

Tremor: Sorting Through the Differential Diagnosis

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Tremor is an involuntary, rhythmic, oscillatory movement of a body part. It is the most common movement disorder encountered in primary care. The diagnosis of tremor is based on clinical information obtained from the history and physical examination. The most common tremors in patients presenting to primary care physicians are enhanced physiologic tremor, essential tremor, and parkinsonian tremor. All persons have low-amplitude, high-frequency physiologic tremors at rest and during action that are not reported as symptomatic, but can be enhanced by anxiety, medication use, caffeine intake, or fatigue. Features consistent with psychogenic tremor are abrupt onset, spontaneous remission, changing tremor characteristics, and extinction with distraction. Other types of tremor include cerebellar, dystonic, and drug- or metabolic-induced. The first step in evaluating a patient with tremor is to categorize the tremor based on its activation condition, topographic distribution, and frequency. Resting tremors occur in a body part that is relaxed and completely supported against gravity. Action tremors occur with voluntary contraction of a muscle and can be further subdivided into postural, isometric, and kinetic tremors. The most common pathologic tremor is essential tremor, which affects 0.4% to 6% of the population. In one-half of cases, it is transmitted in an autosomal-dominant fashion. More than 70% of patients with Parkinson disease have tremor as the presenting feature. This tremor is typically unilateral, occurs at rest, and becomes less prominent with voluntary movement. If there is diagnostic uncertainty, single-photon emission computed tomography can be used to visualize the integrity of the dopaminergic pathways in the brain, and transcranial ultrasonography may be useful to diagnose Parkinson disease. (*Am Fam Physician*. 2018;97(3):180-186. Copyright © 2018 American Academy of Family Physicians.)

Tremor is an involuntary, rhythmic, oscillatory movement of a body part and is the most common movement disorder encountered in primary care practices.¹⁻³ Aside from careful clinical examination and imaging when needed, there is no standard test to distinguish between common types of tremor, which can make the evaluation challenging. However, establishing the underlying cause is important because prognosis and specific treatment plans vary considerably. The most common tremors in patients presenting to primary care physicians are enhanced physiologic tremor, essential tremor, and

parkinsonian tremor.^{1,3-6} All tremors are more common in older age.⁷

Classification

Tremors are classified as resting or action (*Table 1*).^{1,8,9} A resting tremor occurs in a body part that is relaxed and completely supported against gravity (e.g., when resting on the arm of a chair). It is typically enhanced by mental stress (e.g., counting backward) or movement of another body part (e.g., walking), and diminished by voluntary movement.^{3,10,11} Most tremors are action tremors, which occur with voluntary muscle contraction. Action tremors are subdivided into postural, isometric, and kinetic tremors.^{8,10} A postural tremor is present while maintaining a position against gravity (e.g., arm elevation). An isometric tremor occurs with muscle contraction against a rigid stationary object (e.g., when making a fist). A kinetic tremor is associated with voluntary movement and includes intention tremor, which is produced with target-directed movement.²

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 167.

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Patient information: A handout on this topic, written by the authors of this article, is available at <http://www.aafp.org/afp/2011/0315/p703.html>.

Enhanced Physiologic Tremor

All persons have an asymptomatic physiologic tremor. It is a low-amplitude, high-frequency tremor at rest and during action. This tremor can be enhanced by anxiety, stress, certain medications, and metabolic conditions. Patients with a tremor that comes and goes with anxiety, medication use, caffeine intake, or fatigue do not need further testing.^{1,8}

Essential Tremor

The most common pathologic tremor is essential tremor, which is an action tremor. Essential tremor has been described as postural, kinetic, and even as a sporadic resting tremor.^{3,12} One study found that 95% of patients with essential tremor had primarily kinetic, rather than postural, characteristics.¹² Essential tremor is most obvious in the wrists and hands when patients hold their arms in front of them; however, it can also affect the head, lower extremities, and voice.¹³ It is generally bilateral, is present with different tasks, and interferes with activities of daily living.^{1,5}

