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Pharmacotherapy of Essential Tremor

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ABSTRACT: Essential tremor (ET) is a common movement disorder but its pathogenesis remains poorly understood. This has limited the development of effective pharmacotherapy. The current therapeutic armamentaria for ET represent the product of careful clinical observation rather than targeted molecular modeling. Here we review their pharmacokinetics, metabolism, dosing, and adverse effect profiles and propose a treatment algorithm. We also discuss the concept of medically refractory tremor, as therapeutic trials should be limited unless invasive therapy is contraindicated or not desired by patients.

KEYWORDS: essential tremor, pathogenesis, propranolol, primidone, topiramate, gabapentin, pregabalin

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Introduction

Essential tremor (ET) is one of the most common neurologic movement disorders affecting 0.5% to 5% of the general population.[1,2] The relatively high variability of estimated prevalence reflects the lack of uniform diagnostic criteria or a reliable biomarker. In spite of these limitations, clinical observation has led to clinical trials demonstrating effectiveness of several pharmacological classes of medications in controlling tremor. Medications targeting ET may be classified as first line (propranolol and primidone) and second and third line therapies based on the level of clinical evidence and risk-benefit ratio. Nonpharmacological therapies, including chemodenervation with botulinum toxin and surgical approaches, will not be reviewed here.

Essential Tremor: Diagnosis and Differential Diagnosis

The diagnosis of ET remains exclusively clinical and several sets of diagnostic criteria have been proposed. The consensus criteria of the Movement Disorders Society's Tremor Investigation Group are probably most widely used.[3] Occurrence of bilateral, largely symmetrical postural tremor with or without kinetic tremor affecting hands or forearms lasting for more than 5 years and presenting with a gradual onset is typically considered definite ET. Tremor may affect also other body segments, including neck or vocal cords. Recent exposure to tremorogenic drugs, significant traumatic brain injury, and a convincing evidence of sudden onset or stepwise deterioration are the most important exclusion criteria for ET (Table 1).

ET has been traditionally viewed as a monosyptomatic disorder, where tremor is the only clinical sign with the exception of Froment's sign, "cog wheeling" on passive manipulations of affected limbs.[4,5] The absence of additional signs or symptoms is, therefore, helpful to distinguish ET from other disorders causing mostly action (postural and kinetic) tremor. However, even patients with "pure" ET commonly develop signs of mild but definitive cerebellar dysfunction, including midline ataxia with a wide-based gait and impaired tandem gait.[6,7] Cerebellar hemispheric dysfunction is also common, and many patients in the advanced stages of the disease manifest intention tremor, defined as a crescendo increase in tremor amplitude during a visually guided movement towards the

Table 1. Differential diagnosis of common types of tremor.

CHARACTERISTICS	ESSENTIAL TREMOR	PARKINSON'S DISEASE	CEREBELLAR TREMOR	DRUG-INDUCED TREMOR	PSYCHOGENIC TREMOR
Arm position	Postural and kinetic tremor, rest tremor in advanced ET	Rest tremor, postural and kinetic in some patients	Kinetic tremor Postural tremor in some patients	Postural and kinetic tremor	Variable
Affected body parts	Arms, legs, neck, vocal cords	Arms, legs, chin	Arms, legs infrequently, neck	Arms, other body segments may be affected in severe cases	Variable
Frequency	5–10 Hz	3–5 Hz	2–7 Hz	5–12 Hz	2–12 Hz
Amplitude	Small in early stages, increases with progression (and lower frequency)	Small to moderate	Moderate to large	Small to moderate	Variable
Symmetry	Typically bilateral, symmetric, about 10% unilateral tremor	Asymmetric onset typical, asymmetry is commonly preserved in bilateral disease	Bilateral in degenerative ataxias, unilateral in acquired ataxias (stroke, multiple sclerosis)	Bilateral and symmetric	Variable
Associated neurologic signs	Subtle midline cerebellar signs May coexist with focal dystonia	Rigidity, bradykinesia, postural instability	Ataxia, oculomotor abnormalities, dysarthria	Typically absent	Variable
Additional features	Rest tremor persist during walking	Symptoms are responsive to dopaminergic therapy	Intention tremor Pyramidal and extrapyramidal features may be present in neurodegenerative ataxias	Drug-induced parkinsonism in antidopaminergic agents	Abrupt onset, distractibility, irregular, inconsistent, suggestibility, entrainment

end of the task.[2,8] This is the result of abnormal activation of antagonistic muscles stopping the movement as it approaches the target. These subtle cerebellar signs further support the role of the cerebellum in ET pathogenesis.

Some variants of ET may also be associated with other neurologic manifestations. The association of tremor and dystonia is perhaps the most confusing clinical scenario and the term "dystonic tremor" has been inconsistently applied in the medical literature.[9] Even though controversies persist, dystonic tremor should be reserved to describe the coexistence of tremor and dystonia in the same body segment. Dystonic tremor is further characterized by directionality, with the increasing amplitude in one particular direction, and by the null point phenomenon, resulting in diminished or absent tremor in certain limb positions.[10,11] Overlap of arm postural and/or action tremor with dystonia affecting other body segments, such as blepharospasm of cervical dystonia, probably represents a variant of ET and should not be classified as dystonic tremor.[12] This distinction is clinically relevant because dystonic tremor usually does not respond to typical ET medications, and its pharmacotherapy is similar to the treatment of generalized or focal dystonia.

