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Efficacy of the long chain alcohol metabolite octanoic acid as an adjunct to standard first line therapy of classical essential tremor

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SCHOOL OF MEDICINE

Thesis

**EFFICACY OF THE LONG CHAIN ALCOHOL METABOLITE OCTANOIC
ACID AS AN ADJUNCT TO STANDARD FIRST LINE THERAPY OF
CLASSICAL ESSENTIAL TREMOR**

by

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B.S., University of Vermont, 2015

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ABSTRACT

Essential tremor (ET) is a common movement disorder resulting in a postural and kinetic tremor that predominantly affects the upper extremities and varies in amplitude across patients. The etiology of ET is unclear; however, three predominant hypotheses exist. The first hypothesis evaluates rhythmical dysfunction originating from the inferior olivary nucleus that is then propagated throughout the brain and ultimately manifests as tremor. The second hypothesis evaluates γ -aminobutyric acid dysfunction as a causal explanation for ET while the third hypothesis evaluates gross cortical and cerebellar changes that result in ET.

The beta-adrenergic blocking medication propranolol and barbiturate primidone are staples for the treatment of this disorder, but often fail to adequately control symptoms. primidone specifically has intolerable side effects for many patients. Ethanol, however, can more effectively treat tremor via a mechanism likely explained by one or more of the aforementioned hypotheses. However, it is not a practical therapeutic option for the treatment of ET primarily as a result of its intoxicating properties among other reasons. Recent attention to the long chain alcohol 1-octanol and its primary metabolite octanoic acid yielded findings of tremorlytic properties, albeit at doses that limit practicality.

This study looks to evaluate octanoic acid as an adjunct to primidone and propranolol for the first time and will attempt to demonstrate that as an adjunct, it can be used at lower, more practical doses.

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LIST OF ABBREVIATIONS

AE	Adverse Effect
BMI	Body Mass Index
BZD.....	Benzodiazepine
CBC.....	Complete Blood Count
CCTC	Cerebellothalamocortical Circuit
CF.....	Climbing Fiber
CNS.....	Central Nervous System
CTCAE.....	Common Terminology Criteria for Adverse Events
DCN	Deep Cerebellar Nuclei
ED50	Median Effective Dose
EKG.....	Electrocardiogram
ET.....	Essential Tremor
EVT.....	Essential Voice Tremor
GABA.....	γ -aminobutyric acid
ION.....	Inferior Olivary Nucleus
KO.....	Knockout
LA	Long Acting
LD50	Median Lethal Dose
LFT.....	Liver Function Test
MTD	Maximum Tolerated Dose
PC.....	Purkinje Cell

PD..... Parkinson's Disease
PET..... Positron Emission Tomography
q3d..... Every third day
q5d..... Every fifth day
qam..... After awakening
qd..... Daily
qhs..... Before bed
T-tCaC..... T-type calcium channels
TETRAS..... The Essential Tremor Rating Scale
THIP4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol
Vim..... Ventral intermediate nucleus
WTWild Type

INTRODUCTION

Background

Essential tremor (ET) is the most common movement disorder world-wide and estimated to affect up to seven million people within the United States alone.^{1,2} It is a postural and kinetic tremor that most commonly involves the bilateral upper extremities, however, it can progress to involve other parts of the body including head, trunk and lower extremities.^{2,3} ET has a strong genetic component and is inherited, to a large extent, in an autosomal dominant pattern.³

Although the exact etiology of the disease is poorly understood, three predominant disease models have been proposed. The first model, or hypothesis, assesses improper functioning of T-type calcium channels (T-tCaC) and gap junction hyperfunctioning in the inferior olivary nucleus (ION).^{3,4} The second evaluates defective γ -aminobutyric acid (GABA) signalling predominantly within the deep structures of the cerebellum.⁵ Finally, the third hypothesis proposes cerebellar degeneration and Purkinje cell (PC) hypodensity as a causal explanation for disease pathology.

First-line treatment for ET involves the use of either primidone or propranolol or a combination of the two. Unfortunately, due to a lack of efficacy and side-effect profile of the two medications, as many as 50% of patients will discontinue them.^{2,6} Ethanol has been shown to significantly decrease tremor amplitude in innumerable subjective reports—as well as recent objective data—in over 70% of patients with ET, and mechanisms of action have been proposed that correlate with the three aforementioned disease models.⁷⁻⁹ Unfortunately, the intoxicating effects of ethanol make it an unsuitable

treatment option for ET. However, longer chain alcohols and their metabolites have been recently considered due to the absence of intoxicating effects even at higher doses.⁹⁻¹¹ The long chain alcohol that has emerged as the most promising potential treatment for ET is 1-octanol, and its metabolite octanoic acid has shown efficacy as well. To this point, studies have been sparse with low participant numbers, but nonetheless promising. This is especially true regarding the use of octanoic acid in reduction of ET tremor amplitude. Currently, safety has been well-established and results point to superiority over placebo, however comparison to current first-line medications such as primidone or propranolol has not been evaluated. Additionally, OA potential use as an adjuvant to these medications has yet to be explored.^{9,10,12}

Statement of the Problem

Essential tremor affects around seven million Americans and has a worldwide prevalence ranging from 0.4-5.0%, however medical treatment as a whole lacks efficacy and side effect profiles lead to discontinuation of first-line treatment by as many as 50% of patients who start it.^{2,3,13} Additionally, medical refractory disease is seen in as many as 50% of patients who undergo any pharmacotherapy.¹³ Procedure-based intervention, such as deep brain stimulation, has proven to be more efficacious, however is associated with adverse neurological effects, device malfunction, and infection.¹³ This results in a conspicuous need for more efficacious pharmacological interventions. While ethanol has proven to have therapeutic benefit, it is not a practical therapeutic tool for obvious social, legal and medical reasons.¹⁰ 1-octanol is a long chain alcohol that appears to skirt the

impracticality of ethanol and further research has demonstrated that its metabolite, octanoic acid, also has significant tremorolytic properties. Unfortunately, investigation of OA as a treatment option has been limited. This is in part due to its only recent discovery as a therapeutic option, but also because of high dose requirements and low dose formulation options.¹⁴ To this point, there have been no studies looking at the potential efficacy of OA as an adjuvant therapy.

Hypothesis

Octanoic acid as an adjunct to a combination therapy of primidone and propranolol will demonstrate superior efficacy in the treatment of ET when compared to primidone and propranolol alone.

