Review Article

REVIEW ON ESSENTIAL TREMOR AND PHARMACOTHERAPY

*Vijai Basker G[1], Gopalakrishnan S[2], Prema R[2], Muthukumaran M[3]
[1]*Haramaya university, Ethiopia.*
[2]*Santhiram College of Pharmacy, Nandyal, Andhrapradesh, India.*
[3]*Padmavathi college of Pharmacy & Research institute, Dharmapuri, Tamilnadu, India.*

Abstract

Essential tremor is a common movement disorder that interferes with the performance of motor tasks and social activities. As a consequence, patients experience a reduction in quality of life. The pathophysiology remains not well understood. Differentiation of essential tremor from other tremor syndromes is important in order for clinicians to better provide patient education and therapy. When pharmacotherapy is indicated, the standard agents remain propranolol and primidone. However, additional agents such as benzodiazepines, gabapentin, topiramate, and zonisamide may provide additional symptomatic benefits. Surgical interventions, such as thalamic deep brain stimulation, and focal injections of botulinum toxin offer patients an alternative treatment modality when oral pharmacotherapy is inadequate. A treatment outline is provided to guide clinicians in the management of patients with essential tremor.

Keywords:- Movement disorder, Tremor syndromes, Pharmacotherapy.

Introduction

Essential Tremor is widely recognized as a common movement disorder[1]. Despite the wide prevalence, understanding of the causes and mechanisms of essential tremor is limited and remains an unmet research need**.** [2]Essential tremor is associated with functional and psychosocial disabilities that range from minimal to severe, with most patients experiencing significant impairment in their quality of life**.** [3]The tremor interferes with daily activities such as eating, writing, body care, and driving. As a result of the visible tremor, many patients with essential tremor will also experience reduced motivation to pursue social and work-related activities. Often patients with essential tremor are misdiagnosed as having Parkinsonism or dystonia, and sometimes the tremor is dismissed as an insignificant clinical finding. [4] The clinical significance of essential tremor, unfortunately, has been trivialized by terms such as "benign essential tremor" and "senile tremor," and they should be abandoned. The goal of therapy for essential tremor is to provide maximal function and comfort and to improve quality of life while minimizing acute and chronic side effects. Toward this end, a better understanding of this common movement disorder will enable clinicians to facilitate improvement of patient outcomes through optimization of therapy and education of patients.

**** Author for Correspondence:***

G.Vijai Basker, M.Pharm,
Dept. of Pharmacy,
Haramaya university,
Ethiopia.
Email: vj_basker@yahoo.co.in

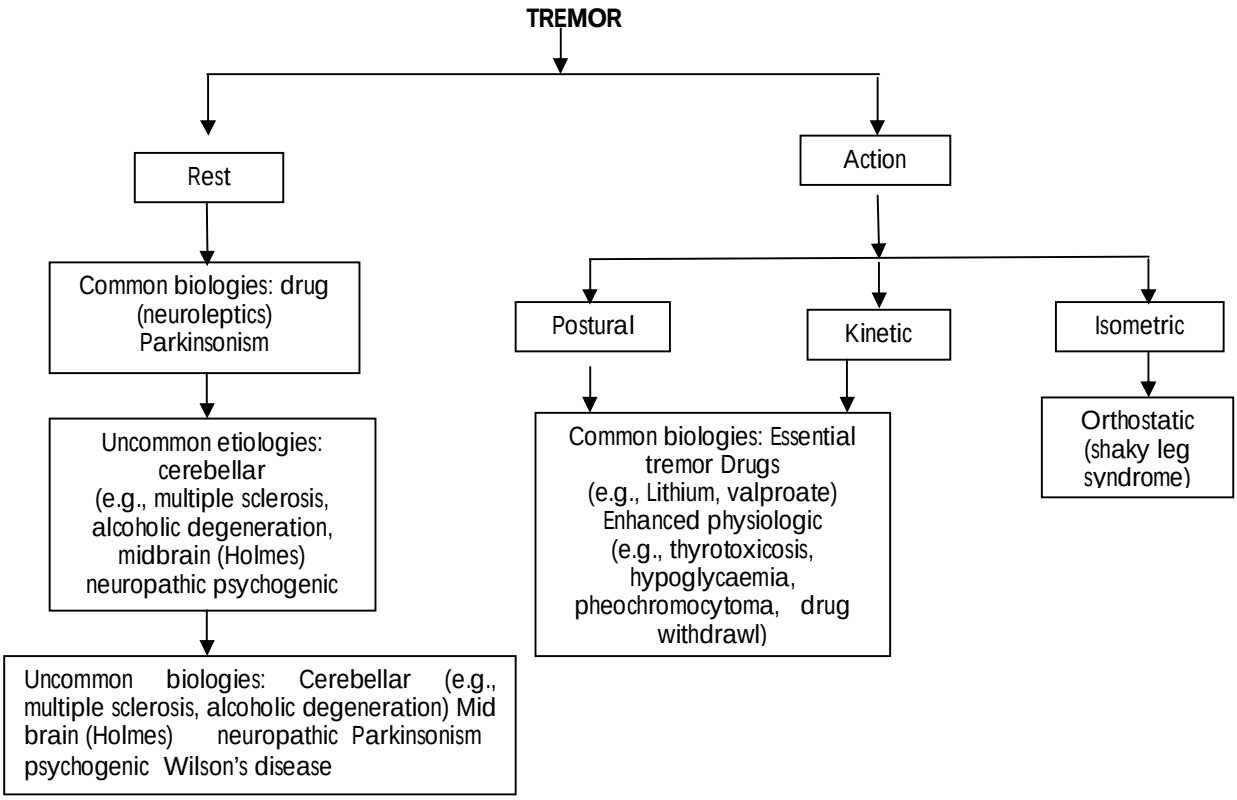
Description and Classification of Tremor