Rest tremor is one of the hallmarks of Parkinson's disease (PD), and its association with rigidity and bradykinesia typically makes the distinction of PD and ET quite straightforward.[2] However, rest tremor can be present in ET patients with advancing disease and approximately one quarter of ET patients without clinical or pathologic signs of PD exhibit rest tremor together with kinetic tremor.[13–15] The presence of rest tremor during walking can be helpful to support the diagnosis of PD because rest tremor associated with ET tends to disappear with gait.[16] Dopamine transporter scintigraphy (DAT) using single-photon emission computed tomography (SPECT) imaging can confirm intact presynaptic nigrostriatal dopaminergic innervations in these patients.[17] Normal DAT imaging in patients with rest tremor can be also classified as SWEDDs (subjects with scans without evidence of dopaminergic deficits), but these patients tend to have dystonic tremor, and it has been suggested that SWEDDS represent a subtype of dystonia rather than ET.[18,19]

Asymmetry of the disease is another common feature suggesting the diagnosis of PD.[4] Indeed, diagnostic criteria for definite ET require the presence of symmetrical postural and kinetic tremor.[3] However, strictly unilateral kinetic tremor may be found in 10% to 20% of patients with presumed ET, and, thus, the involvement of only 1 arm does not rule out the diagnosis of ET.[20] Another confounding factor is the actual overlap of both disorders, and these patients tend to have a tremor-dominant PD subtype.[21,22] There is an ongoing debate whether this is by chance or ET represents a risk factor for PD.[23,24]

ET needs to be differentiated from enhanced physiologic tremor, characterized by predominantly postural tremor with

a low amplitude and high frequency.[25] This may not represent any central nervous system dysfunctions, as it is experienced by almost every individual under certain circumstances, such as anxiety or strenuous physical activity.[26] However, some patients with ET may have prodromal signs more consistent with enhanced physiologic tremor before developing definite ET.[27] The intensity of enhanced physiologic tremor may be bothersome for some patients, and, in general, if provoking circumstances cannot be avoided and treatment is warranted, the same medications used for ET are useful for enhanced physiologic tremor. Application of small weights from 0.5 to 1.5 pounds to the affected limb will result in reduction of amplitude and frequency in enhanced physiologic tremor, while it remains relatively constant in ET.[28,29]

Exposure to tremorogenic drugs may mimic ET, and a long list of tremor-inducing medications include tricyclic, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, neuroleptics, β-2 agonist, theophylline, caffeine, cyclosporine A, tacrolimus, valproic acid, lithium, nicotine, pseudoephedrine, and levothyroxine.[30–34] However, given the widespread use of some of these medications, many ET patients may be exposed to them as well. It needs to be determined whether these medications cause or exacerbate tremor, or do not affect it at all because not every subject develops tremor when treated with potentially tremorogenic medications. Temporal association between newly prescribed medications and the onset of tremor or its significant worsening suggests medication-induced tremor. When medication is suspected as a likely culprit, discontinuation should be attempted to confirm this causality. This is not always feasible, and these patients may be treated with the same medications used for ET if clinically indicated. Likewise, endocrine (hyperthyroidism, hyperparathyroidism, and hypoglycemia) or metabolic abnormalities (hyponatremia, hypomagnesemia, and hypocalcemia) may induce similar type of tremor, and laboratory evaluation is warranted in patients with the sudden onset tremor or with its significant fluctuations.

Cerebellar tremor, also known as Holmes' or outflow tremor, is characterized by a low frequency high amplitude tremor that is mostly generated in proximal limb segments during postural or kinetic tasks.[35,36] Intention tremor is another feature of cerebellar tremor.[37] As previously mentioned, some patients with an advanced ET develop characteristics of cerebellar tremor, but other signs of cerebellar dysfunction, such as limb dysmetria, dysdiadochokinesis, gaze-evoked nystagmus, and cerebellar dysarthria are absent in ET.[7,8] Wing-beating proximal tremor, appearing while holding semiflexed outstretched arms may also resemble cerebellar tremor but is most commonly seen with advanced Wilson's disease.[38,39] Wilson's disease is caused by copper toxicity, and, in earlier stages, tremor may resemble typical ET. The diagnosis should be considered even in familial tremor patients younger than 40 years, particularly if additional neurologic signs, such as dysarthria or Parkinsonism, are present. Elevated 24-hour urine copper is diagnostic of Wilson's disease.[38]

Psychogenic tremor is the most common nonorganic movement disorder and occasionally can be confused with ET.[40] Psychogenic tremor can occur at rest, with posture, or during kinetic tests. Its diagnosis is based on a sudden onset, irregular and inconsistent oscillatory movements with distractibility and suggestibility. Entrainment, defined as changing frequency of psychogenic tremor in adaption to voluntary tasks with determined frequency and performed with controlateral arm such as tapping in time to a metronome, can be very helpful in differentiation from ET.[41] Multiple somatization signs, previous psychiatric diagnoses, and possible secondary gain can be also helpful for the diagnosis of psychogenic tremor.[42]

Essential Tremor: Pathogenesis

Although the pathophysiology of ET remains unknown, abnormal oscillations in the central nervous system have been suggested as crucial to the pathogenesis, as the clinical presentation of tremor involves a rhythmic motor activity.[43,44] Another question is whether ET belongs to the family of neurodegenerative disorders or is due to functional aberrations in the structures serving as central oscillators.[45,46] The olivocerebellar circuit has been implicated in the generation of abnormal synchronizations in the inferior olivary nucleus.[47–49] These are then projected through the cerebellum and its deep nuclei to the motor neurons.[50] Patients with ET have positron emission tomography (PET) evidence for an increased glucose uptake in the ollivocerebellar loop and structural lesions in these regions, including the thalamus and pons, may reduce severity of ET.[51–53] Similar abnormalities may be induced by the tremorigenic β-carboline alkaloids harmaline and harmine.[54,55] Interestingly, ET patients tend to have higher serum levels of harmane, a precursor to harmine.[56] This elevation does not correlate with the dietary intake of red meat, the main nutritional source of β-carbolines, suggesting the possibility of abnormal harmane metabolism in ET.[57,58]

The functional nature of ET has been historically supported by the relative lack of obvious morphologic changes in ET.[45,59] This has been challenged by recent descriptions of structural and biochemical abnormalities in postmortem studies of ET brains.[60] Neurodegenerative changes are most pronounced in the cerebellum with a selective loss of Purkinje cells and signs of their axonal swelling and degeneration with formation of axonal torpedoes.[61] Furthermore, the dentate nucleus in ET exhibits loss of the γ-aminobutyric acid (GABA) receptors that correlate with the duration of the disease.[62] Additional pathologic changes include Lewy bodies in the brainstem structures, such as locus coeruleus with sparing of the substantia nigra, clearly separating these findings from idiopathic Parkinson's disease.[63] Even though there is disagreement about the specificity of these findings, these pathologic changes further support the role of cerebellar degeneration in ET.