Objectives and specific aims

It is the objective of this study to provide evidence that octanoic acid can be useful in the treatment of essential tremor which remains difficult to control from a pharmacological perspective. Specific aims include:

- Demonstrating that the addition of OA to a drug regimen of primidone and propranolol significantly reduces tremor when evaluated with The Essential Tremor Rating Assessment Score (TETRAS) performance subscale.
- Demonstrating that the use of OA as an adjunct can prove efficacious at lower doses which do not pose feasibility limitations or gastrointestinal adverse effects.

- Demonstrating that OA retains its high safety profile when combined with propranolol and primidone.

REVIEW OF THE LITERATURE

Overview

ET is widely considered the most common movement disorder and estimated to affect between 0.4 to 5% of the general population.^{1,13,15} It has a prevalence ranging between 3-4% in patients 40 years or older and grows to plague 22% of individuals who live beyond 90.^{15,16} In the United States, ET is estimated to affect as many as 7 million people.²

ET is a slightly asymmetric, postural and kinetic tremor meaning that it is present while maintaining a position against gravity and occurs during any voluntary movement.^{1,17} ET predominantly affects the hands and upper extremities; however, it can affect the face, voice, trunk and lower extremities as well.^{1,2,18} 50% of ET patients have an intention component, meaning that guided movement such as reaching for an object or bringing a cup to one's mouth elicits the tremor.¹⁷ Age and family history are the only established risk factors for the disease and onset of the disease can occur at any age.¹⁷ ET is progressive in nature and there is a wide spectrum of disease severity, largely based on tremor amplitude. This spectrum can range from nominal functional impairments without medications, to medical refractory disease, resulting in a disabling high-amplitude tremor.^{3,10,16} This condition can be so severe that one study estimates it renders 15-25% of patients unable function adequately within their occupation.¹⁷ Recently, additional attention has been drawn to non-motor manifestations of ET such as psychiatric manifestations including social phobia, insomnia, fatigue, secondary depression and anxiety.^{15,19} Additional studies have pointed to earlier cognitive decline and risk for

conversion to dementia with a specific study citing a 1.32x higher rate of mild cognitive impairment in ET patients when compared to the general population.¹⁹

The etiology of essential tremor is poorly understood. There is a clear genetic component with more than 50% of patients having a positive family history and 90% concordance among monozygotic twins.³ Additionally, first-degree relatives of ET patients are about five times as likely to develop the disease while that likelihood doubles if said first-degree relative developed ET at an earlier age.¹⁷ Despite an autosomal dominant mode of inheritance being proposed, it fails to fully describe the mode of inheritance that ET demonstrates which is evidenced by incomplete concordance of monozygotic twins, cases without family history and substantial variation in age of onset. These factors point to the potential for de novo mutations or other modes of inheritance such as autosomal dominant with incomplete penetrance, and encourage consideration of environmental causes or other more complex, non-mendelian modes of inheritance.^{3,15} More likely though, this imperfectly described mode of inheritance can be attributed to the fact that ET is a genetically and clinically heterogeneous disease that encompasses multiple different entities and varies in predominance of tremor component.^{17,19}

ET is largely a diagnosis of exclusion. There are no serum markers or imaging findings that can definitively diagnose a patient and although some postmortem brains have shown the presence of Lewy Bodies and/or decrease in PC density, these findings are not ubiquitous across ET brains.^{17,20,21} In addition, certain loci have recently been discovered, but these findings too do not show consistency across populations and more likely coincide with different pathological variants.¹⁵

Further complicating genotypic insight, is recently discovered data that one third of ET patients in a study group had been misdiagnosed, increasing the plausibility that attempts to further understand the genetics and neuropathology are based on patients carrying an alternative, more appropriate diagnosis such as dystonia or Parkinson's Disease (PD).²²

Finally, others have posited that the discord between ET genotypes and phenotypes is in part due to environmental factors such as beta-carboline alkaloids and lead while others have demonstrated a modest correlation between heavy alcohol consumption and inception of the disease.^{17,23}

Despite an inability to match phenotype with genotype, three predominant pathophysiological hypotheses have evolved and are, to an extent, interconnected via central nervous system (CNS) circuitry.²⁴

Oscillating Network Hypothesis:

The oscillating network hypothesis was first developed in the early 1970's and evaluates pathological changes of the inferior olivary nucleus (ION). Although it has recently begun to fall out of favor, there are aspects of the hypothesis that continue to be the basis for ongoing research. Furthermore, the oscillating network hypothesis offers clinical insight into potential drug mechanisms of action including that of ethanol and other alcohols.¹⁷

