A 62-year-old woman presents with a tremor that affects both of her hands, which started in her early 50s. She reports that the tremor started slowly and symmetrically and has progressed gradually. The tremor affects her fine-motor movements and results in impaired handwriting, which is often illegible, and difficulty in such activities as eating soup and putting on a necklace. The tremor gets worse with stress. Her mother had a similar tremor. She has a more recent history of depression, which is now well controlled with fluoxetine and bupropion. The neurologic examination shows a postural and action tremor of both hands in the medium (4 to 8 Hz) frequency range with postural tremor amplitudes of 1 to 3 cm bilaterally; the examination is otherwise unremarkable. How would you evaluate and treat the patient?
drome and not as a single disease, while concomitantly narrowing its phenotypic scope to increase its homogeneity, recognizes that there are multiple possible causes, which may facilitate progress in understanding the pathogenesis.

Essential tremor is often familial, with a typically autosomal dominant pattern. Mutations have been found in some families but not others, and not in patients who fit the current definition of essential tremor.\(^5\) Genomewide association studies have shown that several single-nucleotide polymorphisms are associated with essential tremor, but the only one that has been well replicated is associated with the gene that encodes LINGO1,\(^6\) a protein that appears to inhibit cell differentiation during development as well as axonal regeneration and synaptic plasticity.

Whether there are defined pathophysiological features of essential tremor is controversial. However, several lines of evidence point to cerebellar dysfunction. Magnetic resonance spectroscopy has revealed decreased levels of N-acetylaspartate in the cerebellum, a finding that indicates loss or dysfunction of neurons.\(^7\) Some,\(^8,9\) although not other,\(^10\) pathological studies have shown a loss of Purkinje’s cells in the cerebellum; studies with this finding have also shown an increased number of so-called torpedoes, thought to be swollen axons of Purkinje’s cells, and loss of dendritic arborization of Purkinje’s cells. Increased LINGO1 levels\(^11\) and \(\gamma\)-aminobutyric acid (GABA) dysfunction\(^12\) have also been reported in the cerebellum of persons with essential tremor. In addition, quantitative clinical testing of gait and limb movement has shown mild incoordination similar to that observed in patients with ataxia.\(^13,14\)

The pathophysiology of essential tremor almost certainly involves rhythmic activity in the cortico–ponto–cerebello–thalamo–cortical loop, although the origin of the oscillation is unknown (Fig. 1). Cerebellar metabolism is high at rest, increases with arm extension,\(^15\) and decreases with administration of ethanol (which suppresses essential tremor).\(^16\) Cellular bursts in the cerebellar receiving zone of the thalamus (ventral intermediate nucleus) correlate strongly with the tremor itself.\(^17\)

### Key Clinical Points

**Essential Tremor**

- Essential tremor is considered to be a tremor syndrome characterized by isolated bilateral upper-limb action tremor with a duration of at least 3 years, with or without tremor in other locations, such as head, larynx (voice tremor), or lower limbs.
- Essential tremor frequently manifests with additional mild neurologic signs of diagnostic uncertainty, such as mild ataxia, questionably abnormal posturing of the limbs, or impaired memory. This presentation is classified as “essential tremor plus.”
- The diagnosis is generally based on a comprehensive history taking and neurologic examination. Routine laboratory testing, including the measurement of thyrotropin and electrolyte levels and liver and kidney function, is reasonable to rule out abnormalities that can confer a predisposition to enhanced physiologic tremor.
- First-line treatment of essential tremor involves pharmacotherapy with propranolol or primidone.
- Interventional treatment approaches for essential tremor that is refractory to pharmacotherapy and that causes substantial disability include deep-brain stimulation or focused ultrasound thalamotomy guided by magnetic resonance imaging.