A positive family history of ET can be found in 30% to 80% of all affected patients, suggesting a strong genetic contribution to its etiology.[64] Linkage analysis using parametric methods have identified several putative genetic loci on chromosomes 3q13, 2p24.1, and 6p23, with additional evidence for further genetic heterogeneity.[65–67] Yet, the discovery of disease-causing genes within these loci is still lacking. Two non-synonymous amino acid changes in the D3 dopamine receptor (*DRD3*) and in the HS1-Binding protein (*HS1BP3*) have been proposed as causative genes accounting for positive linkage to the ETM1 and ETM2 loci, respectively.[68,69] Unfortunately, subsequent analyses clearly determined that both are common polymorphisms with allelic frequencies and did not differ between patients with ET and normal, healthy controls.[70,71] At present, only a few susceptibility genes have been identified using genome-wide association approaches with the leucin-rich repeat and Ig domain containing NOGO receptor gene (*LINGO1*) gene being the most reliably replicated.[72,73] This class of genes is not felt to be directly causative and cannot fully account for a familial aggregation of ET. Whole-exome sequencing identified apparent disease-causing mutations in the fused in sarcoma *(FUS*) gene.[74] These mutations are rare in familial ET but overall lend additional support to the hypothesis that some forms of ET are the result of a neurodegenerative processes, as *FUS* are also associated with rare forms of familial amyotrophic lateral sclerosis and frontotemporal dementia.[75]

Future insights into the pathogenesis of ET will undoubtedly widen our therapeutic options. At this point, detected morphological and biochemical changes support the role of GABA and glutamate receptor alterations in ET pathogenesis. Further research is likely to reveal more neuromodulators of tremor that can be explored in ET pharmacotherapy.

Essential Tremor: Pharmacotherapy

In spite of mounting new insights into ET pathogenesis, its therapy remains purely symptomatic, and virtually all medications used for the reduction of tremor have initially been developed and approved for other indications. Antitremorogenic action of these compounds was discovered incidentally. As of 2013, only propranolol has been approved by the US Food and Drug Administration (FDA) for the treatment of ET in 1967.[76] There are a number of other agents supported by various levels of clinical evidence that have become standard of care for the symptomatic control of ET. We divide available medications into first, second, and third line therapies (Table 2). First line therapy is either approved by the FDA or supported by double-blinded, placebo controlled studies that meet criteria for the class I evidence as defined by the US Preventive Service Task Force, with primary outcome and exclusion/inclusion criteria clearly defined, adequate accounting for potential bias due to dropouts and crossovers, and sufficient baseline characteristics are described for both treated and placebo groups. Second line therapy is supported by double-blinded, placebo controlled trials that do not meet other requirements for the class I evidence studies, and third line therapies are based on open-label studies or case series.[77–79]

First Line Therapies

Propranolol. *Mechanism of action.* Propranolol is a non-selective β-adrenergic receptor antagonist possessing no other autonomic nervous system activity.[80] The specific mechanism of propranolol's antitremor effects has not been fully established. Although it is widely accepted that ET generated within the central nevous system (CNS), blocking effects of peripheral noncardiac beta-2 receptors located in the muscle spindles are most likely responsible for the efficacy of propranolol in ET.[81] Less lipophilic beta blockers are also effective in suppressing ET (see below), further supporting a peripheral mechanism for this class. Epinephrine upregulates the sensitivity of muscle spindles, leading to increased rhythmic afferent activity and, thus, higher synchronization of afferent signals and enhanced reflex activity.[82] Propranolol is highly lipophilic and easily penetrates the blood-brain barrier (BBB), and additional central activity has not been conclusively ruled out.[83]

Pharmacokinetics and metabolism. Propranolol is almost completely absorbed after oral administration.[76] It undergoes high first-pass hepatic metabolism and, on average, only about one-quarter of administered drug reaches the systemic circulation. Time to peak plasma concentration (T_{max}) is 1 to 4 hours and the elimination half-life ($t_{1/2}$)is 3 to 6 hours. Propranol is highly protein bound, and a high intake of protein can increase its bioavailability up to 50% with no change in T_{max} or $t_{1/2}$. Propranolol is metabolized through aromatic hydroxylation, N-dealkylation, and direct glucuronidation. CYP2D6, CYP1 A2, and CYP2C19 play a role in its metabolism, even though various polymorphisms in CYP2D6 (poor, intermediate, and extensive metabolizers) do not significantly alter plasma levels or $t_{1/2}$. Most metabolites are eliminated through the urine.[76,83]

Clinical studies, efficacy, and safety. The effect of propranolol on tremor was first shown in 1965, and, since then, several controlled trials have confirmed the efficacy of this medication in ET.[84–92] The daily dose varied from 60 to 800 mg/day with an average dose of 182.5 mg/day.[85,87] There is no convincing evidence that doses higher than 320 mg/day provide any additional benefit.[87,88] The proportion of subjects responding varied from 50% to 70%, and the average tremor reduction was about 50% when compared with placebo. Thus, patients with severe baseline tremor may have clinically insufficient functional outcome. Propranolol is also available in a long-acting formulation, and comparative trials have shown equal safety and efficacy profiles.[85,86] Efficacy of both forms of propranolol is established only for tremor affecting the upper extremities, while head tremor response is quite limited. Propranolol is also beneficial in treatment of exaggerated physiological tremor that cannot be reliably distinguished from early stages of ET.

Table 2. Overview of pharmacological agents for essential tremor.