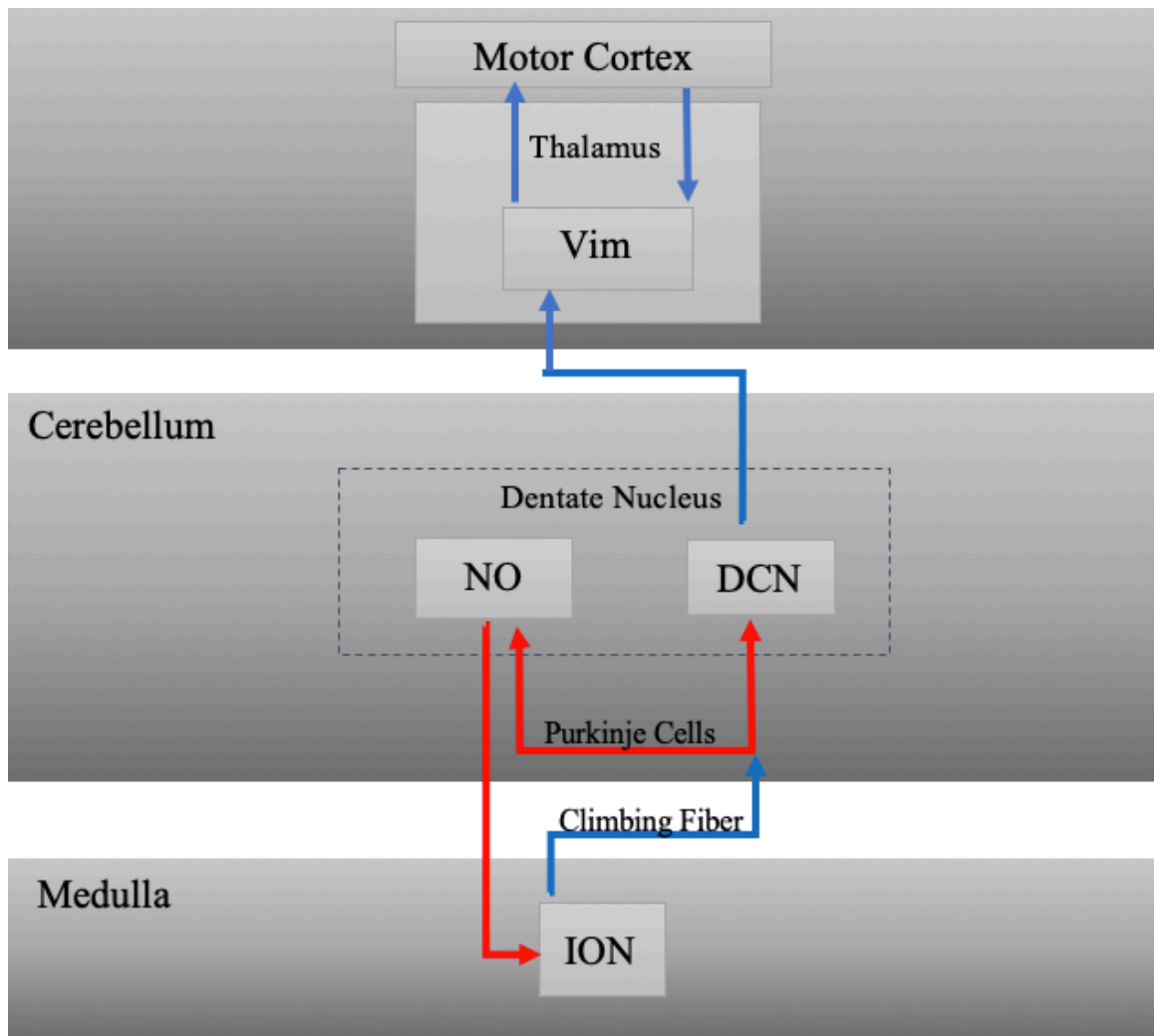


Figure 1: Cerebellothalamocortical Circuitry (Adapted from Zhang & Santaniello, 2019). GABAergic projections shown in red and glutamatergic projections shown in blue. NO, nucleoolivary neurons; ION, inferior olivary nucleus; DCN, deep cerebellar nuclei; Vim, ventral intermediate nucleus

The ION is a group of nuclei in the lower medulla and one of many structures within the CNS that contains neurons with pacemaker properties.²⁵⁻²⁷ Subthreshold oscillations of ION neurons occur synchronously at a frequency of ~5-10 Hz and determine timing of ION action potentials.²⁸ ION neurons give rise to climbing fibers

(CF) that monosynaptically innervate cerebellar PC (Figure 1): the cerebellar cortex's lone output neuron.^{29,30} Thus, the ION and its auto-oscillatory activity is implicated in cerebellar functioning, and by extension, motor control.^{28,29} The oscillating network hypothesis evaluates two potential electrophysiological alterations within the ION as a pathological explanation for ET.^{25,31}

Firstly, oscillations generated by the ION can be induced via the activation of Cav3.1 T-type Ca²⁺ channels (T-tCaC).^{4,9,32} There are three isoforms of T-tCaC, Cav3.1, 3.2 and 3.3, however Cav3.1 is the predominant isoform found within the ION, PC and deep cerebellar nuclei (DCN).³³ As above, the rhythmic activity generated within the ION is transmitted to CF innervating PC and thus these channels play a critical role in cerebellar output and motor function. The excitation of Cav3.1 T-tCaC found within the ION can be artificially enhanced via the administration of the alkaloid harmaline, leading to hyperfunctioning of oscillatory neuronal activity.^{9,31} When evaluated in a rat model, administration of harmaline induced 4 to 10 Hz rhythmic bursts from the ION which manifested a phenotype similar to that of ET. However, in Cav3.1 knockout rats, the same rhythmic activity and phenotypic tremor were not observed leading researchers to conclude that hyperfunctioning of ION T-tCaC's could be considered as a pathological explanation for ET.^{11,32}

Alterations in gap junction functioning within the ION is the second component of the oscillating network hypothesis. The subthreshold oscillations of ION neurons are coupled through gap junctions which permits for coordinated ION action potentials that propagate to PC.²⁸ It is the hypersynchronization of these discharges, mediated by

extensive gap junctions in the ION, that has been proposed as an underlying etiology of ET.^{9,34} This is supported by the understanding that compounds which are known to cause broad-spectrum gap junction blockade have been demonstrated to suppress harmaline-induced tremor in a mouse model, whereas structurally similar compounds without gap junction blocking properties have not.²⁷ However, further findings seem to contradict the notion that gap junctions are necessary for tremor production. In a knock-out model of mice deficient in a protein necessary for functional olivary gap junctions, the harmaline-induced tremor persisted in a manner comparable to wild type (WT) mice.³⁵

Within the past 10 years, advances in neuroimaging such as positron emission tomography (PET) and functional magnetic-resonance imaging have served to further discredit the oscillating network hypothesis.^{25,31} Additionally, the findings that lesions to locations outside of the olivocerebellar projections improve ET, along with the lack of efficacy in the use of T-tCaC blockers such as Ethosuximide, have shifted lines of thinking towards alternative hypotheses.^{24,26,36}

GABA Hypothesis:

The GABA hypothesis evaluates GABAergic dysfunction within the brain—and most commonly the cerebellum—as a possible, if not probable, pathological explanation for ET.^{5,37} There is an interplay between the GABA hypothesis and the oscillatory network hypothesis. For starters, harmaline induced tremor is responsive to benzodiazepines (BZDs) such as Valium.³⁸ Additionally, the ION has been implicated in circuitry propagating oscillatory activity caused by GABAergic dysfunction.^{26,39} This could be a

result of incomplete negative modulation of the olivary glomeruli by GABA projections originating from the dentate nucleus (Figure 1).