**Essential Tremor Plus**

- Tremor with the characteristics of essential tremor and additional neurologic signs of uncertain clinical significance such as impaired tandem gait, questionably dystonic posturing, memory impairment, or other mild neurologic signs that do not suffice to make an additional syndrome classification or diagnosis
- Essential tremor with additional tremor at rest should be classified as essential tremor plus

### Assessment

A history taking and neurologic examination provide a phenotypic characterization of the tremor
syndrome. The history taking should include information about age of onset, family history, temporal evolution, and any exposure to potentially tremor-inducing drugs (e.g., valproate, selective serotonin-reuptake inhibitors, sympathomimetic agents, or lithium) and toxins (e.g., mercury, lead, or manganese). The neurologic examination should assess the distribution of tremor and activation condition (i.e., whether tremor appears during rest, posture [defined as isometric extension of a body part, such as a limb, against gravity], or goal-directed movement), include a visual estimation of the tremor frequency range (low [<4 Hz], medium, [4 to 8 Hz],...
or high (>8 Hz)), and assess any signs to suggest systemic illness or other neurologic disease. (See text box for diagnostic criteria and characteristic presentation of essential tremor and Table 1 for differential diagnoses.) Rating scales are useful to assess severity and effect of tremor on activities of daily living (the Essential Tremor Rating Assessment Scale [TETRAS], detailed in the Supplementary Appendix) as well as health-related quality of life in patients with essential tremor.18-20

According to the classification by the International Parkinson and Movement Disorder Society (see text box), if a workup reveals a cause for essential tremor, the diagnosis is “essential tremor due to that [cause].” Other conditions causing tremor must be considered. The differential diagnoses of isolated tremor syndromes without other neurologic signs include enhanced physiologic tremor, isolated focal tremors (e.g., isolated tremors of head, voice, or palate), and orthostatic tremors. Tremor syndromes with prominent additional neurologic signs include dystonic tremors, tremors combined with parkinsonism, intention tremor syndromes, Holmes tremor (combined low-frequency rest, posture, and intention tremor due to lesions in the cerebellar outflow tract), and myorhythmia (Table 1).

LABORATORY TESTING

A comprehensive medical history and neurologic examination are often sufficient to make a diagnosis. Ancillary laboratory testing is infrequently indicated if the clinical presentation is suggestive of other relevant diagnoses (Table 1). In particular, early Parkinson’s disease with predominant action tremor and little or no resting tremor or bradykinesia can reliably be distinguished from essential tremor by single-photon-emission computed tomography using the tracer 123I-ioflupane, which gives a measure of the striatal presynaptic dopamine-transporter density. Alternatively, patients may be followed over time to determine whether more definitive signs of parkinsonism arise.22 Routine laboratory tests should be performed to rule out metabolic or hormonal disturbances that may cause enhanced physiologic tremor, which may mimic mild essential tremor (Table 1).

Additional electrophysiological testing, including surface electromyography and accelerometry to evaluate muscle-activation characteristics, rhythmicity, and frequency, may be helpful to distinguish essential tremor from rhythmic cortical myoclonus (cortical tremor), functional tremor, and enhanced physiologic tremor. However, such testing is not performed in routine practice, and availability is limited to specialized centers.22

TREATMENT

Treatments for essential tremor can be broadly grouped into three categories: pharmacologic, surgical, and other nonpharmacologic or non-surgical treatment approaches.

Pharmacotherapy

Propranolol and primidone are the two compounds with the highest level of evidence to treat essential tremor by reducing the severity of upper-limb symptoms.21 The nonselective beta-blocker propranolol has been shown to be an effective treatment in randomized, controlled trials at doses ranging from 120 to 240 mg per day.24-26 Across randomized, controlled trials, tremor amplitudes that were measured by accelerometry were reduced by a mean of 55%.27 Adverse effects include bradycardia and bronchospasm. In one small, randomized, controlled trial, long-acting propranolol had efficacy similar to that of the short-acting formulation in reducing the amplitude of essential tremor.28