PHARMACOLOGICAL AGENT	LINE OF THERAPY	INITIAL DOSE	TYPICAL DAILY DOSE	TYPICAL THERAPEUTIC RESPONSE RATE AND DROPOUT RATE	MOST COMMON ADVERSE EFFECTS
Propranolol	First line	20 mg BID 10 mg BID in elderly patients	60 to 320 mg/day BID dosing for short-acting or QD dosing for propranolol LA	50%–70% response rate with average 50% improvement of tremor dropout rate 20%	hypotension, bradycardia, fatigue, erectile dysfunction, drowsiness, exertional dyspnea seen in 60% of patients
Primidone	First line	50 mg QHS 25 mg QHS in elderly patients	250 to 750 mg/day QHS dosing, higher doses given as BID	30%–50% response rate average 50–70% of tremor improvement dropout rate 20%–30%	sedation, fatigue, dizziness, ataxia, confusion, nausea, flu-like symptoms seen in 22%–72% of patients
Gabapentin	Second line	300 mg TID 100 mg TID in elderly patients	1200 to 3600 mg/day TID dosing	~30% response rate with 30%–40% tremor improvement dropout rate 10%	sedation, dizziness, ataxia, nausea, weight gain in 30%–40% of patients
Pregabalin	Second line	50 mg BID 25 mg QD in elderly patients	150 to 600 mg/day BID dosing	30%–50% response rate with 30%–40% tremor improvement dropout rate 10%	sedation, dizziness, ataxia, nausea, weight gain frequency and dropout rates similar to gabapentin
Topiramate	Second line	25 mg BID 25 mg QHS in elderly patients	150 to 300 mg/day BID dosing	30%–40% response rate with 20%–37% tremor improvement dropout rate 30%	paresthesias, concentration difficulties, nausea, somnolence, fatigue, malaise, dyspepsia, weight loss, confusion, abnormal taste perception, acute angle closure glaucoma seen in 50% of patients
Clonazepam	Second line	0.5 mg QD 0.25 mg QD in elderly patients	0.5 to 4 mg/day BID dosing	50%–75% response rate with 30%–50% improvement of tremor Dropout rate was <10% in small ET trials	sedation, cognitive impairment, tolerance, dependency, abuse, withdrawal symptoms side effects seen in 50% patients with ET
Alprazolam	Second line	0.25 mg QD 0.125 mg QD in elderly patients	0.125 to 3 mg/day TID dosing	75% response rate with 50% tremor reduction Dropout rate was <10% in small ET trials	sedation, cognitive impairment, tolerance, dependency, abuse, withdrawal symptoms frequency of side effects similar to clonazepam
Atenolol	Second line	50 mg QD	50 to 150 mg/day QD dosing	only patients responding to propranolol improve with 37% tremor reduction dropout rate similar to other β-blockers	similar to propranolol but without possible bronchospasm
Metoprolol	Second line	50 mg BID 25 mg BID in elderly patients	100 to 300 mg/day BID dosing	similar to propranolol but long-term efficacy is not maintained dropout rate similar to other β-blockers	similar to propranolol
Nimodipine	Third line	30 mg QD	120 mg/day QID dosing	50% tremor reduction in more that 50% patients responding but overall number of reported patients is very small and dropout rate is unknown	hypotension, edema, headaches in 10%–20% of patients
Clozapine	Third line	25 mg QD 12.5 mg QD in elderly patients	25 to 75 mg/day QD dosing	50% tremor reduction with 75% response rate in small clinical trials Dropout rate has not been determined for ET patients	sedation, orthostatic hypotension, tachycardia, syncope, weight gain, bone marrow suppression with agranulocyosis Side effects seen in approximately 50% patients but they tend to be transient Overall risk of neutropenia is 3% but it was not observed in ET trials

Adverse effects (AE) associated with propranolol are seen in up to 66% of treated subjects, but they tend to be mild due to the exclusion of patients with contraindications from these trials. The most common AE is lightheadedness with symptomatic hypotension and bradycardia, fatigue, erectile dysfunction, drowsiness and sedation, exertional dyspnea, and headaches. Dropout rates in clinical trials due to significant side effects were below 20%, and dropouts were generally seen with daily doses more than 120 mg.[85,86]

Absolute contraindications include cardiogenic shock or unstable congestive heart failure, sinus bradycardia, and greater than first degree atrioventricular block, asthma, and a known hypersensitivity to propranolol. This medication can be cautiously used in a stable congestive heart failure with left ventricular systolic dysfunction.[76] Concomitant use of propranolol and calcium channel blockers should be avoided. Propranolol may also block the symptoms of hypoglycemia, such as tachycardia and blood pressure changes, in patients with diabetes mellitus. Abrupt discontinuation of propranolol may exacerbate angina pectoris, and, in some cases, acute myocardial infarctions have been reported. Thus, the dose should be gradually reduced. Propranolol is classified by the US FDA as pregnancy risk category C.

Dosing and clinical approach. Even though the FDA drug monograph states the starting dose of 40 mg twice a day, generally it is prudent to start somewhat lower at 20 mg BID and titrate the dose based on efficacy and tolerability. The initiation dose in the geriatric population should be even lower, and 10 mg twice a day may be better tolerated in these patients. The doses above 120 mg may be administered as three times a day dosing. The target dose varies, and, again, therapeutic goals should be discussed before the initiation of pharmacotherapy. Propranolol LA can be directly started at 80 mg/day dose, but it may be sensible to start a regular form and when the stable dose is achieved, switch to a long-acting form with a one-to-one conversion ratio. Direct comparison of both forms of this medication showed that 87% treated patients preferred a long acting form, and its usage may improve the overall adherence. Patients with a mild tremor that is frequently aggravated by stress or anxiety may be initially treated on an as needed basis with a single dose of 10 or 20 mg.

Other beta-adrenergic receptor antagonists. Even though only propranolol is supported by sufficient data to consider it as a first line therapy, other nonselective and selective β-blockers have been trialed in ET.[93] None of these is FDA approved for tremor control. Nadolol is a nonselective β-blocker, and, unlike other members of this therapeutic class, it does not undergo hepatic metabolism and is renally excreted unmetabolized. It has also the longest $t_{1/2}$ up to 24 hours, allowing once-daily dosing. A small study of 10 ET subjects showed that doses of 120 or 240 mg were effective but only in patients who previously responded to propranolol.[94] Sotalol is another nonselective β-blocker that was directly compared with metoprolol and atenolol but not propranolol.[95] Efficacy of sotalol was observed at doses ranging from 75 to 200 mg/day using twice a day dosing schedule. AE were seen in about one-quarter of patients. Reduced alertness was the most common side effects. This was somewhat unexpected as sotalol is much less lipophilic than propranolol and, thus, theoretically, should have a limited penetration of the blood-brain-barrier (BBB).