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. [5]A growing body of evidence suggests that normal physiologic tremor 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, the state of muscle β-receptor activation, and stretch reflex and muscle spindle feedback. [5]Physiologic tremor can be enhanced by certain circumstances, including exercise, emotional stress, metabolic abnormalities (eg, thyrotoxicosis, hyperparathyroidism, hypoglycemia, pheochromocytoma), and drugs (eg, sympathomimetic agents, lithium, valproate). [6]Treatment of abnormal physiologic tremor focuses on removing the underlying causative condition. In some situations, such as a lecturer with stage fright, a single dose of propranolol (10-40 mg) is often helpful when administered before the tremor-inducing function. Tremor types are most commonly classified in the clinical setting by phenomenology (ie, tremor activating behaviors; Table 1) and etiology (Figure 1). Essential tremor is characterized by an action tremor (ie, tremor that occurs upon voluntary muscle contraction) such as postural or kinetic tremor. [7]Postural tremor is triggered upon voluntarily attempting to maintain a position against the force of gravity; for example, postural tremor of the upper extremities can be detected by having the patient extend their 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. In general, kinetic tremor is associated with greater disability relative to postural tremor.

Table 1
Tremor activation behaviors

Behavior	Definition
Rest	Tremor occurring in the absence of voluntary muscle contraction in the affected body part. The tremulous body part must be completely supported against gravity (eg, hands in the lap).
Action	Tremor occurring during voluntary muscular contraction. Includes postural, kinetic, and isometric tremors.
Postural	An action tremor present while voluntarily main taining a posture against gravity (eg, hand and arms outstretched).
Kinetic	An action tremor present during movement (eg, writing, bringing a drinking cup toward the mouth, inserting a key). Also includes intention tremor and task-specific tremor.
Isometric	An action tremor occurring as a result of muscular contraction against a rigid stationary object (eg, making a fist).

Fig 1. Tremor classification



Clinical Presentation and Diagnosis

The diagnosis of essential tremor is determined by clinical examination and investigation. Assessment of tremor generally includes a medical history, physical examination for tremor-inducing behaviors (rest, postural, kinetic) and other neurologic signs, exploration for family history of tremor or other neurologic disorders, and inquiry about time of tremor onset and factors that exacerbate or alleviate the tremor. Many patients will confirm that consuming small quantities of alcohol often results in transient tremor improvement. Although not confirmatory, this finding is helpful in strengthening the diagnosis of essential tremor, because other tremor syndromes are rarely suppressed by alcohol ingestion. Laboratory testing is also performed to exclude underlying treatable medical conditions associated with tremor, such as hyperthyroidism. In all patients presenting with tremor, drug induced tremor should always be ruled out. A variety of drugs and substances can produce resting, postural, or action tremors (Table 2) characterized by a relatively abrupt onset in relation to drug therapy initiation. If tremor is due to a medication, the therapeutic intervention is to reduce the dose and, if necessary, discontinue the offending drug. If this is not possible, propranolol is effective for controlling drug-induced tremors. Clinicians should also keep in mind that heavy metal toxicity and chronic alcoholism, as well as states of alcohol and drug withdrawal, is potential sources of tremor. Essential tremor has been traditionally viewed as a monosymptomatic condition, one that occurs with insidious onset in the absence of other neurologic abnormalities. If the tremor onset is abrupt or there are concomitant neurologic symptoms, an alternative diagnosis should be suspected. As essential tremor progresses, tremor amplitude increases, and the patient's ability to perform basic manual tasks becomes impaired.

The hallmark symptom of essential tremor is a bilateral postural or kinetic tremor affecting the distal upper extremities. The second most frequent body part affected is the head, with concurrent upper extremity involvement. Essential tremor of the head is characterized by either a horizontal "no-no" pattern (tremblement negatif) or a vertical "yes-yes" pattern (tremblement affirmatif) or a combination of both. Other body parts such as the legs, chin, trunk, tongue, soft palate, and rarely, the lips and eyebrows, may also be affected. Dysarthric speech may develop in patients with a combination of voice, tongue, or palatal tremors. If head tremor occurs without concurrent upper extremity tremor, the possibility of dystonic tremor associated with cervical dystonia should be considered, especially if neck pain is also present. Core and secondary criteria for probable essential tremor, derived from the Tremor Investigation Group Criteria7 and the Consensus Statement of the Movement Disorder Society on Tremor, [8] are listed in Table 3. The presence of one or more secondary criteria, although not required for the diagnosis of essential tremor, strengthens the diagnosis. If red flag findings are present, tremor of another type should be suspected. The presence of rigidity, bradykinesia, or resting tremor should alert to the possibility of Parkinsonism. Additional red flags include a sudden or rapid onset of symptoms and concurrent therapy with tremorogenic agents.