Primidone, which is metabolized to phenylethylmalonamide and phenobarbital, has been effective in doses ranging from 250 to 750 mg per day, with reductions of 60% in tremor amplitudes, similar to reductions observed with propranolol monotherapy.27 These effects on tremor amplitudes translated to benefits in patient evaluations of disabilities related to eating and dressing and assessment of the performance of manual tasks.29 Early adverse effects — including dizziness, fatigue, and malaise — occurred in 23 to 32% of patients on initiation of treatment with primidone (vs. in 8% taking propranolol) but typically resolved within 1 to 4 days, and the majority of patients who had such effects continued therapy.29,30 A randomized, controlled trial of propranolol–primidone combination therapy versus placebo showed a treatment effect of up to a 70% difference in tremor amplitude.31 However, despite efficacy, in a survey of persons who received propranolol or primidone for es-
<table>
<thead>
<tr>
<th>Tremor Syndrome</th>
<th>Activation Condition</th>
<th>Body Area Affected</th>
<th>Typical Tremor Frequency</th>
<th>Other Features</th>
<th>Causal Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td>Posture and kinetic movement</td>
<td>Upper limbs bilaterally, with or without tremor in other locations (e.g., head, larynx [voice tremor], or lower limbs)</td>
<td>4–12 Hz</td>
<td>Duration of ≥3 yr and absence of other neurologic signs (e.g., dystonia, ataxia, or parkinsonism); if additional neurologic signs of uncertain clinical significance are present (e.g., impaired tandem gait, questionable dystonic posturing, or memory impairment), the classification is “essential tremor plus”</td>
<td>Genetic risk variants have been described in LINGO1, SLCA12, STK32B, PPARGC1A, and CTNNA3; environmental risk factors may include higher exposure to beta-carboline alkaloids (harmane and harmine) that are present in overcooked meat</td>
</tr>
<tr>
<td>Enhanced physiological tremor</td>
<td>Posture and kinetic movement</td>
<td>Predominantly upper limbs; may also affect head, voice, tongue, or face</td>
<td>4–12 Hz</td>
<td>An isolated tremor syndrome, which typically appears without other symptoms; may be triggered by stress, anxiety, fatigue, or exposure to cold temperature</td>
<td>Metabolic disturbances, such as hyperthyroidism, hypoglycemia, hyperparathyroidism, hyponatremia, hypocalcemia, hepatic failure, and kidney failure; exposure to drugs, including caffeine, nicotine, cocaine, theophylline, amphetamines, thyroid hormones, antidepressants (especially tricyclics, SSRIs, or SNRIs), lithium, valproic acid, amiodarone, glucocorticoids, and immunosuppressants (cyclosporine A and tacrolimus)</td>
</tr>
<tr>
<td>Isolated head tremor</td>
<td>Posture of the head; subsides when head is rested</td>
<td>Head</td>
<td>2–5 Hz</td>
<td>Tremor may be present in flexion–extension (“yes–yes”), left–right rotation (“no–no”), or mixed directions; rule out signs of cervical dystonia (e.g., abnormal posture or symptom relief by sensory trick) or tremor elsewhere than head</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>Occurs with dystonia in same body area (termed “dystonic tremor”) or in other body areas (“tremor associated with dystonia”)</td>
<td>Head, face, jaw, voice, hands, arms, or other body parts</td>
<td>&lt;7 Hz</td>
<td>Typical signs of dystonia include sensory trick (involuntary movement mitigated by touch on a body part), overflow dystonia (involuntary activation of additional muscle groups during voluntary movement), and mirror dystonia (induction of dystonia in the dystonic body part by voluntary movement of the other side of the body); tremor can occur in patients with focal, multifocal segmental, and generalized dystonia</td>
<td>Idiopathic or genetic; examples of genetic causes that may manifest with a predominant dystonic tremor phenotype include mutations in ANO3 (DYT24) and GNL (DYT25); may also be present in other genetic dystonias, caused by mutations in TOR1A (DYT1) and THAP1 (DYT6)</td>
</tr>
<tr>
<td>Tremor combined with parkinsonism</td>
<td>Rest; may also be present during posture and kinetic movement</td>
<td>Hands (asymmetric tremor), lower limbs, jaw, tongue, or foot</td>
<td>4–7 Hz</td>
<td>Tremor characteristically pauses during limb movement from rest to posture and reemerges after brief delay</td>
<td>Environmental or genetic causes of and risk factors for Parkinson’s disease (e.g., variants in GBA, LRRK2, or VPS13C and pesticide exposure)</td>
</tr>
<tr>
<td>Cortical tremor</td>
<td>Posture and kinetic movement</td>
<td>Arms (unilateral or bilateral involvement)</td>
<td>9–18 Hz</td>
<td>May coexist with epilepsy; is refractory to therapies that help essential tremor; marked by cortical excitation, with giant somatosensory potentials and cortical spikes on back-averaging EEG</td>
<td>Autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME) or symptomatic cortical myoclonus</td>
</tr>
</tbody>
</table>