Atenolol is a competitive, β-1 selective (cardioselective) adrenergic antagonist that may be useful for tremor control in patients with an increased risk of bronchospasms. It is minimally metabolized, renally eliminated, and has a longer plasma half-life allowing once a day dosing. Due to its low lipid-solubity, atenolol has a lower potential for inducing central nervous side effects than propranolol. Higher doses result in attenuated or lost selectivity for the β-1 receptors. Atenolol produced a 37% reduction of tremor at doses of 50 to 150 mg/day.[95,96] Atenolol was demonstrated inferior to propranol in a direct head-to-head study, further supporting the importance of action on adrenergic peripheral beta-2 receptors. Metoprolol (metoprolol tartrate for a short-acting form or metoprol succinate for a long-acting form) is very similar to atenolol with the exception of a shorter plasma half-life. Metoprolol is metabolized in liver by cytochrome CYP2D6 with an extensive first-pass effect. The rate of metabolism is dependent partly on the genetic polymorphism in CYP2D6 with 3 to 4 hours in rapid metabolizers and 7 hours in slow metabolizes. Although single dose studies suggested equal efficacy of metopranol with propranolol, propranolol was proven superior with more chronic administration. Administration of a single dose of propranolol of 120 mg and 150 mg of metoprolol showed comparable effects on tremor.[95,97–99] However, for chronic use after a crossover study using 2 oral dosage regimes (150 mg and 300 mg daily for metoprolol and 120 mg and 240 mg daily for propranolol), only propranolol produced a statistically significant reduction in tremor. Again, individual patients either responded to both propranolol and metoprolol or to neither drug.[95,97]

Overall, other beta-blockers are inferior in efficacy to propranolol. Metoprolol and atenolol may be considered in patients who experience bronchospasm when treated with propranolol, but their tremor control tends to be much less robust and transient.

Primidone. *Mechanism of action.* Primidone is an anticonvulsant that is metabolized to phenobarbital and phenylethylmalonamide (PEMA).[100,101] The anticonvulsant action of primidone is attributed to both the parent drug and to the active metabolites. In contrast, primidone is much more effective in suppressing tremor than phenobarbital or phenylethylmalonamide alone.[102] The antitremorogenic mechanism of action of primidone is still not fully understood.[103] Unlike phenobarbital, primidone does not directly interact with GABA-A receptors or chloride channels. Primidone reduces high-frequency repetitive firing of neurons and alteration of transmembrane sodium and calcium channels ion movements. This has been

suggested as an explanation of both its anticonvulsant and antitremor activities.[103]

Pharmacokinetics and metabolism. Orally administered primidone has up to an 80% rate of absorption, with peak plasma levels in 2 to 3 hours and a half-life of 10 to 12 hours.[104] It is minimally bound to protein and penetrates the BBB well.[104,105] Antitremorogenic effects of primidone can be observed at plasma levels that are much lower than those used for treatment of epilepsy.[106] Serum concentrations of 5 to 12 μg/mL are recommended to effectively control seizures, while significant efficacy for ET has been observed at levels less than 5 μg/mL.[100] Moreover, there is no clear correlation between plasma levels and efficacy for tremor control.[106] Primidone undergoes partial hepatic transformation through the cytochrome oxidase complex to phenobarbital and PEMA. Unmetabolized primidone is excreted renally and phenobarbital is metabolized mostly through CYP2C9 enzyme. Primidone is a potent hepatic enzyme inducer, mostly affecting CYP3 A4 and CYP1 A2 members of the cytochrome P450 family.[100]

Clinical studies, efficacy, and safety. The efficacy of of primidone in ET was originally reported in 1981.[107] Primidone was introduced for treatment of partial complex and generalized tonic-clonic seizures in the 1950s, and these are its only FDA-approved indications.[100] Clinical observations of tremor reduction in patients who were treated with primidone for seizures lead to a systematic exploration of this medication in ET.[108–113] Indeed, several double-blinded, placebo controlled studies demonstrated reduction of tremor in patients treated with doses ranging from 50 mg/day to 1000 mg/day and the average dose was around 500 mg/day.[112,113] There is no clear correlation between the dose and efficacy and a long-term use of 250 mg/day versus 750/day did not result in a higher proportion of patients with better tremor control.[113] This is an agreement with studies that did not find any correlations between the plasma levels and the degree of tremor control.[106] Average tremor improvement is up to 75% reduction from the baseline, even though most studies reported approximately 50% improvement.[106,108–113] In summary, published reports suggest little additional benefit of doses higher than 250 mg/day, but selected patients may require a higher dose.

Adverse effects associated with primidone are relatively common and can be seen in 22% to 72% of patients, resulting in a dropout rate from therapeutic studies ranging from 20% to 30%.[112,113] Some patients experience acute adverse reactions even at very low doses of 50 mg/day or lower, with confusion, ataxia, and nausea, and even very slow titration did not resolve these problems. Pretreatment with phenobarbital, inducing the metabolism of primidone, was suggested in these patients, even though there is no conclusive data about the usefulness of this approach. Another form of acute reaction to primidone is the development of flu-like symptoms. Additional potential side effects are sedation, drowsiness, fatigue, and dizziness, and these can be more frequent at higher daily doses and in elderly patients.

The maximum recommended daily dose is 2000 mg/day, even though this is based on indications for epilepsy.[100] Patients with ET typically requite lower doses than 1000 mg/day. Primidone is contraindicated in patients with hypersensitivity to phenobarbital and porphyria. Metabolized phenobarbital can stimulate the activity of δ-aminolevulinic acid synthase, enhancing porphyrin synthesis and, thus, exacerbating porphyria symptoms. Severe hepatic and chronic renal insufficiency with a creatinine clearance <10 mL/minute require reduction of the dose, and it may be prudent to avoid this medication in these patients. Bone marrow suppression with agranulocytosis and pulmonary disease with possible respiratory depression are other conditions where primidone is contraindicated. Primidone should be withdrawn gradually, especially in patients who have been treated for more than 6 months. There is an increased risk of depression and suicidal ideation in patients receiving anticonvulsants, even for indications other than epilepsy.[100] Patients and caregivers should be informed of the increased risk of suicidal thoughts and behaviors and should be advised to immediately report the emergence or worsening of depression and the emergence of suicidal thoughts or behavior. Primidone is classified as FDA pregnancy risk category D and should be used during pregnancy only if the benefits clearly outweigh the risks. The use during the third trimester can also cause physical dependence in the neonate. Women of childbearing age should be advised about a higher risk of possible fetal malformations, and supplementation with folic acid is also recommended.