Patients with ET have demonstrated a decrease of GABA in their CSF.²⁴ Additionally, microinjections of GABA_A within the ventral intermediate nucleus (Vim) have effectively reduced tremor.²⁷ However, sparsity of GABA receptors and their structural defects—rather than a decrease in the neurotransmitter itself—have provided a more compelling pathological explanation. Additionally, drugs that increase GABA availability such as Tiagabine have not proven efficacious in the management of ET.⁴⁰

Regions of the thalamus, pons, cerebellum and motor cortex have all been implicated in the GABA hypothesis. In the pons, a marker for GABAergic neurons was significantly decreased in the locus coeruleus of ET patients when compared to controls.⁴¹ In a study by Boecker et al, there was shown to be increased binding of ¹¹C-flumazenil in the Vim, premotor cortex and dentate nucleus in ET brains as seen on PET.⁴² Increased BZD antagonist binding as a marker for GABA receptor abnormalities could be explained by a separate study that examined $\alpha 1$ GABA_A receptor subunit knockouts (KO) ($\alpha 1^{-/-}$) in mice. KO mice not only demonstrated a tremor consistent with ET, but had a compensatory upregulation of the $\alpha 2/3$ subunit of the GABA_A receptors. As a result, it can be considered that mutant GABA_A receptors with compensatory increases in $\alpha 2/3$ subunits have an increased affinity for BZD antagonists while not maintaining WT functionality, thus resulting in kinetic tremor and lack of motor coordination.⁴³ Supporting this notion is the understanding that alpha subunits have a significant effect on the functional properties of the receptor as well as binding and modulation of different

drugs.⁴⁴ However, KO mice demonstrated a 50% reduction of GABA_A receptors in cerebellar structures and postmortem studies have also shown reduction in GABA_A and GABA_B receptors in human ET brains when compared with brains of subjects afflicted with PD.^{43,45} Therefore, if the neuropathological explanation for ET is a result of a mutation leading to loss of the GABA_A $\alpha 1$ subunits with compensatory $\alpha 2/3$ subunit upregulation, the resulting GABA_A receptor would have to express a BZD antagonist affinity that outweighs a significant reduction in the density of GABA_A receptors. Nonetheless, other mouse models have demonstrated that similar $\alpha 1$ subunit knockouts result in increased tonic GABA_A receptor-mediated current, leading to dysregulation of neuronal excitability.⁴⁶ However, while the $\alpha 1^{-/-}$ mice may have demonstrated a tremor similar to that of ET, missense, nonsense and splice site mutations in the coding region of the GABRA1 gene (codes for a portion of the $\alpha 1$ subunit) in humans has not demonstrated a causal link to ET in caucasians.⁴⁷

Other subunits of the GABA_A receptor have been evaluated for their potential role in ET pathology as well. Golgi cells are involved in controlling cerebellar activity through their release of GABA onto synaptic and extrasynaptic GABA receptors found on cerebellar granule cells (Figure 2). The predominant extrasynaptic GABA_A receptors contain both δ and $\alpha 6$ subunits which are involved in modulation of tonic inhibition.⁴⁸ Mice with a harmaline induced tremor will respond to a specific GABA agonist gaboxadol; 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP), however when the δ and $\alpha 6$ subunits are knocked out, they no longer respond to THIP. This finding posits that extrasynaptic GABA_A receptors and mutations of the δ and $\alpha 6$ subunits may play an

important role in ET pathophysiology as well.⁴⁹ Furthermore, extrasynaptic GABA receptors are not responsive to BZDs, which could explain their limited clinical utility in ET.⁹

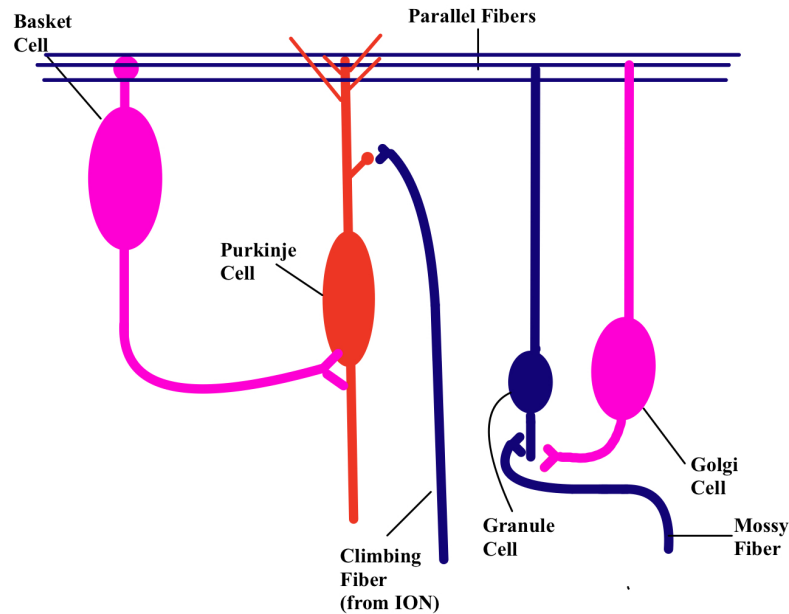


Figure 2: Schematic of Cerebellar Neuronal Network. Partial rendering of vital neuronal components of the cerebellum. Interneurons outlined in pink, GABAergic neurons are in red and glutamatergic neurons are in blue.

While the exact mutation leading to dysregulation of the GABAergic transmission remains unclear, a general consensus is that reduced GABAergic tone within the cerebellum likely plays a central role in the neuropathology of ET.^{24,26} Additionally, evaluation of the neurocircuitry of the cerebellothalamocortical circuitry (CCTC) pathway (Figure 1) has provided a rationale for how decreased GABAergic currents between PC and deep cerebellar nuclei could result in the tremor observed in ET patients. In the CCTC network model, alterations in GABAergic currents to the dentate nucleus allows for inappropriate transmission of oscillatory activity innately generated in the ION. This

oscillatory activity propagates from the dentate nucleus to the thalamocortical system including the Vim and motor cortex resulting in bursting activity within the thalamus and a resultant tremor.²⁶ Interestingly, the Vim is the traditional target for electrodes placed in ET patients who have undergone deep brain stimulation⁵⁰.

Regardless of the incompletely understood complexities of GABAergic transmission within ET brains, the hypothesis is best supported by the efficacy of drugs such as primidone, topiramate and gabapentin in reducing tremor, findings that are conserved in $\alpha 1$ subunit KO mice.^{24,43}

Neurodegeneration Hypothesis:

The neurodegeneration hypothesis of ET focuses on a loss of cerebellar PC as a pathological explanation of ET.^{9,51} Because PC are the sole output neuron of the cerebellar cortex and the major store for GABA in the CNS, there is a strong association between the neurodegeneration hypothesis and the GABA hypothesis.^{4,29} Furthermore, the neurodegeneration hypothesis also incorporates facets of the oscillatory network hypothesis, but evaluates the cerebellum's intrinsic pacemaker properties as opposed to the ION. The neurodegeneration hypothesis proposes that cerebellar degeneration with accompanying loss of PC results in decreased GABAergic activity within deep cerebellar nuclei. This consequently results in the disinhibition of the intrinsic pacemaker activity of deep cerebellar nuclei which are under tonic control from PC.^{37,52} Rhythmic activity is then propagated to the thalamus and thalamocortical circuit which manifests as tremor³⁷ (Figure 3).

