action is unknown but may be related to GABAergic augmentation resulting from interaction at the benzodiazepine receptor–GABA receptor–chloride channel complex. Alternatively, the agents relieve or prevent essential tremor exacerbated by emotional stress or anxiety. Diazepam commonly is prescribed, but its efficacy is largely anecdotal as clinical studies have not been conducted. In a double-blind, placebo-controlled study, 22 elderly patients each received 4 weeks of alprazolam, acetazolamide, primidone, and placebo, in a crossover manner separated by 2-week washout intervals. Alprazolam and primidone were similarly effective and both were more effective than placebo. Acetazolamide was no more effective than placebo. The mean effective alprazolam dosage was 0.75 mg/day, and the drug was well tolerated. Clonazepam is particularly effective for orthostatic tremor, a variant of essential tremor, and should be started at 0.25 mg/day and slowly increased over several weeks to 1.0–6.0 mg/day in divided doses. Because of their anxiolytic properties, benzodiazepines may be more beneficial in frequently anxious patients, and small doses (lorazepam 0.25–0.5 mg) may be prescribed judiciously (as needed) and administered 30 minutes to 1 hour before an important event. However, due to central side effects (sedation, confusion, memory loss) and an increased risk of falls, benzodiazepines must be taken with caution by the elderly. Lorazepam may be preferred due to its mild sedative profile.

**Botulinum Toxin**

Botulinum toxin is the most potent biologic toxin known and is a powerful therapeutic tool in certain hyperkinetic movement disorders. Seven serologically distinct neuroparalytic toxins (types A–G) have been derived from *Clostridium botulinum*, and although they have similar molecular structures, each differs in pharmacologic characteristics. In the United States, botulinum toxin type A (BTX-A) is available as Botox (Allergan, Irvine, CA) and subtype B (BTX-B) is available as Myobloc (Elan Pharmaceuticals, South San Francisco, CA). It is important to note that, in addition to Botox, another BTX-A preparation is available outside the United States (Dysport; Ipsen, Berkshire, United Kingdom). These two preparations possess different potencies (Botox 20 U/ng, Dysport 40 U/ng). However, although the relative potencies are different, the clinical activity of 1 U Botox is equivalent to approximately 3–4 U Dysport.

Three steps are involved in the paralytic mechanism of BTX-A. The toxin is composed of two chains, heavy and light, linked by a disulfide bond. The heavy chain binds to a specific membrane acceptor on the presynaptic cholinergic terminal of the neuromuscular junction. Endocytosis of the light chain occurs. Finally, the light chain targets and cleaves the 25-kDa synaptosome-associated protein, a protein involved in the fusion of acetylcholine vesicles at the presynaptic membrane. The release of presynaptic acetylcholine is inhibited without impeding the synthesis and storage of acetylcholine. The mechanism is similar for BTX-B except that it prevents release of acetylcholine by cleaving a different cytosolic protein, synaptobrevin-2 or vesicle-associated membrane protein.

The size of the denervation field is determined by dose and volume (10 U BTX-A diffuses up to 4.5 cm). Once paralyzed, nerve terminals begin to form temporary neuronal sprouts and eventually motor neuron function is completely restored with reinnervation of the parent terminal and degeneration of auxiliary sprouts. Typically, a single treatment involves multiple point injections, and retreatment is required approximately every 3–4 months. The most common adverse effect to be expected is focal weakness due to unwanted diffusion of toxin into adjacent muscles (injections in the hands are associated with finger weakness, in the larynx with dysphagia). When administered parenterally, the lethal dose for 50% of organisms for Botox is approximately 40 U/kg or 3000 U for a 75-kg individual. Therapeutic dosages represent 1–10% of this lethal threshold.

Data from open-label and randomized, controlled studies support BTX-A in selected patients with hand, head, vocal, or palatal tremor. In a randomized, double-blind, placebo-controlled trial, 25 patients with moderate-to-severe essential hand tremor were injected with BTX-A 50 or 100 U into wrist
flexors and extensors and followed for 16 weeks. Based on accelerometric data and ratings of tremor severity scales, 75% of BTX-A–treated patients experienced mild-to-moderate improvement 4 weeks after treatment compared with 27% of placebo-treated patients (p<0.05). No significant functional improvement was seen, however, because BTX-A injections in the hand also result in hand weakness. Greater improvement was noted for postural tremor compared with kinetic tremor. These results were confirmed in a randomized, double-blind, controlled trial involving 133 patients with essential tremor who were injected with BTX-A 50 or 100 U into wrist flexors and extensors and followed for 16 weeks. Improvements in motor task performance and functional disability were inconsistent and appeared to be offset by the adverse effect of dose-dependent hand weakness. After long-term experience, many clinicians now give reduced doses of 15 U or less in forearm extensors to reduce tremor and to minimize finger extensor weakness. Because voice and head tremors are often resistant to oral agents, BTX-A often is considered the drug of choice for them, and in experienced hands, the risk of dysphagia after cervical or laryngeal muscle injection is reduced significantly.

Contraindications to botulinum include myasthenia gravis, post-polio syndrome, Eaton-Lambert syndrome, motor neuron disease, aminoglycoside antibiotics, and pregnancy. Serious systemic side effects (generalized botulism-like syndrome) from local BTX are rare. A more common systemic effect is formation of neutralizing antibodies after several years of repeated injections. Because this results in therapeutic failure, steps to minimize antibody formation are important and include administering the minimum effective dose and extending the retreatment interval as long as possible, typically no earlier than every 3 months.