Essential tremor affects 0.4% to 6% of the population.⁴ In about one-half of cases, it is transmitted in an autosomal-dominant fashion.⁸ Although essential tremor can manifest by early adulthood, most patients do not present for treatment until 60 to 69 years of age because it tends to progress slowly. Sometimes called benign essential tremor, essential tremor often causes social embarrassment, and up to 25% of those affected retire early or modify their career path.^{4,8,9} Importantly, 30% to 50% of those initially diagnosed with essential tremor eventually receive an additional tremor diagnosis or a different diagnosis entirely after further evaluation.¹²

The diagnosis of essential tremor is clinical, based on classic symptoms and tremor features.² Persons with essential tremor typically have no other neurologic findings; therefore, it is sometimes considered a diagnosis of exclusion.¹³ A video of this tremor is available at <http://www.youtube.com/watch?v=xVRKO-Sz0x4&NR=1>.

Parkinsonism

Parkinsonism is a clinical syndrome characterized by tremor, bradykinesia, rigidity, and postural instability. Many patients also have micrographia, shuffling gait, and masked facies.^{11,14-16} Various medications cause parkinsonism by blocking or depleting dopamine levels (e.g., methyl dopa, metoclopramide [Reglan], haloperidol).^{10,11} The most common form is

idiopathic Parkinson disease, a chronic neurodegenerative disorder with a prevalence of 1%.¹⁷

Approximately 70% of patients with Parkinson disease have resting tremor as the presenting feature.^{1,11} The classic parkinsonian tremor begins as a low-frequency, pill-rolling motion of the fingers, progressing to forearm pronation/supination and elbow flexion/extension. It is typically unilateral, occurs at rest, and fades with voluntary movement. It can reemerge after latency with maintenance of posture, which can create diagnostic confusion. Tremor can involve the leg and jaw as well.^{3,9} A video example of this tremor can be found at <https://www.youtube.com/watch?v=ZMx07OagyJw>.

Drug- and Metabolic-Induced Tremors

Dozens of medications can cause or exacerbate any type of tremor (*Table 2*).¹⁸ Patients with new-onset tremor should have a comprehensive medication review with specific

TABLE 1

Broad Classification of Tremor

Tremor type	Description
Resting	Occurs in a body part that is relaxed and completely supported against gravity and reduces activation of musculature Most commonly caused by parkinsonism, but may also occur in severe essential tremor
Action	Occurs with voluntary contraction of muscle Includes postural, isometric, and kinetic tremors
Postural	Occurs when the body part is voluntarily maintained against gravity Includes essential, physiologic, cerebellar, dystonic, and drug-induced tremors
Isometric	Occurs as a result of muscle contraction against a rigid stationary object
Kinetic	Occurs with any form of voluntary movement Includes classic cerebellar, dystonic, and drug-induced tremors; essential tremor can cross over to this category
Intention	Subtype of kinetic tremor amplified as the target is reached Presence of this type of tremor implies that there is a disturbance of the cerebellum or its pathways

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TREMOR

attention to any medications started before the onset of tremor.⁸ Medications that stimulate the sympathetic nervous system (e.g., amphetamines, terbutaline, pseudoephedrine) and psychoactive medications (e.g., tricyclic antidepressants, haloperidol, fluoxetine [Prozac]) are most likely to cause a postural tremor.^{1,8,12,13} When the medication review reveals a likely culprit, a trial discontinuation should be attempted if clinically possible.

The features and causes of metabolic tremor are varied.⁸ Initial workup of tremor may include blood testing for hepatic encephalopathy (e.g., ammonia level), hypocalcemia, hypoglycemia, hyponatremia, hypomagnesemia, hyperthyroidism, hyperparathyroidism, and vitamin B₁₂ deficiency.⁸

Cerebellar Tremor

The classic cerebellar tremor presents as a disabling, low-frequency, slow-intention, or postural tremor, and is typically caused by multiple sclerosis with cerebellar plaques, stroke, or brainstem tumors. Most patients have other neurologic signs of cerebellar dysfunction, including dysmetria (overshoot on finger-to-nose testing), dysynergia (abnormal heel-to-shin testing), and hypotonia.^{8,19} A video example of this tremor is available at <http://www.youtube.com/watch?v=GQm8klm6ub8>.