* This list is not comprehensive; see Table S1 in the Supplementary Appendix, available at NEJM.org, for a comprehensive version. Posture describes isometric extension of a body part (e.g., a limb) against gravity. EEG denotes electroencephalography, SNRI serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.
ential tremor, approximately half reported that they had eventually discontinued the drugs.32 The most likely reasons for discontinuation are limited efficacy and unacceptable side effects.

Limited data from randomized, controlled trials are available to support the use of other medications in essential tremor, including topiramate, alprazolam, gabapentin, and other beta-blockers besides propranolol (e.g., atenolol, nadolol, and sotalol).23,27 Randomized, controlled trials have shown no significant benefit for several other agents for essential tremor, including levetiracetam, amifampridine, flunarizine, trazodone, pindolol, acetazolamide, mirtazapine, nifedipine, and verapamil.23

**Neurostimulation and Ablative Therapies**

Deep-brain stimulation (unilateral and bilateral) and thalamotomy (only unilateral) targeting the thalamic nucleus ventralis intermedius are used for the treatment of medically intractable upper-limb tremor in essential tremor. Although conventional stereotactic thalamotomy was the first available interventional treatment of tremor, its application is limited to unilateral interventions owing to the high risk of irreversible dysarthria or ataxia after bilateral thalamotomy.33,34 In a randomized trial involving patients with tremor (with essential tremor in the minority), deep-brain stimulation resulted in greater functional improvements than thalamotomy and fewer adverse events, such as dysarthria, sensory disturbances, and gait disturbances.35 At a 5-year follow-up, half the patients with essential tremor who were assigned to deep-brain stimulation reported a diminished effect, which has been attributed to disease progression or the development of tolerance to stimulation.36,37 Adverse events are more common with bilateral than unilateral deep-brain stimulation.37,38 Adverse effects of deep-brain stimulation may include reversible stimulation-induced ataxia, dysarthria, paresthesias, tonic muscle contractions, and impaired balance.39

In 2016, the Food and Drug Administration approved a focused ultrasound device to treat essential tremor that is refractory to medical therapy.40 The approval was based on the results of a randomized, controlled trial involving 76 participants with essential tremor, in which unilateral thalamic thermoablation using focused ultrasound with magnetic resonance imaging (MRI) guidance resulted in a significantly greater reduction in hand tremor and better quality of life over a period of 12 months than a sham intervention. The most common adverse events with focused ultrasound thalamotomy were intraprocedural discomfort, as well as postoperative paresthesia or numbness (in 38% of participants) and gait disturbance (in 36%). At 12 months after the intervention, the rate of paresthesia or numbness was 14%, and the rate of gait disturbance was 9%.41

**Areas of Uncertainty**

The relationship between pathological, neurophysiological, and genetic factors in essential tremor requires further study. The extent of degenerative processes in the cerebellum in affected patients and their relevance to the broad spectrum of essential tremor remain unclear.42

More data are needed from randomized trials to provide information regarding the effectiveness and risks of treatments for essential tremor. Clinical rating scales and transducer-based methods to objectively quantify tremor have been developed for use in clinical trials as well as in routine practice.18,22 However, the clinical meaningfulness of observed changes in these instruments is uncertain, and data are needed on patient-reported outcomes and quality of life.

Potential molecular targets for treatment of essential tremor include the T-type calcium channel42 and GABA type A receptors.43 On the basis of the tremor-suppressing effect of ethanol and its presumed molecular action on these targets,44 the long-chain alcohol 1-octanol and its metabolite octanoic acid have been proposed for treatment of essential tremor; preliminary data have suggested benefit,45 although further study is needed.

Although the ventral intermedius nucleus of the thalamus has been the primary target for surgical treatment of tremor, two regions below the thalamus — the zona incerta and the white-matter tract of cerebellothalamic fibers (the prelemniscal radiation) — have been proposed as alternative targets (Fig. 1), with uncontrolled studies suggesting a potentially greater effect than with the conventional target.46-48 However, controlled trials are needed to confirm efficacy.