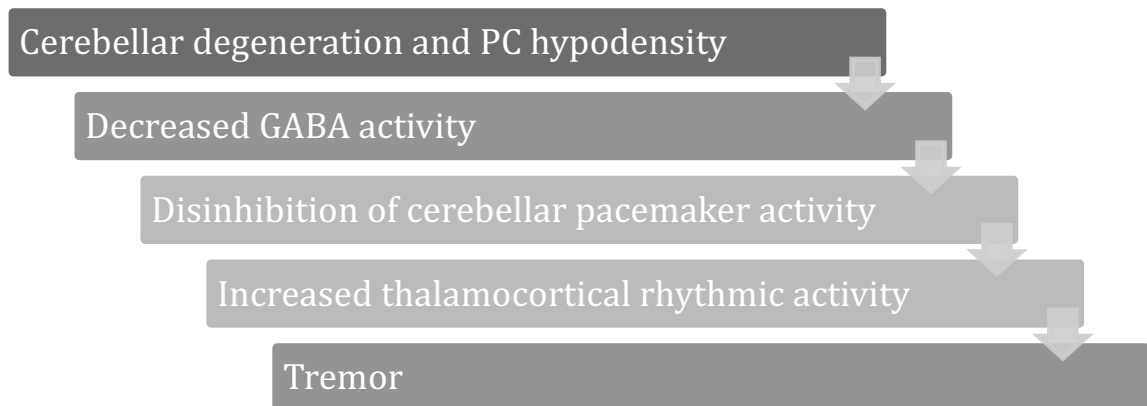


Figure 3: Stepwise Progression of the Neurodegeneration Hypothesis (Adapted from Gironell, 2014)³⁷

This hypothesis has largely been supported by postmortem studies that have demonstrated reduction of PC and decreased GABA receptors. One postmortem evaluation of ET brains, demonstrated a 35% reduction in GABA_A receptors and 22-31% reduction in GABA_B receptors in the dentate nucleus when compared to PD controls.⁴⁵ However, the neurodegeneration hypothesis extends beyond just cerebellar involvement. Disease severity has also been linked to atrophy of the cortex and neurodegenerative changes to the pons. A postmortem study that demonstrated a reduction of PC by as much as 25%, also interestingly demonstrated Lewy Bodies in the locus coeruleus of 24% of subjects.⁵¹ The finding of reduced PC density in addition to PC axonal swelling has been recounted across other studies, however the presence of Lewy Bodies has not been as ubiquitous.^{20,21} Thus, the preservation of gross cerebellar changes makes a compelling argument for the neurodegeneration hypothesis, however the inability to consistently demonstrate changes outside of the cerebellum argues against the hypothesis as a whole. These inconsistent gross pathological findings could, of course, be a result of patients

carrying an inaccurate diagnosis or due to the genetic and clinical heterogeneity of the disease.^{17,19} Cortical atrophy and Lewy Bodies could also explain the cognitive impairment observed in ET patients and does coincide with insidious, progressive nature of the disease.^{19,24} Yet, the presence of Lewy Bodies, cortical atrophy and PC swellings fail to explain why alcohol effectively manages ET.¹⁹

Synthesis of Existing Research

Ethanol is understood to be one of the most potent tremor suppressors in patients with ET with a response rate ranging between 46-74%.^{9,53} While not reducing frequency, it has a substantial effect on the amplitude of tremor and has proven more efficacious in tremor reduction in ET patients than the first-line medications propranolol and primidone.^{34,54} Although predictors of ethanol sensitivity have not been established, there is generally a preserved response amongst family members and responsiveness appears to be independent of age of disease onset.^{53,55,56} And while the exact tremorolytic mechanism of action of ethanol on ET is incompletely understood, it is largely believed to be mediated by action involving both the GABA and oscillating network hypotheses.

Ethanol increases GABAergic neurotransmission via an increase in presynaptic release of GABA and the dephosphorylation of GABA_A receptors which promote increased GABA sensitivity.⁴⁸ Ethanol can also modulate extrasynaptic GABA_A receptors containing δ and $\alpha 6$ subunits whereas BZD cannot. This realization offers insight into the greater therapeutic effect offered by ethanol when compared to BZDs.^{9,49} Studies that have examined GABAergic dysfunction as a causal explanation for ET, have also demonstrated benefit with ethanol administration. The subunit $\alpha 1$ KO mice not only demonstrate tremor consistent with ET, but also demonstrate a responsiveness to ethanol.⁴³

Ethanol also exerts an inhibitory effect on harmaline-induced tremor via a mechanism involving the regulation of low-threshold calcium channels found within the ION.⁵⁵ These are the same T-tCaC implicated in the oscillating network hypothesis.

Ethanol thus leads to a decreased neuronal firing rate in the ION and decreases subsequent propagation of bursting activity to the PC of the cerebellar cortex, deep cerebellar nuclei and by extension the CCTC.⁵⁷ Ethanol has also demonstrated antagonistic properties of gap junction function within the ION. Hypersynchronization of auto-oscillatory firing between ION neurons could therefore be interrupted via the effects of ethanol.³⁴

Ethanol as a therapeutic option for ET is not realistic for obvious reasons. For one, ethanol provides therapeutic benefit at doses relatively close to the median effective dose (ED50) for intoxication.⁵⁸ Furthermore, a brief duration of action and well-established rebound tremor make its clinical role impractical.⁵⁵ Finally, routine use of ethanol can lead to potential medical, social and legal consequences and there is concern that ET management with ethanol could lead to use dependence and alcoholism.¹⁰ ET has even been proposed as an important cause of secondary alcoholism as a result of self-medicating.⁵⁹