Table 2
Tremorogenic Drugs and Substances

Alcohol (chronic)
Antiarrhythmics (amiodarone, mexiletine, procainamide)
Carbamazepine (especially when combined with
neuroleptic and lithium)
Corticosteroids
Cyclosporine
Heavy metals (arsenic, lead, manganese, mercury)
Lithium
Metoclopramide
Methylxanthines (caffeine, theophylline)
Neuroleptics
Nicotine
Phenytoin
Reserpine
Sympathomimetics (eg, albuterol, salmeterol, amphetamine,
cocaine, ephedrine, methylphenidate, pseudoephedrine)
Selective serotonin reuptake inhibitors (eg, fluoxetine,
paroxetine, sertraline)
Thyroid preparations
Tricyclic antidepressants (eg, amitriptyline, imipramine)
Valproate

Table 3
Criteria for Diagnosing Essential Tremor

Criteria	Description
Core criteria	Bilateral postural tremor (with or without kinetic tremor) of hands or forearms; predominantly symmetrical; tremor is visible May have isolated head tremor (with no abnormal posturing) Absence of other neurologic signs (except Froment sign)
Secondary criteria	Duration greater than 3 years Positive family history Positive response to alcohol
Red flags	Presence of tremor at rest, bradykinesia, rigidity, unilateral tremor, dystonia, leg tremor, gait disturbance

a. Some red flags (eg, bradykinesia, rigidity) may develop slowly and may not be immediately apparent.

Table 4
Differential Characteristics of Essential Tremor and Parkinsonian Tremor

Characteristic	Essential Tremor	Parkinson Disease
Tremor type	Postural, kinetic; uncommonly resting	Resting and postural (re-emergent); uncommonly kinetic
Age of onset, y	Varies; childhood to adulthood	55-65
Symmetry	Bilateral	Unilateral or bilateral
Frequency (Hz)	4-10	4-6(resting); 4-10 (postural)
Family history of tremor	50%	<10%
Response to agents*		
Alcohol	+3	0
Anticholinergics	0	+2
Levodopa	0	+3
Primidone	+3	0
Propranolol	+3	1
Worsened by stress	Yes	yes
Body part affected	Hands > heads > voice;(rarely legs)	Hands > Legs(rarely head or voice)
Bradykinesia	Absent	Present
Rigidity	Absent	Present
Postural instability	Absent	Present

(*0 = not effective, +1 = mildly beneficial; +2 = moderately beneficial; +3 = most beneficial)

Because essential tremor and parkinsonian tremor are 2 common and chronic forms of tremor, it is important to be able to differentiate them (Table 4). Of note, in many patients with essential tremor, a cogwheellike phenomenon (Froment sign), can be elicited by having the patient perform repetitive movements with the contralateral arm. This can often be mistaken for the "cogwheel" rigidity of Parkinsonism. The classic "pill-rolling" rest tremor of Parkinson disease is rarely observed in essential tremor.

Epidemiology

The incidence of essential tremor increases with age, but the condition may occur at any age from childhood to adulthood. Individuals with a family history of essential tremor tend to have a younger age of onset (< 20 years old). [9] In one well-conducted study, the prevalence was approximately 626 per 100 000 individuals older than 19 years, and 3535.4 per 100 000 individuals aged 70 years or older. [10] Another study reported an age-adjusted prevalence of 4020 per 100 000 individuals aged 65 years or older [11].

Pathophysiology

No specific pathology or structural lesion has been identified in the brains of patients with essential tremor**.** [12]Animal models of harmaline-induced tremor implicate the inferior olivary nucleus, a brainstem structure, as the origin of abnormal oscillatory activity that is amplified by the cerebellum, entrained by the thalamus-cortical-spinal system, and then expressed peripherally as pathologic tremor. [5]However, neuroimaging studies with positron emission tomography and magnetic resonance imaging in patients with essential tremor support the theory that abnormal tremorogenic activity may originate from within the cerebellum. [13]In terms of neurochemistry, evidence supports the involvement of both γ-aminobutyric acid (GABA) and the adrenergic systems. [14, 15, 16] Approximately 50% of

essential tremor cases are inherited as an autosomal dominant trait. [17] Although specific genes (eg, ETM1, ETM2) associated with uncommon subtypes of familial essential tremor have been identified, a genotype responsible for most familial essential tremor has not been identified. [18] In families with a history of essential tremor, the onset of tremor generally occurs during adolescence or young adulthood. In families with familial essential tremor, the chances that it will develop decline with age. One study found that if it had not developed in the child by age 10, the risk that essential tremor would develop at a later age was less than 39%; if the child remained unaffected by age 25, the risk that it would develop at a later age was less than 20%, and less than 6% if the child remained unaffected at age 50. [19] Understanding of the extent of genetic influence and mode of inheritance in essential tremor remains an unmet need.[2]