New developments in stimulation therapies for essential tremor include closed-loop stimula-
tion using sensors to monitor tremor activity to
to trigger and adjust stimulation in real time and
“on demand.”44 A tremor-cancelling spoon, which
uses tremor sensors that drive micro-motors to
counteract the tremor and stabilize the utensil,
has been developed.50 More data are needed to
inform the efficacy of this and other assistive
devices for essential tremor.

GUIDELINES

The 2017 consensus statement on tremor of the
International Parkinson and Movement Disorder
Society represents a major update in the classifi-
cation scheme of tremor disorders, since it de-
defines essential tremor as a tremor syndrome and
includes the recommendation to classify pa-
tients with tremor according to both clinical
characteristics and cause.4 The American Acad-
emy of Neurology (AAN) published guidelines in
2011 summarizing recommendations for medi-
cal and surgical approaches.23 The AAN has de-
veloped an Essential Tremor Quality Measure-
ment Set that aims to ensure the quality of
diagnosis and the identification of appropriate
pharmacologic and surgical treatment options,
with attention to quality-of-life measures, coex-
isting depression and anxiety, and education of
patients.31 Recommendations in the present
article are generally consistent with guideline
recommendations for evaluation and treatment,
with the exception that data to support MRI-
guided focused ultrasound thalamotomy for
treatment-refractory essential tremor were not
available at the time these guidelines were pub-
lished.

CONCLUSIONS AND
RECOMMENDATIONS

The patient described in the vignette presented
with approximately a 10-year history of a slowly
progressive bibrachial tremor during action and
posture, such as limb extension against gravity.
On the basis of the history taking and the
neurologic examination (including the observed fre-
quency and amplitude of tremor), a diagnosis of
essential tremor is most likely. In the absence of
any other abnormal neurologic signs, the main
differential diagnosis would be enhanced physi-
ologic tremor, which can be induced by meta-
bolic disturbances or certain medications (in-
cluding fluoxetine, which the patient is taking).
We would recommend routine laboratory stud-
ies, including tests of liver and kidney function
and measurement of blood levels of electrolytes
and thyrotropin. However, the long-standing
course and positive family history of tremor
make essential tremor more likely.

Because the patient has not yet received any
therapy for essential tremor and reports that
tremor interferes with daily life tasks, we would
recommend treatment initiation with either pro-
pranolol or primidone, with a gradual dose
adjustment to target doses (propranolol, 120 to
240 mg per day; primidone, 250 to 750 mg per
day). The choice of first-line therapy should be
made after assessment for any contraindications
(e.g., symptomatic bradycardia or hypotension
when beta-blocker therapy is considered) and
may also take the patient’s preference into ac-
count after education regarding short-term and
long-term effects of these drugs, such as dizziness,
hypotension, and sedation. After the pa-
ient is taking a dose of either drug that provides
sufficient benefit without unacceptable side
effects, we recommend annual assessments of
tremor severity with the use of rating scales such
as TETRAS. For second-line treatment, we would
recommend switching to the other first-line
agent, if not contraindicated; if either was ef-
efective alone, combination therapy with both
propranolol and primidone could be considered.
For patients whose symptoms cause substantial
disability and who do not have an adequate re-
sponse to pharmacotherapy, which may also in-
clude treatments with lower levels of evidence of
efficacy (e.g., topiramate, alprazolam, or gabap-
entin), we would discuss the option of deep-
brain stimulation or MRI-guided focused ultra-
sound thalamotomy with the patient, weighing
possible risks of the surgical intervention and
potential benefit.

Dr. Haubenberger reports receiving devices for use in re-
search studies from Cala Health; and Dr. Hallett, receiving
devices for use in research studies from and serving on an un-
paid scientific advisory board for Cala Health and holding a
patent (US 7,407,478), licensed to Brainsway, for the H-coil. No
other potential conflict of interest relevant to this article was
reported.

Disclosure forms provided by the authors are available with
the full text of this article at NEJM.org.
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