Dosing and clinical approach. Primidone is best introduced at bedtime because drowsiness is one of the most common problems, and this can alleviate these symptoms. Typical starting dose is 50 mg at bedtime, but in elderly patients, it may be prudent to start with a 25 mg dose. The dose should be titrated based on efficacy and tolerability, and a gradual increment by 50 mg each week is generally tolerated and allows for the assessment of possible side effects. Even though there is no clear correlation between the dose and tremor improvement, it is sensible to find the most effective and most tolerated dose rather than using an arbitrary final amount. Most ET patients require doses below 1000 mg/day, and doses higher than 500 mg can be administered in 2 divided doses.

Second Line Therapies

Benzodiazepines—alprazolam and clonazepam. *Mechanism of action.* Benzodiazepines potentiate GABAergic neurotransmission.[114] They directly bind to the $GABA_A$ receptor complex, and their presence triggers more influx of chloride ions through the increased binding of GABA. This results in hyperpolarization of the cell membrane and, thus, inhibition of action potential firing. This accounts for their anxiolytic, anticonvulsant, sedative, muscle relaxant, and likely also antitremorogenic effects.

Pharmacokinetics and metabolism. Orally administered benzodiazepines are rapidly absorbed, and their peak

concentrations vary from minutes to several hours. Different members of this pharmacological class have different lipid solubility that influences their pharmacokinetics, accessibility to the CNS, and diffusion in various tissues.[114] Alprazolam and clonazepam have been the most extensively studied in ET patients, and we will review only these 2 compounds. Alprazolam has a fast onset of action, and the peak effects are achieved within the first hour with the plasma half-life around 11 hours. Clonazepam has an intermediate onset of action, with peak blood levels occurring 1 to 4 hours after oral administration and elimination half-life between 30 and 60 hours.[114] Both compounds are extensively metabolized, primarily by CYP3 A4. Alprazolam has 2 active metabolites, but their plasma levels are low; clonazepam does not have any active metabolites. They are further eliminated in urine.

Clinical studies, efficacy, and safety. Alprazolam was studied in a double-blinded crossover study, and a mean dose of 0.75 mg/day ranging from 0.125 to 3 mg/day improved tremor.[115,116] These were short-term studies, and side effects were mild, with sedation and fatigue most common, reported, in 50% of patients. Clonazepam showed mixed results, and one study with the dose of 4 mg/day did not show any improvement of tremor, even though it was well tolerated.[117,118] Potential shortcomings of benzodiazepines include tolerance, dependency, abuse, withdrawal symptoms, sedation, cognitive impairment, falls, and potential drug interactions.

Dosing and clinical approach. Benzodiazepines need to be used with caution in ET due to the short duration of action and rapid onset. These characteristics limit its long term therapeutic potential. Judicious use of alprazolam (0.125–0.5 mg) may be effective in patients whose tremor is frequently aggravated by anxiety or other stressor. These patients may benefit from an intermittent dosing to prevent tolerance and careful monitoring for potential abuse. Even though clinical data for clonazepam are less robust, it may be more suitable for a long-term therapy using the same precautions as for alprazolam. Twice a day dosing with a daily dose ranging from 0.5 mg to 4 mg may be helpful in patients who failed other first and second lines of therapy.

Gabapentin. *Mechanism of action.* Gabapentin was developed as a structural analog of gamma-aminobutyric acid (GABA), but it does not directly bind to $GABA_A$ or $GABA_B$ receptors.[119] It has been proposed that gabapentin interacts with auxiliary subunits of voltage-gated calcium channels. However, it remains unclear whether this fully accounts for its action as an anticonvulsant, pain modifying agent, and its antitremorogenic properties.

Pharmacokinetics and metabolism. Orally administered gabapentin is absorbed via L-amino acid transporters, and its bioavailability decreases with increased doses.[120] It is highly lipophilic and easily crosses BBB via the same transporters. Gabapentin does not undergo any metabolization and is excreted unchanged in urine. It does not bind to plasma proteins and does not have any enzyme induction properties. Plasma half-life in patients with normal renal function ranges between 5 and 7 hours. The dose needs to be adjusted in patients with chronic renal insufficiency or those on hemodialysis.

Clinical studies, efficacy, and safety. Gabapentin has been studied both as monotherapy compared with either placebo or in a crossover design with propranolol and in combination with other first line therapies in ET patients.[121–123] Overall, these were relatively small studies with mixed results. Although one study reported tremor reduction comparable with propranolol at a dose of 1200 mg/day of gabapentin, other trials showed either modest results or were negative.[121–123] Doses varied from 1200 to 3600 mg per day; however, no dose response was detected when 1800 mg/day dose was compared with 3600 mg.[121]

Studied doses for ET were in general well tolerated, and the dropout rates were around 10%. Sleepiness, dizziness, ataxia, nausea, and weight gain were observed in approximately a third of patients, but, overall, these side effects were considered mild. Gabapentin should be withdrawn gradually because abrupt discontinuation has been associated with increased anxiety, insomnia, and nausea. Increase risk of depression and suicidal behavior is similar to that with other anticonvulsants. Gabapentin is classified as FDA pregnancy risk category C, and a possibility of a higher incidence of fetal malformations after in utero exposure has not been fully settled.

Dosing and clinical approach. Oral administration of gabapentin is typically given in 3 divided doses with a starting dose of 300 mg 3 times a day. In the elderly, it is prudent to use 100 mg 3 times a day dosing with a gradual titration. The final dose is determined by the efficacy and tolerability, but there is no data supporting doses higher than 3600 mg/day for ET patients. At best, the benefit in ET is modest, and the likelihood of gabapentin being helpful in patients who have failed primidone or propranol is very low. Thus, gabapentin as a monotherapy should be mostly considered for those patients who had either contraindications or had idiosyncratic adverse effects on very low doses of propranolol or primidone. Combination therapies can be also explored based on presumed different modes of action of various antitremor medications.