It is therefore clear that while ethanol has proven efficacious in reduction of tremor amplitude in patients with ET, and has a mechanism of action explained by leading hypotheses of ET pathology, it is not a plausible therapeutic option. However, alcohols as a class involve other compounds beyond just ethanol. This evident understanding led to evaluation of other alcohols as potential treatment options for patients with ET. In particular, the eight-carbon alcohol 1-octanol garnered moderate interest and attention. Not only was it understood that high molecular weight alcohols such as 1-octanol could inhibit low threshold calcium channels in the ION of animal

models, it was also discovered that in 1989, 1-octanol proved efficacious in the treatment of harmaline-induced tremor.⁶⁰ 1-octanol is also understood to have a favorable safety profile being previously approved by the U.S. Food and Drug Administration as a food additive at a daily intake of 1mg/kg/day and animal studies demonstrated a median lethal dose (LD50) at substantially higher doses ranging from 3500-20000 mg/kg. In 2003, a pilot trial of 1-octanol involved administration of the alcohol to 12 ET patients at a dose of 1 mg/kg. The results showed an improvement of ET at 90 minutes. Furthermore, no signs of intoxication were noted, there was no change in liver function tests (LFTs) or vital signs and the only adverse effects (AE) noted were mild dysgeusia and a headache that was responsive to Tylenol.¹¹ Dose escalation trials of 1-octanol demonstrated a trend toward dose response with prolonged response at higher doses. Patients who received 64mg/kg saw a progressive reduction in tremor amplitude starting at 4 hours of 39% and ultimately improving to a 74% reduction at 6 hours. 10% of the patients described lethargy at a dose of 64mg/kg, but there was again no lab or electrocardiogram abnormalities appreciated, nor were signs of intoxication observed.⁵⁸ The main limitation of the 1-octanol stemmed from the substantial dose required for clinically significant improvement of tremor. The largest capsule of 1-octanol available is 800mg, and therefore the average American male weighing about 90kg, would require in excess of 14 capsules to maintain a dose of 128mg/kg.⁹

Octanoic acid (OA) is an 8 carbon, saturated medium-chain fatty acid. It occurs naturally in mammalian milk and can also be found in coconut and palm kernel oil.⁶¹ More importantly though, it is the primary metabolite of 1-octanol, and was first

determined by Nahab et al. in 2011 to have tremorolytic properties in ET patients.¹⁴ OA had been used previously for treatment of refractory epilepsy and dietary studies have shown a dose of 710mg/kg is considered safe.¹² Since the Nahab paper, further trials evaluating the efficacy and safety profiles of OA have been limited. A double-blind, placebo-controlled, crossover phase I/II clinical trial demonstrated doses of 4mg/kg resulted in significant improvement in dominant hand tremor when compared to placebo. Although the study failed to meet its primary outcome (significant improvement of dominant hand tremor at t=80 minutes when compared to placebo), there was a significant reduction of dominant hand tremor at 300 minutes post administration with a trend toward benefit starting at t=150 minutes.⁶² An additional study evaluated the maximum tolerated dose (MTD)—among other pharmacokinetic properties—in patients with ET using a 3+3 dose-escalation design starting at a dose of 8mg/kg of OA. The study was unsuccessful in determining MTD since none of the 15 patients demonstrated dose limiting toxicity, however they did demonstrate a dose-dependent reduction of tremor using a PK (concentration)/PD (effect) model employing TETRAS as a tool for evaluating effect. The AEs of this study were predominantly self-limited abdominal discomfort which was attributed to patients having to take up to 26 capsules within a minute once they had reached a dose of 128mg/kg.¹⁰ The most recent study evaluating efficacy of OA in ET looked at the efficacy in treatment of essential voice tremor (EVT). Results demonstrated no improvement of EVT with dose escalation to 32mg/kg.⁶³ OA can thus be summarized as a drug with a favorable safety profile that is efficacious in

treating tremor amplitude in patients with ET, but at doses that require ingestion of a quantity of capsules that detracts significantly from its feasibility.

METHODS

Study design

The proposed study will be a double-blinded, parallel-group, placebo-controlled randomized control trial assessing the effect of OA as an adjuvant used in combination of propranolol and primidone as evaluated by the performance section of TETRAS (Appendix 1). The experimental group will receive OA in combination with propranolol and primidone, while the control group will receive placebo capsules in addition to propranolol and primidone.

Study population and sampling

The study population for this trial will include patients who meet consensus criteria for classical ET.¹ Patients must have failed the first-line treatments primidone and propranolol to the extent that MTD did not meet desired outcome. Failure of first-line medication cannot be the result of significant AE. Further inclusion and exclusion criteria are outlined in Table 1. Patients will be recruited over the course of one year. The estimated sample size will be 260 subjects with 130 subjects per arm. Sample size calculated assuming an α of 0.05, β of 0.2 effect size of 4 and standard deviation of 11.5.^{10,64}

Subjects will be recruited from the outpatient neurology clinics of four greater Boston area hospitals including Tufts Medical Center, Massachusetts General Hospital, Boston Medical Center and Brigham and Women's.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Classical ET as previously diagnosed by board certified neurologist and outlined by the consensus criteria for classical ET ¹	Substantial non-essential tremor neurological conditions demonstrated on initial evaluation
Consenting Individual ages 21-65	Warfarin or NSAID use
Prior failure of primidone and propranolol due to lack of efficacy or those currently on either medication with substandard control of symptoms	Contraindications or significant AEs to primidone or propranolol
Predominant ET component involving the upper limbs	Patients of East Asian or Native American descent as they may possess variant alleles influencing alcohol metabolism, resulting in higher sensitivity to toxic effects of alcohol ¹⁰
Agreeable to abstain from alcohol or caffeine within 48 hours of TETRAS evaluation	Hepatic impairment as demonstrated by elevated transaminases and/or total bilirubin
Agreeable to discontinue other tremorlytic medications for greater than 4 plasma half-lives prior to initiation of the study and to refrain from restarting these medications until after the completion of the study	Renal impairment as demonstrated by CKD stages 2-5
	Known deficiency of medium-chain acyl-CoA dehydrogenase
	Patients who have undergone invasive procedures for tremor control

Treatment

The eligible study population will be randomly assigned to a study group in a 1:1 ratio based off of a random number generator. Once assigned, patients will be scheduled to undergo baseline evaluation including vital signs electrocardiograms (EKGs), LFTs, chem-7, complete blood count (CBC), and urinalysis. A subsequent evaluation to assess baseline TETRAS performance subscale (Appendix 1) will be performed. Patients will be asked to abstain from alcohol or caffeine use 48 hours prior to this visit. Primidone and propranolol will then be optimized over the course of the following six weeks with the

assistance of patients' primary neurologists. Patients who have discontinued the medications will be started on primidone at 25mg PO every night at bedtime (qhs). This will be escalated by doses no less than 25 mg and no more than 100mg every third day (q3d) until either optimization is achieved, the patient reaches maximal recommended daily dose of 750mg or the patient has reached their MTD.⁶⁵ On day five of primidone titration, 60mg of propranolol long acting (LA) will be added and dosed in the morning. Subsequent increases of 20-40 mg will occur every fifth day (q5d) until optimization, 320mg/day or MTD.⁶⁵ Manifestations of symptomatic bradycardia including syncope, near-syncope and lightheadedness will be discussed with patients before initiating or further optimizing propranolol LA. At three weeks of optimization patients undergoing optimization protocol will have video conference virtual visits with their primary neurologists to allow for appropriate alterations in dose titration and to evaluate for AEs. Patients will be asked not to adjust medication doses within five days of the completion of the six-week optimization. If a patient is optimized prior to six weeks they can contact the study to arrange for earlier intervention. At the end of week six, patients will report to testing sites where repeat vital signs, EKGs, LFTs, chem-7, blood counts and urinalyses will be performed. Serum primidone and propranolol levels will be evaluated with LabCorp assays 007856 and 808491 respectively. The chronological outline of this process is demonstrated in Figure 4.