PSYCHOGENIC TREMOR

Differentiating between organic and psychogenic tremor can be difficult. Features consistent with psychogenic tremor are abrupt onset, spontaneous remission, changing tremor characteristics (including location and frequency), and extinction with distraction^{8,20} (Table 3⁸). Often, there is a stressful life event that precedes the tremor.³

DYSTONIC TREMOR

Dystonic tremor is rare, appearing in 0.03% of the population. It typically occurs in patients younger than 50 years. The tremor is usually irregular and jerky, and certain hand or arm positions extinguish the tremor. Other signs of dystonia (e.g., abnormal flexion of the wrists) are always present.^{8,21}

WILSON DISEASE

Wilson disease is a rare, autosomal-recessive disorder that manifests in persons five to 40 years of age, sometimes with a wing-beating

tremor. Measurement of serum ceruloplasmin level and 24-hour urinary copper excretion should be considered in young patients presenting with tremor to exclude this potentially life-threatening disease.^{16,22} A video example of this tremor is available at <http://www.youtube.com/watch?v=JgDvQUwUOo0>.

TABLE 2

Select Medications and Substances That May Exacerbate Tremor

Amiodarone	Lithium
Amphetamines	Methylphenidate (Ritalin)
Atorvastatin (Lipitor)	Metoclopramide (Reglan)
Beta-adrenergic agonists (e.g., albuterol)	Pseudoephedrine
Caffeine	Second-generation antipsychotics
Carbamazepine (Tegretol)	Terbutaline
Corticosteroids	Theophylline
Cyclosporine (Sandimmune)	Thyroid hormones
Epinephrine	Tricyclic antidepressants
Fluoxetine (Prozac)	Valproic acid (Depakene)
Haloperidol	Verapamil
Hypoglycemic agents	

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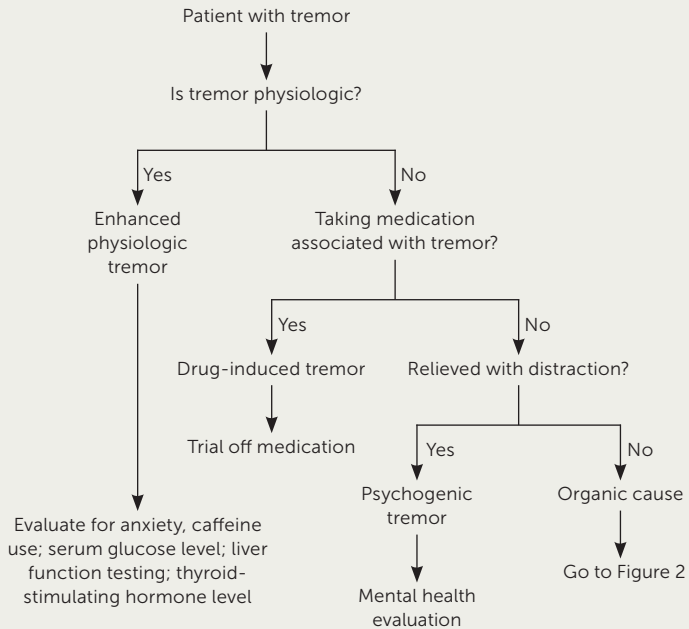
TABLE 3

Characteristics of Psychogenic Tremor

Abrupt onset	Presence of psychiatric disease
Absence of other neurologic signs	Presence of secondary gain
Changing tremor characteristics	Reported functional disturbances in the past
Clinical inconsistencies	Responsive to placebo
Multiple somatizations	Spontaneous remission
Multiple undiagnosed conditions	Static course
No evidence of disease by laboratory or radiologic investigations	Tremor increases with attention and lessens with distractibility
Patient employed in allied health professions	Unclassified tremor (complex tremors)
Patient involved in litigation or compensation issues	Unresponsive to antitremor medications

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FIGURE 1



Diagnostic algorithm for tremor.