Pregabalin. *Mechanism of action.* Pregabalin is another structural derivative of GABA, and similar to gabapentin, it does not display any affinity to GABA-ergic receptors.[124] Mechanism of action is similar to gabapentin with a high affinity binding to the alpha2-delta site (an auxiliary subunit) of voltage-sensitive channels.[125]

Pharmacokinetics and metabolism. Orally administered pregabalin has more than 90% bioavailability, and it is also a substrate of L-amino acid transporters.[124,125] Pregabalin undergoes minimal metabolization into the N-methylated derivative of pregabalin, and the rest is eliminated renally unchanged with a plasma half-life between 6 and 7 hours. Similar to gabapentin, pregabalin dose needs to be reduced in patients with chronic renal insufficiency or those on hemodialysis.

Clinical studies, efficacy, and safety. Placebo-controlled clinical trials assessing the efficacy of pregabalin in controlling ET yielded mixed results, with the initial study demonstrating efficacy at the average daily dose of 286 mg/day and a maximum dose of 600 mg/day.[126] However, this was not replicated in another study where no statistically significant changes were observed at doses ranging from 150 to 600 mg per day.[127] This was a crossover study, and patients reported worsening of quality of life on active treatment. The most common adverse effects included dizziness and sedation, resulting in a third of treated patients dropping out of the study. Overall, the AE profiles of pregabalin and gabapentin, including use in pregnancy, are very similar with the exception of an increased incidence of angioedema that was noted in postmarketing experience of pregabalin.

Dosing and clinical approach. Pregabalin may be initiated at doses ranging from 25 mg twice a day to 75 mg twice a day, but higher doses may be associated with decreased quality of life due to adverse effects in treated patients. This suggests that a slower titration may be of benefit. The dose needs to be titrated to the most effective dose, and the highest daily recommended dose is 600 mg. Moreover, the incidence of side effects is increased past the daily dose of 300 mg.[127] The role of pregabalin in treatment of ET is even less certain for gabapentin, and it may be tried in the same manner.

Topiramate. *Mechanism of action.* Topiramate appears to have a complex mechanism of action including blocking of voltage-gated sodium channels, augmenting of GABA activity at the $GABA_A$ receptors, antagonizing the AMPA/kainate glutamate receptors, and inhibiting the carbonic anhydrase enzyme, especially isozymes II and IV.[128] These complex mechanisms account for its anticonvulsant properties, but it remains unknown which of these play a role in tremor control.

Pharmacokinetics and metabolism. Orally administered topiramate is rapidly absorbed and has about 20 hours average plasma half-life when renal function is normal.[129] Topiramate is 15% to 40% bound to human plasma proteins. It is only partially metabolized and almost three-fourths of the administered dose is eliminated unchanged in the urine. Hepatic metabolization includes hydroxylation, hydrolysis, and glucuronidation. Topiramate is a weak inhibitor of CYP2C19 and induces CYP3 A4.

Clinical studies, efficacy, and safety. Topiramate was clinically tested as a monotherapy or adjuvant ET therapy.[130,131] Every study showed a statistically significant and clinically robust reduction of tremor in treated patients. The maximum allowed dose was 400 mg/day, even though the highest tolerated dose in most of the treated patients was approximately 300 mg/day.[131] Another consistent feature of these trials was a relatively high dropout rate with roughly a third of the patients discontinuing therapy because of adverse effects, most commonly paresthesias, concentration difficulties, nausea, somnolence, fatigue, malaise, dyspepsia, appetite decrease with weight loss, confusion, psychomotor slowing, and an abnormal taste perception.

Additional potential adverse effects include secondary acute angle closure glaucoma, and suspicion for medication problems should be higher in bilateral cases. The primary intervention is immediate discontinuation of topiramate because, if untreated, increased intraocular pressure may cause visual loss. Additional adverse effects include oligohidrosis with hyperthermia, metabolic acidosis, and increased risk of kidney stones. Anticonvulsant medications class warning includes an increased risk of depression and suicidal behavior. Topiramate is classified as FDA pregnancy risk category D, and there is an increased risk of oral clefts (lip or palate).

Dosing and clinical approach. Topiramate is typically dosed twice a day, but it can be also introduced at bedtime to minimize side effects. The typical starting dose is 25 mg/day, and it should be titrated gradually by adding 25 to 50 mg every week. The highest recommended dose is 400 mg/day, but most elderly patients are unlikely to tolerate this final dose. Even though the second line therapies were not directly compared, topiramate appears to be most effective with its overall efficacy approaching the first line therapies. However, it has also one of the highest incidences of treatment-limiting adverse effects.

Third Line Therapies

Nimodipine. *Mechanism of action.* Nimodipine belongs to the calcium channel blockers class of medications, and it binds to the L-type voltage-gated calcium channels. It shows a higher affinity to vascular smooth muscle calcium channels in cerebral vasculature, and it is approved for treatment of vasospasms induced by subarachnoid bleeding.[132]

Pharmacokinetics and metabolism. Nimodpine is highly lipophilic and easily penetrates BBB, which may account for its efficacy for the treatment of cerebral vasospasm. It has a high first pass metabolism and undergoes extensive hepatic metabolism with a plasma half-life of 8 to 9 hours.

Clinical studies, efficacy, and safety. Nimodipine at the dose of 30 mg 4 times a day improved tremor in 8 patients out of the 16 enrolled, and, overall, the medication was well tolerated.[133] The most common side effects of nimodpine include hypotension, edema, and headaches, which are common adverse effects of all calcium channel blockers.