Miscellaneous Agents

Many other agents have been studied for the treatment of essential tremor, and preliminary results from open-label and controlled studies suggest that acetazolamide, clonidine, clozapine, methazolamide, mirtazapine, nicardipine, nimodipine, quetiapine, theophylline, and topiramate may be effective. Clinical data for topiramate are encouraging. Results of double-blind, placebo-controlled, crossover trials suggest that topiramate up to 400 mg/day monotherapy or in combination with antitremor agents significantly improves tremor scores and tremor-related functional disability scores. However, paresthesias, cognitive impairment, and anorexia may limit therapy.

Surgical Interventions

Surgical interventions should be considered for selected patients with disabling tremor that is not adequately controlled with pharmacotherapy. Improvements in neuroimaging and stereotactic techniques allow physiologists and neurosurgeons to identify anatomic targets (contralateral to the affected limb) accurately, resulting in enhanced efficacy and reduced surgical morbidity. The two proved techniques are stereotactic thalamotomy and chronic thalamic deep brain stimulation (DBS), with DBS preferred. Surgery is contraindicated in patients who are poor candidates due to underlying medical conditions and those with marked cognitive problems. Both procedures, when successful, allow patients to become drug free.

Stereotactic Thalamotomy

Stereotactic thalamotomy for essential tremor is an ablative technique (thermocoagulation) using a Cartesian coordinate system to target the ventralis intermedius (Vim) nucleus, a group of neurons located within the thalamus. Theories suggest that creation of a lesion in the Vim nucleus disrupts abnormal tremorogenic activity in the cerebellar-thalamic circuitry.

Most thalamotomies are unilateral, performed on the side of the brain contralateral to the dominant or most severely affected limb. Bilateral thalamotomies generally are avoided due to high risk of severe, permanent dysarthria or even complete mutism. The procedure takes 2–3 hours and is performed under local anesthesia to allow the patient to participate in physiologic examinations. Because brain tissue is devoid of pain sensation, the procedure is relatively painless. The efficacy of unilateral thalamotomy is high, with greater than 80% of patients experiencing long-lasting and complete (or near complete) suppression of the targeted tremor. Often concomitant midline tremors (head, voice) also improve. If the procedure results in incomplete lesioning, the patient may experience a mild residual tremor or eventually reemergence of the targeted tremor. In such cases, repeating the operation may be an option.

With an experienced neurosurgical team, the occurrence of severe, persistent morbidity
Thalamic Deep Brain Stimulation

Unilateral and bilateral DBS is effective for patients with disabling tremor that is not adequately controlled by pharmacotherapy. It has gained wide acceptance and is preferred over thalamotomy due to advantages related to its nonablative and adjustable nature. These include reversibility due to minimal lesioning of the Vim and the ability to change impulse variables to minimize side effects and increase efficacy. An additional benefit of thalamic DBS is the ability to perform bilateral procedures with a reduced risk of permanent morbidity.

The specific mechanism of action of DBS in essential tremor remains unknown but it may suppress tremor by providing chronic artificial “neural noise” that essentially disrupts cyclic activity within the motor circuit pathway. The efficacy of the procedure is at least equivalent to that of thalamotomy, and significant improvements in disability and health-related quality of life can be expected. In a randomized, controlled study of 68 patients with drug-resistant tremor (45 with parkinsonism, 13 with essential tremor, 10 with multiple sclerosis), DBS was more effective than thalamotomy in improving functional ability in patients with essential tremor and parkinsonism. However, after 2 years, the benefits in some patients with essential tremor appeared to have waned. Midline symptoms such as voice and head tremor were also improved, although less predictably than hand tremor. Excluding one fatality due to intracerebral hemorrhage, DBS was safe, with few patients experiencing cognitive decline, dysarthria, facial paresis, gait imbalance, or arm ataxia.

The disadvantages of thalamic DBS include increased expense over thalamotomy (mainly due to the cost of the hardware and programming instruments), the need for labor-intensive follow-up and monitoring, and the potential risk of inflammatory responses and infection due to implantation of foreign material. Batteries for the implanted pulse generator (IPG) require replacement, and the IPG or lead wires may have to be replaced due to malfunction or breakage. For patients living in rural areas where mandatory follow-up for IPG adjustments are not feasible, DBS maintenance can be problematic.

Summary

Essential tremor is the most common type of pathologic tremor. Although commonly described as benign, it can be significantly disabling. In the presence of functional or psychosocial disability, drug therapy should be started in an attempt to achieve optimal tremor reduction with a minimum of side effects. Although complete tremor eradication is unrealistic, drug therapy with propranolol, primidone, and gabapentin will benefit most patients with disabling hand tremor. Small doses of alcohol or benzodiazepine may be helpful as adjunctive, intermittent agents to be taken before special events. For patients with head or voice tremor, chemodenervation with local injections of botulinum toxin may be considered first-line therapy but must be performed by a trained and experienced specialist to minimize dysarthria, dysphagia, and neck weakness. Thalamic DBS and thalamotomy are reserved for patients with hand tremor after suboptimal response to pharmacologic therapies.

References