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Diagnostic Approach

The diagnosis of tremor is generally based on clinical information obtained from the history and physical examination.¹⁷ Although there is overlap and variability among tremor syndromes, the intrinsic features of the tremor usually provide key diagnostic clues (*Figure 1*¹⁸; *Table 4*¹⁸). The first step is to categorize the tremor based on its activation condition, topographic distribution, and frequency. The activation condition should be described as resting, kinetic (or intention), postural, or isometric. The examiner can have the patient sit with his or her hands in the lap to check for rest tremor. A sequential test for postural and kinetic tremors can involve the patient stretching his or her arms and hands out, followed by a simple finger-to-nose test.^{2,3} A resting tremor is virtually pathognomonic for parkinsonism, whereas an intention tremor often indicates a cerebellar lesion.¹¹ Frequency is generally classified as low (less than 4 Hz), medium (4 to 7 Hz), or high (more than 7 Hz). The topographic distribution of the tremor (e.g., limbs,

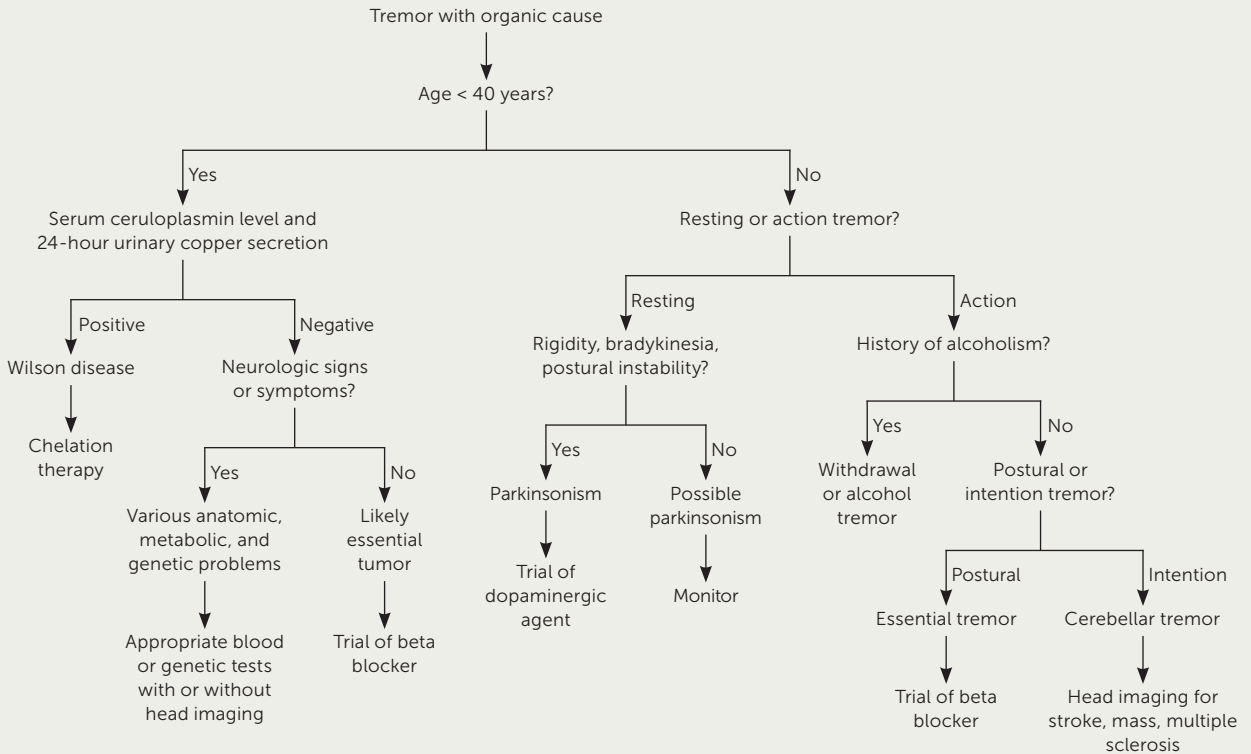
TABLE 4

Features of Common Tremor Syndromes

Tremor syndrome	Clinical features	Diagnostic tests	Treatment
Cerebellar tremor	Intention tremor; ipsilateral involvement to lesion; abnormal finger-to-nose test; imbalance; abnormal heel-to-shin test	Head computed tomography or magnetic resonance imaging	Treat underlying cause; deep brain stimulation
Enhanced physiologic tremor	Postural tremor; low amplitude; use of exacerbating medication	History of caffeine use or anxiety; glucose (for hypoglycemia), thyroid-stimulating hormone, liver function testing	Treat underlying cause; reassurance
Essential tremor	Postural tremor; symmetric; involves hands/wrists, lower extremities, head, or voice; family history; improvement with small amount of alcohol intake	No specific test; complete blood count; thyroid function testing; serum chemistry profile may rule out other disease	Propranolol; primidone (Mysoline); surgery
Parkinsonian tremor	Rest tremor; asymmetric; involves distal extremities; decreases with voluntary movement; bradykinesia and rigidity; postural instability	No specific test; positron emission tomography or single-photon emission computed tomography for atypical presentation	Dopamine agonists; anticholinergics; surgery; deep brain stimulation
Psychogenic tremor	Abrupt onset; spontaneous remission; changing tremor characteristics; extinction with distraction	Careful history	Mental health counseling

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FIGURE 2



Diagnostic algorithm for tremor with an organic cause.