Disability

For practically all patients, the psychosocial disability associated with essential tremor is much more significant than the functional disability. For example, in patients with head tremor, significant embarrassment may arise from situations requiring social interaction and patients may progressively withdraw from social activities. Although many patients with essential tremor experience only mild functional disability, some experience significant difficulties with performing daily activities. Hand tremor, for example, often becomes more pronounced as the hands near the face, making eating, drinking, and facial care more difficult. If severe, patients may also avoid eating, drinking, and writing in public. Voice tremor may also be severe enough to inhibit activities such as singing and talking. Such disabilities may interfere with job performance and result in lack of promotion, job changes, or premature retirement. In addition, some activities such as handling sharp objects may become unsafe. Although antitremor drug therapy tends to improve tasks such as writing, drinking, and eating, fine manipulations such as using a screwdriver or typing may not improve. Head and voice tremor are less responsive to drug therapy, and psychosocial disability due to these highly noticeable tremors remains significant. Most tremor-rating scales used in routine clinical practice are based on a simplistic rating score in which tremor is rated as absent (0), mild (1), moderate (2), or severe (3). The Washington Heights– Inwood Genetic Study of Essential Tremor (WHIGET) tremor rating scale is a valid and reliable rating scale. [20] Once essential tremor has been diagnosed, the severity of functional or psychosocial disability will determine the need for pharmacotherapy. Several objective functional performance tests are inexpensive and user-friendly. Tests such as handwriting samples and water transfer tasks evaluate the performance of actions involved in real-life tasks. The handwriting will generally be shaky and relatively large. Kinetic tremor can also be assessed by asking the patient to transfer water from one cup into another, and postural tremor can be assessed by asking the patient to hold the cup of water for 60 seconds. Other tests include having the patient carry a plastic cup and saucer or to use a key and lock. In addition to objective performance tests, subjective instruments are also very useful. For example, the Tremor Disability Questionnaire is a valid and reliable disability questionnaire specific for essential tremor that can be completed within 10 minutes. [21] Although subjective, the results are highly correlated with level of functional disability. Both objective and subjective methods can be used to monitor the effectiveness of therapy. Physiologic assessment techniques are used to capture tremor-related measurements such as amplitude and frequency and include systems based on linear accelerometry, electromyography, optical, photosensory, and gyroscopic techniques, as well as computerized tracking and digitizing technology. These physiologic techniques generally are not utilized for routine clinical assessment and are better suited for the research setting.

Therapeutic Management

The selection of treatment options for patients with essential tremor is determined largely by patientspecific factors such as tremor severity, coexistent disease, current medications, and response to previous therapy. Treatment options include physical therapy, behavioral and psychologic interventions, lifestyle changes, pharmacotherapy, and surgery. Therapies do not cure, prevent, or slow the rate of disease progression; therefore, all treatment measures are considered symptomatic. Often, if functional disability is minimal, treatment is not required. A treatment outline is presented in Figure 2 with the dosages of selected drugs listed in Table 5.

Behavioral Techniques and Physical Therapy

Most patients with mild essential tremor are able to minimize functional disability, social embarrassment, and personal injury by using adaptive techniques; these are numerous, and patients can be very creative. Examples include learning to write with the least disabled hand, placing a napkin between cup and saucer to avoid rattling, using a straw to drink fluids, avoiding difficult foods such as soup and spaghetti, using blunt-tip safety scissors, using clip-on ties and laceless shoes, using auto dial on a telephone or having the operator place the call, using voice activation software for computer typing, learning deep breathing and other relaxation techniques, avoiding awkward or uncomfortable situations, and explaining the condition to people they encounter. Physical and occupational therapists can provide suggestions for using wrist weights, plate guards, and other adaptive devices that can provide considerable benefit in activities of daily living.

Medical Therapy

For patients with mild tremor, all that is required is minimizing exposure to tremorogenic factors such as emotional stress, tremorogenic foods, and drugs. Judicious and intermittent administration of a β-blocker or small amounts of alcohol may be useful for special situations of social life. For patients with tremor that significantly interferes with daily activities, long-term pharmacotherapy can be initiated. Propranolol and primidone are currently

the mainstays in the symptomatic management of essential tremor. If propranolol is not tolerated or effective, various agents may be used, including gabapentin, primidone, topiramate, and zonisamide. The primary goal is to minimize drug adverse effects while providing maximal improvement in functional disability. Clinicians should inform patients that although significant benefit may be derived from drug therapy, complete tremor eradication is not a realistic expectation and performance for tasks requiring fine hand manipulations may not improve. β-blockers. Propranolol is currently the only agent that has labeling approved by the United States Food and Drug Administration for the management of essential tremor. The antitremor properties of propranolol, a lipid-soluble, nonselective β -blocker, have been recognized for at least 45 years. [22] The efficacy of propranolol was confirmed in several double-blind, placebo-controlled, crossover trials that supported its status as a mainstay for the symptomatic treatment of essential tremor. [23] Lipid-solubility does not appear to be critical for antitremor activity, because water-soluble agents such as nadolol are also effective. Also somewhat effective are β-1 receptor selective agents (eg, atenolol and metoprolol), but β-2 receptor blockade appears to be required, and the efficacy of selective β-1 receptor blockers may be due to spillover β-2 receptor blockade. In general, a lack of response to propranolol predicts a lack of response to other β -blockers. Approximately 50% to 60% of propranolol-treated patients obtain some improvement in functional disability, although total tremor suppression is rarely achieved. The greatest improvement is observed for hand tremor and the least for head or voice tremor. In patients with underlying cardiovascular disease, abrupt discontinuation of chronic propranolol therapy should be avoided owing to possible rebound adverse cardiovascular events. Relative contraindications to propranolol include severe heart failure, cardiac conduction blocks, and bronchospastic conditions. Although propranolol is not contraindicated in patients with diabetes mellitus, caution is urged because propranolol can inhibit sympathetically mediated hypoglycemic symptoms and the benefits of therapy should be weighed against the risks.