Day	-2	0	3	5	6	9	10	12	15	18	20	21	24	25	27	30	33	35	36	37	40	42
	Red	Blue	Green	Purple	Green	Green	Yellow	Green	Green	Green	Yellow	Green	Green	Yellow	Green	Green	Green	Yellow	Green	Orange	Red	Black
									Yellow			Purple										

Red	Discontinue caffeine and alcohol	Yellow	Increase propranolol LA 20-40 mg as tolerated
Blue	Initiate primidone 25mg qhs	Orange	No further increases in dosing
Green	Increase primidone 25-100mg as tolerated	Purple	3 Week video evaluation
Purple	Initiate propranolol LA 60 mg qam	Black	6 Week evaluation and OA/ placebo testing

Figure 4: Subject Scheduling: Outline of dose escalation along with other clinical trial obligations

Subsequent TETRAS performance subscale will be performed prior to the administration of OA (time 0). Patients in the experimental group will then receive 32mg/kg dose of octanoic acid soft gel capsules. Placebo group will receive the same capsule quantity as if they were receiving a 32mg/kg dose of OA. Soybean oil in identical softgel capsules will serve as placebo.⁶³ Evaluation will again be performed via TETRAS subscale at 80, 150 and 300 minutes post administration. The primary outcome of the study will be reduction of TETRAS performance subscale at 300 minutes when compared to time 0. For subjects wishing to discontinue propranolol LA upon completion of the study, they will be tapered down over the following 1-2 weeks to avoid acute myocardial infarction or angina as a result of abrupt discontinuation.⁶⁶ Those wishing to discontinue

primidone, specifically those undergoing treatment prior to the trial, will do so under the supervision of their primary neurologist to avoid potential withdrawal symptoms.

Study variables and measures

The method of assessment used in this trial will be TETRAS performance score on a scale of 0-64. The details of the scoring system can be found in Appendix 1. Adverse effects will be measured by common terminology criteria for adverse events (CTCAE) v5.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/). The primary outcome of the study will be reduction of TETRAS performance subscale at 300 minutes when compared to placebo.

Recruitment

The outpatient neurological clinics of the four medical centers mentioned in the *Study Population and Sampling* section will develop a list of potential candidates from clinic visits. The patients' primary neurologists will develop this list based off of patients who meet inclusion criteria 1-3 in table 1. Consent will be signed by potential subjects and co-signed by their primary neurologists. Following referral, potential subjects will be evaluated by clinical members of the study to evaluate remaining inclusion and exclusion criteria as outlined in Table 1.

Data collection

Participant sex, age, race, vital signs, body mass index (BMI), liver and kidney function, serum electrolytes, CBC and EKG will be performed on study day one and again at the end of study week six. Serum primidone and propranolol levels will also be collected the end of study week six. These results will be recorded in Microsoft Excel with corresponding participant demographics.

AEs will be reported by participants to either their primary neurologist or to the study directors. Subjects will be asked to inform either the study directors or their neurologists of AEs as they occur, but participants will also be evaluated for AEs at virtual visits on optimization week three and on week six prior to and after the administration of OA. AEs will be recorded in association with subject age, sex and race and graded according to the CTCAE v5.0.

Tremor severity and change will be measured using TETRAS as outlined in Appendix 1. Examiners will be certified to perform TETRAS evaluation prior to initial subject evaluations. Examiners will view the “TETRAS Lecture” and watch video examples 1-6 as provided by *The Tremor Research Group*. Scoring on the TETRAS Performance subscale (0-64 points) will be recorded and logged with the corresponding subject identifier.

Data analysis

Serum primidone and propranolol levels as well as phenobarbital:primidone ratios will be compared to expected levels for chronic compliance. Expected levels will be determined

based off of time and dose of most recent drug administration and known pharmacokinetics for both medications. Inconsistencies between expected and measured serum levels, consistent with non-compliance, will result in the voiding of that subject's data. A Wilcoxon rank-sum test or two sample, unpaired t-test as appropriate, will be used to analyze primary outcome: significant reduction in TETRAS performance subscale at 300 minutes post-OA administration when compared to placebo. Linear regression will be used to evaluate trend in TETRAS performance subscale over time. Time points will include study day 1, before administration of OA (time 0) and at three time points (80, 150 and 300 minutes) after the administration of OA. Linear regressions will be used to compare TETRAS performance subscale at 300 minutes and serum levels of primidone and propranolol in both arms. Mean, median, range and standard deviation of TETRAS performance subscale will be calculated for each study arm at corresponding time points. Participant demographics will be analyzed using descriptive statistics to summarize data: Age and BMI will be reported using mean and standard deviation while race and AEs will be reported using proportions.

Timeline and resources

Table 2: Timeline

Fall of 2021	<ul style="list-style-type: none">• IRB submission and approval• Recruitment of personnel to implement study design and perform TETRAS evaluations
January 2022- January 2023	<ul style="list-style-type: none">• Participant recruitment• Treatment Intervention
Spring 2023	<ul style="list-style-type: none">• Data analysis• Completed study to be submitted for peer review

This study will require evaluators to administer the TETRAS performance examination and the learning materials to educate them which will be provided by *The Tremor Research Group*. The study will also require the collaboration of neurologists working with subjects to optimize dose. Private examination rooms will be required to perform these evaluations. OA will be required in different formulations of 200, 400 and 600mg gel capsules. Identical soybean oil capsules will need to be obtained to serve as placebo. Furthermore, this study will require ample primidone tablets in 50 and 250 mg formulations as well as propranolol LA 60, 80, 120 and 160 mg formulations.

Institutional Review Board

The study will be submitted for full IRB review protocol under INSPIR II criteria of the Boston University Medical Campus as well as the corresponding IRBs of the other four participating Medical Institutions.