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head, voice) can also provide useful information. For example, a high-frequency tremor involving the head is more likely to be essential tremor than parkinsonian tremor.^{2,3}

Several historical clues can play important roles in differentiating tremor (Figure 2⁸). Tremor in older patients and gradual onset are more likely to be Parkinson disease or essential tremor. Sudden onset of tremor is more likely to be caused by medication use, toxins, a psychogenic cause, or, in rare cases, a brain tumor. A list of clinical features that help differentiate between essential tremor and Parkinson disease is available at <http://www.aafp.org/afp/2003/1015/p1545.html#afp20031015p1545-t3>.

Caffeine intake and fatigue are often exacerbating factors in essential tremor with few alleviating factors. Associated conditions and diseases should be identified. For example, fatigued muscles from sleep disorders amplify physiologic tremor, and polyneuropathy from lack of innervations causes small involuntary movements that may be interpreted as tremor. A family history of neurologic disease or tremor suggests a genetic component, which is common in essential tremor. A medication history should be obtained to rule out drug-induced tremor. Patients should be screened for drugs of abuse as well as alcohol overuse and withdrawal because these can cause

tremor. Conversely, small amounts of alcohol (30 to 60 g) can temporarily relieve essential tremor and can be a historical clue to the diagnosis.^{2,3}

The assessment of tremor also includes examination for signs associated with tremor syndromes. Bradykinesia and postural abnormalities, which are late findings, strongly suggest parkinsonism.²² Difficulty rising from a seated position, micrographia, reduced arm swing while walking, and masked facies are also features of bradykinesia.²³ Postural abnormalities can be demonstrated by a positive pull test, where the patient stands in a neutral position and the examiner causes him or her to become unsteady by pulling on the upper arms from behind. This can help isolate cerebellar tremor and prompt evaluation for multiple sclerosis or stroke.²⁴ Similarly, coactivation sign is resistance during passive movement of a tremulous limb, but with disappearance of the tremor, which indicates psychogenic tremor. If essential tremor and parkinsonism are both possible diagnoses, the patient should be asked to draw a clockwise spiral. A large, shaky spiral points to essential tremor; however, a small, quivery spiral means that parkinsonism is likely.²⁵ The examiner should also look for dystonia (i.e., sustained muscle contraction), cerebellar signs (e.g., ataxia, incoordination), pyramidal signs, neuropathic signs, and