Dosing and clinical approach. Clinical experience with nimodipine in ET is limited, and it may be considered in patients who failed other commonly used medications. Other calcium channel blockers were also tried in ET, but there is no evidence to support the use of verapamil, flunarizine, nicardipine, or nifedipine as third line options in medically refractory ET.[134–138]

Clozapine. *Mechanism of action.* Clozapine belongs to the group of atypical antipsychotics because it has relatively less affinity to the dopamine D_2 receptors and, thus, a low potential for extrapyramidal side effects. Clozapine mainly blocks dopamine D_1 and D_4 receptors, and, in addition, it may

inhibit serotonin type 2 receptors and affect levels of GABA. Additionally, it blocks α_1-adrenergic receptors and has a strong anticholinergic effect on muscarinic receptors. It is approved for treatment-resistant schizophrenia.[139]

Pharmacokinetics and metabolism. Orally administrated clozapine is rapidly absorbed and extensively crosses BBB. It is 97% bound to plasma protein and completely metabolized via the CYP1 A2, CYP2D6, and CYP3 A4 hepatic microsomal isoenzymes. Plasma half-life is about 8 hours.

Clinical studies, efficacy, and safety. Clozapine reduced tremor up to 50% from the baseline in 2 small studies using doses of 25 mg to 75 mg/day.[140,141] The most common problem in these studies was sedation, which was self-limiting within the first 2 months. There were no signs of bone marrow suppression in these patients.

The main risk of clozapine is agranulocytosis that can be seen in up to 1% and neutropenia in 3% of all treated patients. Currently clozapine is available only through the Clozapine Registry, and the therapy cannot be initiated if the patient's baseline white blood cell count is less than 3500/mm^3 or absolute neutrophill count is less than 2000/mm^3. It is also contraindicated in myeloproliferative disorders. Hematologic parameters with total white blood cell counts and absolute neutrophil counts need to be monitored weekly during the first 6 months of therapy, and the medication can be dispensed for 1 week only. If there is no change in hematologic parameters, the intervals can be biweekly for next 6 months and then monthly. Changes in blood counts require either reduction of the dose and, if neutropenia develops with the absolute neutrophil count less than 1500/mm^3, the medication must be stopped immediately; however, if clozapine is stopped, the prognosis is generally favorable.

Clozapine is associated with an increased risk of sudden death due to cardiomyopathy, orthostatic hypotension, prolongation of QT interval, tachycardia, and syncope. Additional significant adverse effects include weight gain with metabolic syndrome and risk of seizures.

Dosing and clinical approach. Clozapine may be considered in medically refractory ET if other nonpharmacological options are either contraindicated or not desired by the patients. Used doses in ET were much smaller than for schizophrenia. The maximum recommended daily dose is 900 mg/day, while the highest dose used in ET was 75 mg/day. The medication needs to be introduced gradually at 25 mg/day and titrated biweekly based on efficacy and side effects. However, the need for weekly blood draws and other potential side effects clearly limits this option to refractory patients who have failed all other options.

Other atypical neuroleptics—olanzepine at a mean dose of 14.8 mg/day and quetiapine up to 75 mg/day—were also tried in ET, but there is no evidence to support the use of these compounds as a third line option in medically refractory ET.[142,143]

Additional pharmacological agents tried in ET include levetiracetam, lacosamide, mirtazapine, amantadine, memantine isoniazid, methazolamide, acetalozamide, and clonidine, but at present there is no sufficient evidence to support their use on a trial and error basis even in medically refractory cases.[78,79,144–156]

Treatment Algorithm

The therapeutic approach to ET many times follows a trial and error approach, and patients should be challenged by several medications if the first choice is ineffective or associated with debilitating adverse effects.[157] Treatment of ET is only symptomatic. and patients' disability, including psychological burden, needs to be strongly considered before initiating any pharmacological therapy. An additional important point is the discussion of anticipated therapeutic benefits, because complete tremor control is relatively rare and patients may have unrealistic expectations. Tremor reduction by 70% to 80% is considered an excellent response, but the remaining tremor can still be functionally very disabling. Furthermore, an average response rate to pharmacotherapy is about 50%, and most patients experience only a partial functional control of tremor.[158] This is mostly due to lack of understanding of ET pathology and the clinical and genetic heterogeneity of this entity. There is no clear consensus how to measure the outcome of therapeutic trials, and this also may add to mixed results for the same tried pharmacological agents. Overall, this represents a significant unmet need for better pharmacological options, and elucidation of ET pathogenesis, including the contribution of genetic factors, will hopefully translate into more effective and better tolerated medications.

The order for first line therapy remains open to personal preferences. Primidone (50–250 mg/day) was directly compared with propranolol (80–160 mg/day), and none of these compounds was clearly superior even though some studies suggested a slightly higher degree of tremor improvement for primidone.[159] Acute adverse effects were more common in primidone group, with 32% patients reporting problems compared with 8% on propranolol. However, of those remaining on long-term therapy, primidone appeared to be better tolerated. A long-term use of primidone following a similar dropout rate of 13% for each group did not cause any adverse effects, while 17% of chronic propranolol users developed adverse effects. If patients do not have any contraindications, propranolol can be tried as the first choice, and, if it fails, primidone should be the second choice. An additional approach is a combination of both first line agents, especially if adverse effects were dose dependent.

Topiramate has emerged as the most effective second line treatment but its use may be limited by poor tolerance in a substantial proportion of patients. One of the unanswered questions in the treatment of ET is the likelihood of success of second and third line treatments in patients who did not achieve any improvement on first line treatments at the adequate doses. Despite the absence of evidence, second and

third line therapies may be also used in an add-on fashion to other compounds, especially if medications with various mechanisms of action are combined.

The concept of medically refractory tremor is not uniformly defined.[158,160] We propose that ET patients who failed or did not tolerate both first line and 1 or 2 second line medications to be medically refractory. Each therapeutic trial should be done with escalating doses of tried medications. Patients not achieving a meaningful tremor reduction should experience adverse effects to confirm that the therapeutic attempt was adequate, and the failure was not due to subtherapeutic doses of used pharmacological agents. This is important, as trying a long list of additional medications with unproven track records may delay more potent therapies, such as chemodenervation with botulinum toxins or surgery (deep brain stimulation or lesioning). Thus, clinical trials of third line medications are mostly suitable for patients who are not candidates for surgical therapy.

Author Contributions

Conceived the concept: PH. Analyzed the data: PH. Wrote the first draft of the manuscript: PH. Contributed to the writing of the manuscript: FC, TLD. Agree with manuscript results and conclusions: PH, FC, TLD. Jointly developed the structure and arguments for the paper: PH, FC, TLD. Made critical revisions and approved final version: FC, TLD. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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