Propranolol therapy may be administered on an as-needed or scheduled basis. When propranolol is administered intermittently, the 20-mg tablets are preferred, with instructions to take a half-tablet to 2 tablets about 30 minutes to 1 hour before social activities or anxiety-provoking events that may result in tremor augmentation. If propranolol is administered as long-term suppressive therapy, treatment should be initiated at 10 mg once daily and titrated (eg, every 3 days) to 20 mg twice daily (or 10 mg twice daily for elderly and frail patients). If needed, the dose may be increased to 240 mg/d (administered in divided doses). After 1 year, tolerance to the antitremor effect of propranolol will develop in 10% to 15% of responders and dosage increases may be required. [24] Doses exceeding 240 mg/d do not appear to confer additionalbenefits.

Fig 2. Outline for the management of essential tremor.
***Note: Vim = Ventralis intermedius nucleus of the thalamus; DBS = deep brain stimulation.**

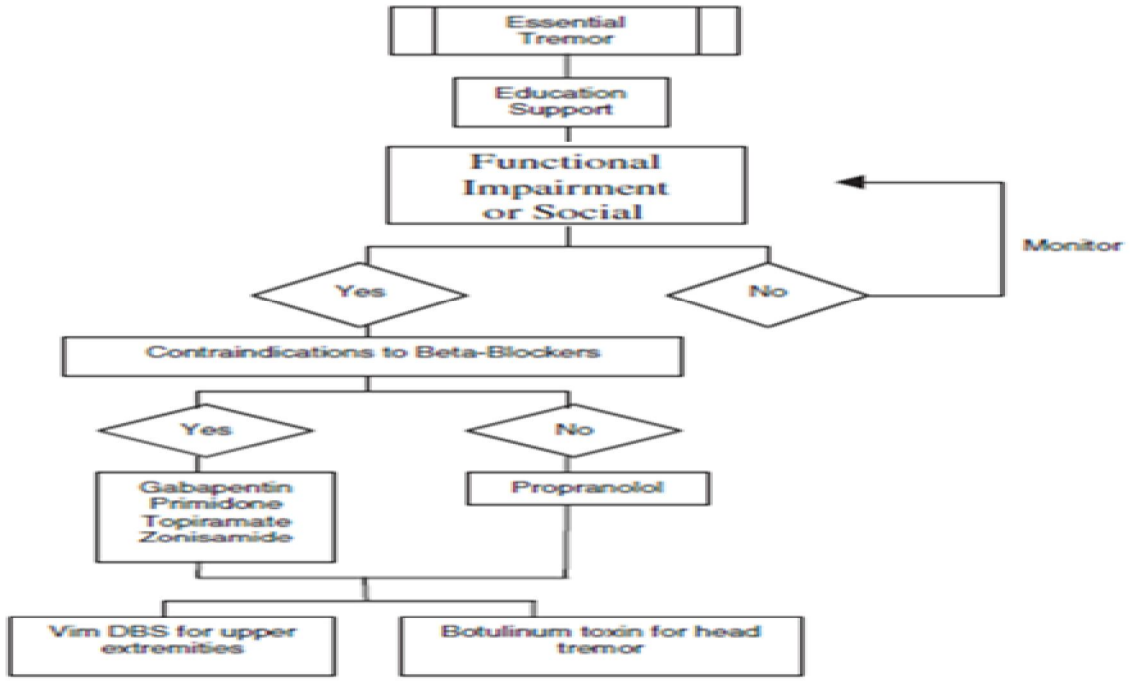


Table. 5
SELECTED DRUGS FOR ESSENTIAL TREMOR

Drug	Dosage
β – blockers	
Propranolol	Initially, 10 mg once daily; may titrate up to 240mg/day.
Tablets: 10,20,40,60,80,90 mg	Initially, 120 mg once daily; may titrate up to 240mg/day.
Propranolol sustained release	Initially, 50 mg once daily; may titrate up to 200mg/day.
Capsules: 60,80,120,160 mg	Initially, 50 mg once daily; may titrate up to 200mg/day.
Metoprolol	
Tablets: 50, 100mg	
Metoprolol extended release	
Tablets: 50, 100, 200mg	
Anticonvulsants	
Primidone	
Tablets: 50, 250 mg	Initially, 12.5 mg at bed time; may titrate up to 250mg/day.
Oral suspension : 50 mg/ml	
Gabapentin	Initially, 300 mg at 3 times daily; may titrate up to 1800mg/day.
Capsules: 100, 300, 400 mg	
Tablets: 600, 800 mg	Initially, 50 mg at bed time; may titrate up to 400mg/day.
Topiramate	
Tablets: 25, 50, 100, 200 mg	Initially, 25 mg at bed time; may titrate up to 200mg/day.
Sprinkle capsules : 15, 25 mg	
Zonisamide	
Capsules : 25, 100 mg	
Benzodiazepines	
Clonazepam	Initially, 0.25 mg once daily; may titrate upto 6 mg/d.
Tablets : 0.5, 1.2 mg	Initially, 1 mg once daily; may titrate upto 10 mg/d.
Diazepam	Initially, 1 mg once daily; may titrate up to 10 mg/d.
Tablets : 2, 5, 10 mg	
Lorazepam	
Tablets : 0.5, 1, 2 mg	