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
A resting tremor is usually caused by parkinsonism.	C	1, 11
Patients with new-onset tremor should have a comprehensive review of medications (prescribed and over-the-counter), with specific attention to medications started before the onset of tremor.	C	8, 12, 13
The diagnosis of tremor is based on clinical information obtained from the history and physical examination.	C	2, 17
Tremor in children is potentially serious; patients should be promptly referred to a neurologist.	C	26, 27
In select cases when there is significant diagnostic uncertainty, single-photon emission computed tomography using ioflupane can be useful for distinguishing Parkinson disease from other tremor types.	C	29, 30, 32

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

signs of systemic disease (e.g., thyrotoxicosis). A shuffling gait is consistent with parkinsonism.^{2,8,25}

Stanford University has a brief tutorial on the approach to tremor available at <https://www.youtube.com/watch?v=myQdK6BuBws>.

TREMOR IN CHILDREN

The diagnosis of tremor in children is challenging because of myriad potential causes, such as Wilson disease, fragile X syndrome, nutritional deficiencies (e.g., vitamin B₁₂), heavy metal poisoning, and essential tremor. Almost one-half of children with traumatic brain injury experience tremor for up to 18 months.²⁶ All childhood tremors are potentially serious and should prompt an in-depth investigation to clarify the cause; patients should be promptly referred to a neurologist.²⁷

Imaging

Although the diagnosis of tremor remains primarily clinical, certain imaging modalities can help differentiate some causes of tremor. Noncontrast magnetic resonance imaging and computed tomography can rule out secondary causes of tremor (e.g., multiple sclerosis, mass lesion, stroke) when the history and physical examination are suggestive of a structural cause, or in parkinsonism with atypical features or that is refractory to levodopa.²⁸

If there is diagnostic uncertainty, single-photon emission computed tomography (SPECT) using ioflupane (123I-FP-CIT SPECT or DaTSCAN), in addition to subspecialty consultation, can be useful for distinguishing Parkinson disease from essential tremor, and to a lesser extent from drug-induced tremor, dystonic tremor, psychogenic tremor, or unilateral postural tremor.^{29,30} When assessing for dopamine transporter dysfunction, 123I-FP-CIT SPECT was 78% sensitive and 97% specific, with a positive likelihood ratio of 26 and a negative likelihood ratio of 0.23 in one case series of 99 patients with suspected Parkinson disease.³¹ A positive test can therefore rule in a diagnosis of Parkinson disease within three years; however, it is not superior to clinical assessment in the diagnosis of Parkinson disease,²⁹ and its specific clinical use remains unclear.³²

Transcranial ultrasonography can also predict Parkinson disease by revealing hyperechogenicity of the substantia nigra. A European study of 49 patients in a neurology clinic demonstrated that ultrasonography compared favorably vs. 123I-FP-CIT SPECT for sensitivity (90% vs. 97%), specificity (60% vs. 70%), positive predictive value (77% vs. 82%), and negative predictive value (80% vs. 93%) for the diagnosis of Parkinson disease. Operator inexperience and limited fusion imaging technology, as well as conflicting results from several clinical studies, limit the use of transcranial ultrasonography.³³

This article updates previous articles on this topic by Crawford and Zimmerman¹⁸; Smaga³⁴; and Charles, et al.³⁵

Data Sources: A PubMed search was completed in Clinical Queries using the key terms tremor, movement disorders, ultrasound, and SPECT. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, Bandolier, Clinical Evidence, FPIN's Clinical Inquiry database, the Cochrane database, the Institute for Clinical Systems Improvement, the National Guideline Clearinghouse database, Essential Evidence Plus, EBM Online, and UpToDate. Reference lists of recent review articles were also searched for articles not previously discovered. Search dates: January 10 and September 10, 2017.

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