CONCLUSION

Discussion

There are some notable limitations of this study. First of all, the subjects recruited are likely to all be from the greater Boston area. While this area does encompass a relatively heterogenous population with diverse demographics, it is nonetheless difficult to generalize the findings to the national or international community. This is especially true when one recalls that no consistent gene loci has been discovered that exists across all ET populations and that more likely than not, there are many different subtypes of ET.²⁴

Due to the subjective nature of TETRAS, poor inter- and intra-rater reliability has the potential for skewing results. However, TETRAS was chosen as a means of evaluating tremor as it has previously demonstrated exceptional inter- and intra-rater reliability.⁶⁴ The degree of reliability will be reduced as greatly as possible by a small number of TETRAS evaluators and formal training provided by *The Tremor Research Group*. To keep the number of observers low and study participants high will result in an evaluator to subject ratio that is demanding of the evaluator. This will be particularly challenging at the end of the six-week optimization trial where evaluators must perform four TETRAS performance subscales over the course of five hours for every subject. Similarly, this will require that subjects be at the testing facility for around six hours on the final day of the study.

Obstacles in this study can be expected during the optimization period of both primidone and propranolol LA. While once daily dosing per medication is intended to

reduce complexity of adhering to medication regimen, lack of direct oversight of the optimization will likely result in imperfect adherence to optimization and compliance.

Summary

Essential tremor is a highly prevalent movement disorder with first line therapies that have not evolved substantially in decades. Additionally, propranolol and primidone often fail to substantially alleviate symptoms and/or have side effect profiles that force discontinuation.^{2,6} Recently, the 8-carbon alcohol, 1-octanol, and its primary metabolite octanoic acid have been investigated for their tremorlytic properties. Early trials have demonstrated efficacy when compared to placebo, however low dose formulations have posed practicality barriers as therapeutic dosing would require the consumption of multiple capsules often leading to gastrointestinal discomfort.^{9,10}

The proposed study primarily looks to evaluate OA as an adjuvant treatment for the first time while simultaneously demonstrating clinically significant tremorlytic properties at doses low enough to warrant clinical utility. If successful, this would provide clinicians with an additional treatment option for a disorder in which consistent, efficacious medical therapy remains elusive.

Clinical and/or public health significance

A portion of the ET population progress to develop tremors that are disruptive to the extent that they are unable to perform functions required by their occupation.¹⁷

Additionally, there is a well-established psychological toll that results from ET as

evidenced by patients developing anxiety and becoming socially withdrawn.³

Furthermore, treating severe ET presentations is becoming more reliant on expensive invasive procedures that carry with them inherent risk.¹³ For these reasons, improving and expanding existing medical therapy for ET should be paramount. This is the goal the proposed study aims to accomplish.

APPENDIX

Appendix 1

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out. Maximum total score is 64.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.
 - 0 = no tremor
 - 1 = slight tremor (< 0.5 cm)
 - 2 = mild tremor (0.5- < 2.5 cm)
 - 3 = moderate tremor (2.5-5 cm)
 - 4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.
 - 0 = no tremor
 - 1 = slight; barely perceptible tremor
 - 2 = mild: noticeable tremor
 - 3 = moderate: obvious tremor, present in most voluntary facial contractions
 - 4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended “aaah” sound and “eee” sound for 5 seconds each. Then assess speech during normal conversation by asking patients “How do you spend your average day?”.
 - 0 = no tremor
 - 1 = slight: tremor during “aaah” and “eee” and no tremor during speech
 - 2 = mild: tremor in “aaah” and “eee” and minimal tremor in speech

3 = moderate: obvious tremor in speech that is fully intelligible

4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral “wing beating” posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

Right	Left	Task
		Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground for 5 seconds. The wrist should also be straight and the fingers abducted so that they do not touch each other.
		Lateral “wing beating” postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
		Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

For all three hand tremor ratings

0 = no tremor

1 = tremor is barely visible

1.5 = tremor is visible, but less than 1 cm

2 = tremor is 1- < 3 cm amplitude

2.5 = tremor is 3- < 5 cm amplitude

3 = tremor is 5- < 10 cm amplitude

3.5 = tremor is 10- < 20 cm amplitude

4 = tremor is \geq 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

Greatest lower limb score	
	0 = no tremor 1 = slight: barely perceptible 2 = mild, less than 1 cm at any point 3 = moderate tremor, less than 5 cm at any point 4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills $\frac{1}{4}$ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

Right	Left	
		0 = normal 1 = slight: tremor barely visible. 2 = mild: obvious tremor 3 = moderate: portions of figure not recognizable. 4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

- 0 = normal
- 1 = slight: untidy due to tremor that is barely visible.
- 2 = mild: legible, but with considerable tremor.
- 3 = moderate: some words illegible.
- 4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an

X) without touching it, (ideally approximately 1 mm) for 10 seconds ”. Each hand is scored separately.

Right	Left	
		0 = no tremor 1 = tremor is barely visible 1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude 2.5 = tremor is 3- < 5 cm amplitude 3 = tremor is 5- < 10 cm amplitude 3.5 = tremor is 10- < 20 cm amplitude 4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject’s side. Tremor is assessed at any point on the legs or trunk

- 0 = no tremor
- 1 = barely perceptible tremor
- 2 = obvious but mild tremor, does not cause instability
- 3 = moderate tremor, impairs stability of stance
- 4 = severe tremor, unable to stand without assistance

Total for Performance Subscale _____ (64 max)

LIST OF JOURNAL ABBREVIATIONS

Arch Neurol.....	Archives of Neurology
Can J Neurol Sci.....	Canadian Journal of Neurological Sciences
Clin Neurophysiol.....	Clinical Neurophysiology
Food Chem Toxicol.....	Food and Chemical Toxicology
Front Neural Circuits.....	Frontiers in Neural Circuits
Gen Pharmacol.....	General Pharmacology
J Clin Invest.....	Journal of Clinical Investigation
J Neurol Neurosurg Psychiatry.....	Journal of Neurology, Neurosurgery, and Psychiatry
J Neurophysiol.....	Journal of Neurophysiology
Neurosci Lett.....	Neuroscience Letters
Parkinsonism Relat Disord.....	Parkinsonism & Related Disorders
Pflugers Arch.....	Pflügers Archiv: European Journal of Physiology
Proc Natl Acad Sci USA.....	Proceedings of the National Academy of Sciences of the United States of America
Rev Neurol (Paris).....	Revue Neurologique
Tremor Other Hyperkinet Mov.....	Tremor and Other Hyperkinetic Movements26

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