Primidone. Although not FDA-labeled for essential tremor, primidone has been commonly used for the management of essential tremor, with clinical efficacy supported by several double-blind, placebocontrolled, crossover trials. [23] Primidone is metabolized to phenobarbital and phenylethylmalonamide. The exact mechanism of action remains unknown and serum concentrations of primidone, phenylethylmalonamide, and phenobarbital are not correlated with antitremor efficacy. [25] The effectiveness of primidone appears to be similar to that of propranolol. [24] It is less well tolerated, however, and during initiation of therapy, acute adverse side effects, including nausea, ataxia, dizziness, sedation, confusion, and malaise, may be significant. The most frequently reported adverse side effect of long-term therapy is sedation. Rare and serious complications include red cell hypoplasia or aplasia, agranulocytosis, and megaloblastic anemia; therefore, a complete blood count should be performed at baseline and then every 6 to 12 months. Primidone is contraindicated in pregnancy, breastfeeding, and porphyria and caution should be exercised in patients with impaired hepatic or renal function.

Primidone therapy is typically prescribed on a constant-use basis. Because primidone provides a long duration of antitremor activity, only once-daily dosing is required, although divided daily dosing is required for high doses. Strategies to minimize acute reactions include initiating primidone at a subtherapeutic bedtime dose (eg. 12.5 mg). The use of primidone suspension formulation is particularly helpful for administering small doses. Strategies to promote patient adherence to primidone include educating patients on the potential acute side effects and reassuring patients that these reactions will disappear after the first few doses. The dosage should be slowly titrated upward for desired tremor control. Most patients generally will achieve optimal benefit with doses of 250 mg/d or less, but occasionally, dosages exceeding 250 mg/d (in divided doses) may be required.

Gabapentin. The use of gabapentin for essential tremor is supported by clinical studies demonstrating that doses of 1200 to 1800 mg/d are effective and well tolerated as monotherapy for essential hand tremor. [26, 27, 28] Using a randomized, double-blinded, placebocontrolled, crossover design evaluated the efficacy of gabapentin 1800 mg/d (in divided doses) for essential tremor. The treatment duration was 2 weeks, with a 5-day washout. All patients had disabling essential hand tremor (mean tremor duration, 33.4 years), and their mean age was 66.5 years. Renal function parameters were not reported. At the conclusion of the study, scores for tremor severity, motor task performance, and activities of daily living subscales of the tremor rating scale were no different from baseline in gabapentin-treated or placebo-treated patients. However, this study was not designed to assess the efficacy of gabapentin monotherapy, because 70% of the 20 enrolled patients were taking one or more tremorlytic agents (eg, propranolol, primidone, clonazepam, or methazolamide) during the study period.

Gironell et al., used a randomized, double-blinded, placebo-controlled, crossover design to conduct a comparative study of gabapentin and propranolol. Sixteen patients received monotherapy with divided doses of gabapentin (1200 mg/d), propranolol (120 mg/d), and placebo for 14 days, with a 1-week washout period between treatments. The patients were a mean age of 66.9 years, and all of them had postural and kinetic hand tremor (mean tremor duration, 12.2 years). Although none of the patients were currently taking antitremor agents, 10 patients (62.5%) had received propranolol or diazepam in the past. Compared with placebo, treatment with gabapentin and

propranolol was associated with statistically significant improvements in all subscales of the tremor rating scale (ie, tremor severity, motor task performance, activities of daily living, and patient's subjective assessment). Although not statistically significant, tremor-rating scores were slightly better for propranolol than gabapentin; however, when asked which treatment was more effective, 50% of patients indicated gabapentin, 38% propranolol, and 12% both. About 38% of patients did not respond to either gabapentin or propranolol, and approximately 19% responded positively to placebo. In a randomized, double-blinded, placebocontrolled, crossover, dose-escalation study, Ondo et al evaluated the efficacy of gabapentin at 1800 mg/d and 3600 mg/d for symptomatic control of essential tremor. All patients had hand tremor. The mean age of the 20 patients who completed the study was 69.9 years, and the mean tremor duration was 29.1 years. This study was not designed to assess the efficacy of gabapentin monotherapy, because most patients were also taking 1 or more tremorlytic agents (ie, primidone, propranolol, benzodiazepine). After a 1-week titration phase, patients were maintained on gabapentin (1800 mg/d) or placebo, in divided doses, for 2 weeks and then evaluated. Patients were then titrated up over another week to achieve 3600 mg/d. After 2 weeks at 3600 mg/d 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. Gabapentin treatment at 1800 mg/d was associated with statistically significant improvements in scores for activities of daily living and pouring water; 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 randomized, double-blind, placebo-controlled trials, suggests that short-term treatment with gabapentin (1200-1800 mg/d) is well tolerated in elderly patients with essential tremor and is effective as monotherapy for essential hand tremor. As add-on therapy to standard antitremor agents, the benefits are less robust and more variable. Gabapentin is associated with few drug–drug interactions, and long-term therapy appears well tolerated in both young and elderly patients, although ataxia, irritability, sedation, and weight gain may be problematic. Additional clinical studies are required to determine the true benefit of gabapentin; however, owing to a favorable safety profile and ease of use, gabapentin may be considered an alternate agent for the management of essential tremor and may also be used as an add-on agent if symptomatic relief is insufficient despite maximally tolerated doses of concurrent antitremor therapy.

Topiramate. The safety and efficacy of topiramate for essential tremor has been evaluated in several double-blinded, placebo-controlled trials. [29, 30] In a placebo-controlled crossover study, Connor evaluated topiramate (up to 400 mg/d) as monotherapy or adjunctive treatment of essential tremor in 24 patients. [29]The mean age of patients was 63.4 years, and 12 patients were receiving stable dosages of 1 or more of the following agents: primidone, a β-blocker, theophylline, a benzodiazepine, cyclobenzaprine, carbamazepine, amitriptyline, carisoprodol, or gabapentin. After the 2-week treatment phase, topiramate (mean dose, 333 mg) was associated with significantly greater reductions from baseline in scores for tremor severity as well as specific motor tasks and tremor-associated functional disabilities. The most common adverse events were appetite suppression, weight loss, and paresthesias. In a 24-week, randomized, double-blind, placebocontrolled, parallel-design trial, Ondo etal evaluated topiramate in 208 patients with moderate to severe essential tremor. The topiramate target dose was 400 mg/d and could be used as monotherapy or as an adjunct to another antitremor agent. Improvement in tremor rating scores were significantly better in the topiramate group (mean final dose, 292 mg /d) than the placebo group, and topiramate was associated with greater improvement in function (such as motor tasks, writing, and speaking) and disability. The most common adverse effects in topiramate-treated patients were paresthesia, nausea, concentration difficulty, and somnolence. In a 6-week, double-blind, placebo-controlled, crossover study, Frima and Grunewald evaluated topiramate in 13 patients with essential tremor. Their results showed no therapeutic benefit of topiramate compared with placebo. The investigators noted that their study might have been underpowered to detect a statistically significant difference between treatment and placebo. Additional clinical studies are required to determine the true benefit of topiramate in essential tremor; however, the drug may be considered an alternate agent for its the management and may also be used as an add-on agent if symptomatic relief is insufficient despite maximally tolerated doses of concurrent antitremor therapy. The development of adverse side effects is a limitation of topiramate therapy. Zonisamide has been studied for essential tremor. [31, 32] Morita et al evaluated zonisamide and arotinolol (a peripherally acting β-blocker approved for use by the Ministry of Health, Labor and Welfare in Japan for essential tremor) in a randomized, crossover study of 14 patients (mean age, 68.4 years; mean tremor duration, 8.3 years). After 2 weeks of treatment at the maximally tolerated dose, there were significant improvements with zonisamide (mean dose, 136 mg /d) and arotinolol (mean dose, 11.4 mg/d) treatment compared with baseline. For the upper extremities, there was no significant difference in the antitremor effect between zonisamide and arotinolol; however, zonisamide was found to be more effective for tremors affecting the voice, face, tongue, and head. Zonisamide was well tolerated, with mild sleepiness reported in approximately half of patients. In a 4-week, double-blinded, placebo-controlled, randomized study, Zesiewicz et al evaluated the efficacy and tolerability of zonisamide in 20 patients (mean age, 60 years), 40% of whom were already taking an agent for essential tremor at study entry. Of the patients who were not taking antitremor therapy, all patients reported previously taking agents that improved their tremor but discontinued them in the past owing to adverse side effects. Zonisamide was initiated at 100 mg/d and increased to 200 mg/d after 2 weeks. After 4 weeks, the mean zonisamide dose was 160 mg/d. The clinical tremor rating scores did not significantly improve, but

tremor amplitude, as assessed by accelerometry, significantly improved in the zonisamide group compared with the placebo group. Subjectively, 60% of zonisamide-treated patients felt that their tremor was unchanged, and the remaining patients felt that their tremor was "minimally improved." Zonisamide was well tolerated, but 30% of patients quit the study because of adverse side effects (fatigue, headache, paresthesias) at 100 mg/d. Additional clinical studies are required to determine the true benefit of zonisamide for the treatment of essential tremor. However, the drug may be considered an alternate for the management of essential tremor and may also be used as an add-on agent if symptomatic relief is insufficient despite maximally tolerated doses of concurrent antitremor therapy.

Pregabalin. Zesiewicz et al performed a 6-week, double-blinded, placebo-controlled, randomized study in 22 patients (mean age, 54 years; mean duration of essential tremor, 17.6 years) to evaluate the efficacy and tolerability of pregabalin in treating essential tremor. Approximately 60% of patients were already receiving an agent for tremor at study entry. The pregabalin was initiated at 50 mg/d and escalated by 75 mg/d every 4 days to a maximum dose of 600 mg/d. At a mean dose of 286 mg/d, pregabalin-treated patients experienced a significant reduction in accelerometry-measured tremor amplitude compared with placebo-treated patients (mean age, 60.4 years; mean duration of essential tremor, 18.3 years). Clinical scores for action tremor also improved in the pregabalin group compared with the placebo group. Subjectively, two thirds of pregabalin-treated patients felt that their tremor improved. Pregabalin was well tolerated, but 27% of patients discontinued the study because of adverse side effects. Additional clinical studies are required to confirm the results of this pilot study and determine the true benefit of pregabalin for the treatment of essential tremor.

Alcohol. Clinicians and patients have long recognized the antitremor activity of alcohol in essential tremor. One study found 67% of ET patients were alcohol-responsive. [33] Studies using positron emission tomography reveal that alcohol reduces the cerebellar hyperactivity in essential tremor. [34] Although not confirmed, GABA may mediate this. A glass of wine or a light cocktail is often enough to attenuate the tremor for up to an hour; however, a rebound exacerbation of tremor often occurs. Although routine ingestion of alcohol is not recommended, many patients do benefit from the sparing and responsible use of alcohol before selected activities such as a social dinner.

Benzodiazepines. Benzodiazepines (eg, alprazolam, clonazepam, diazepam, lorazepam) may be considered as adjunctive or add-on agents for tremor control. [23] The antitremor mechanism of action is unknown but may be related to augmentation of GABA activity resulting from interaction at the benzodiazepine/GABA receptor- chloride channel complex. [35] In addition, these agents may also reduce tremor triggered by emotional stress or anxiety. Clonazepam is particularly effective for orthostatic tremor ("shaky leg syndrome") a rare variant of essential tremor. [36] Because of their anxiolytic properties, benzodiazepines may be more beneficial for the frequently anxious patient. Small doses may be used judiciously and administered 30 minutes to 1 hour before an important social event. However, owing to central nervous system adverse effects, including sedation, confusion, and memory loss, and an increased risk of falls, benzodiazepines must be used with caution in elderly patients. Some clinicians prefer lorazepam because of its milder sedation profile.

Botulinum toxin. Botulinum toxin has become a powerful therapeutic tool in certain hyperkinetic movement disorders, including essential tremor. Because voice and head tremors are often resistant to oral medications, botulinum toxin therapy may be useful for these tremors. Seven serologically distinct neuroparalytic toxins (type A through G) have been derived from the Clostridium botulinum bacteria, and although all have similar molecular structures, each differs in pharmacologic characteristics. In the United States, botulinum toxin type A (BTX-A) and type B (BTX-B) are available. Three steps are involved in the paralytic mechanism of BTX-A. [37] The toxin is composed of 2 chains, a heavy and light chain, linked by a disulfide bond. First, the heavy chain binds to a specific membrane acceptor on the presynaptic cholinergic terminal of the neuromuscular junction. Second, endocytosis of the light chain occurs. And 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 the 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; for example, 10 U of BTX-A can diffuse up to 4.5 cm. Once paralyzed, nerve terminals will begin to form temporary neuronal sprouts, and eventually, motor neuron function is completely restored with the reinnervation of the parent terminal and degeneration of auxiliary sprouts. Typically, a single treatment involves multiple point injections, and retreatment is required no sooner than every 3 to 4 months to minimize the development of neutralizing antibodies. The most common adverse effect to be expected is focal weakness due to unwanted diffusion of toxin into adjacent muscles; for example, injections in the wrist are associated with hand weakness, and laryngeal injections are associated with dysphagia. The lowest effective dose must be used to produce the desired tremor reduction with minimal focal weakness, which can negate the functional benefits of therapy. Relative contraindications to botulinum toxin therapy include myasthenia gravis, postpolio syndrome, Eaton-Lambert syndrome, motor neuron disease, aminoglycoside antibiotics, and pregnancy.

Summary of pharmacologic therapy. For patients with disabling tremor, administration of propranolol is a suitable first-line therapy owing to its good long-term efficacy and tolerability. In the presence of contraindications or

intolerance to β-blocker therapy, other agents such as gabapentin, primidone, topiramate, and zonisamide, may be tried. Therapy should be initiated at low doses and gradually titrated upward to achieve the optimum balance between maximal efficacy and minimal adverse effects. If monotherapy does not produce desired outcomes, the addition of a second agent may be helpful. Small doses of alcohol or a benzodiazepine may also be helpful as intermittently administered adjunctive agents. Although complete tremor eradication is unrealistic, pharmacotherapy will benefit most patients with disabling essential tremor of the hands; unfortunately, head and voice tremors are less responsive. For patients with medication-refractory head or voice tremor, chemical denervation with localized injections of BTX-A may be an option but must be performed by a trained and experienced specialist to minimize adverse side effects.

Surgical Interventions

Surgical interventions should be considered for selected patients with disabling tremor that is not adequately controlled with pharmacotherapy. The 2 proven techniques are stereotactic thalamotomy and chronic thalamic deep brain stimulation (DBS). [38] Both procedures, when successful, allow patients to become virtually medication-free. Surgical intervention is contraindicated in patients who are poor surgical candidates owing to underlying medical conditions and in patients with marked cognitive impairment. Deep brain stimulation of the thalamic ventralis intermedius is currently favored over thalamotomy owing to advantages related to the nonablative and adjustable nature of DBS therapy. These include reversibility due to minimal lesioning of the ventralis intermedius and the ability to change impulse variables to minimize side effects and increase efficacy. An additional benefit of thalamic DBS includes 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 may involve suppression of tremor by providing chronic artificial "neural noise" that essentially disrupts the cyclic activity within the motor circuit pathway. [39] After thalamic DBS, health-related quality of life, including disability in activities of daily living and social life, are significantly improved. [40] However, DBS benefits on the kinetic tremor component of essential tremor appear to wane with time. [41] Midline symptoms such as voice and head tremor are also improved, although less predictably than with hand tremor.

Conclusion

Essential tremor is a common form of pathologic tremor and is associated with degrees of disability (psychosocially and functionally). Pharmacologic therapy should be initiated in an attempt to achieve optimal tremor control with a minimum of side effects. In general, the first agent is propranolol. Other agents that have also demonstrated efficacy include gabapentin, primidone, topiramate, and zonisamide. Surgical interventions, such as DBS of the ventralis intermedius, are very effective but are generally considered for patients with severe upper extremity tremor not adequately controlled with pharmacotherapy.

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