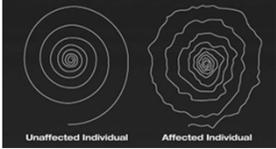


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## Essential Tremor

*Diagnosis and Treatment*



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## Essential Tremor- Objectives

- Recognize key features distinguishing essential tremor from other tremor syndromes
- Understand the natural history, epidemiology and pathophysiology of essential tremor
- Review current and emerging medical, non-medical and surgical treatment options for essential tremor

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## Conflict of Interest, Off-Label Use

- Research Support from
  - NIH, MJ Fox Foundation
  - Pharmaceutical
    - UCB, Aspen Pharmaceutical, Aeon Pharmaceuticals, Neuroderm, Sage Pharmaceuticals, Cerevel, Annovis, Inhibikase, Buckwang
- Off label uses of drugs will be discussed for treatment of essential tremor
  - Propranolol is the only FDA approved drug indicated for treatment of essential tremor

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## Tremor Terminology

- **Tremor:** rhythmic, oscillating, alternating contraction of agonist and antagonist muscles
- **Action tremor:** occurs during voluntary contraction of skeletal muscles.
  - Kinetic: during guided voluntary movements; e.g., writing, touching finger to nose.
  - Postural: in a body part maintained against gravity; sustained arm extension, arms extended/abducted with elbows flexed
- **Rest tremor:** when a limb is fully relaxed  
 \* *observing upper limbs while walking is a valuable tool*
- **Intention tremor:**
  - tremor with visually guided movement
  - Increases in amplitude with approach of the target
  - most often seen with other signs of cerebellar dysfunction

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## Essential Tremor-Overview

- Most common adult-onset movement disorder
- Can start at any age
- **SLOWLY** progressive (2-5%/yr)
  - increased tremor amplitude
  - extension to previously unaffected body parts
- AKA- Hereditary Tremor,  Essential Tremor
  - Not associated increased mortality; Absence of other neurological signs
  - Not **benign for many patients**. (Function & Quality of Life)
- **Possibly** accompanied by:
  - Other motor features (e.g. ataxia, rest tremor, dystonia)
  - Spasmodic dysphonia
  - non-motor features (e.g. cognitive impairment, depression and personality disturbances)

Louis, et al., Parkinsonism Relat Disord. 2011)

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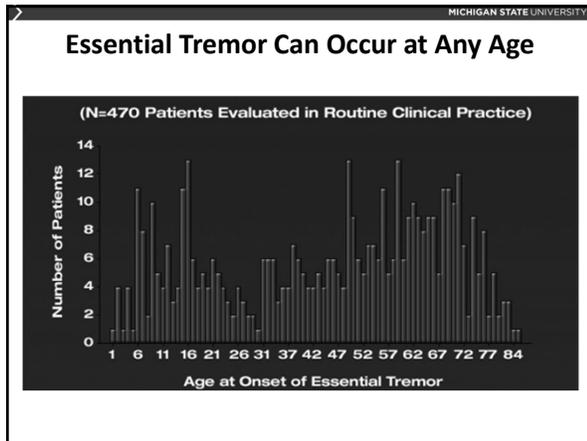
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## Essential Tremor can be Disabling

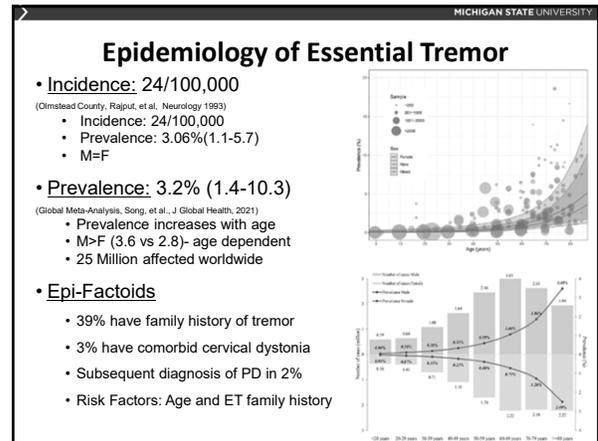
- 85% of ET patients have impaired socialization & work performance
- 15–25% of ET patients are disabled and can't work
- Social withdrawal & isolation
- Tremor worsens with anxiety, fatigue and illness
- Anxiety and depression
- Medication side effects
- Factors associated with disabling tremor
  - Physical disability related to age
  - Tremor amplitude
  - Ability to execute fine motor tasks
    - e.g., writing, drinking, eating and other ADLs

**Kinetic Tremor**

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### Genetics of Essential Tremor

- Familial clustering noted as early as 1836
- Family history of ET in 1<sup>st</sup> degree relative in 30-70%
  - Higher risk if relative had younger onset ET
- Complex Genetics
  - Most likely autosomal dominant, variable penetrance
  - Genome-wide linkage:
    - Loci ETM1, ETM2, ETM3
  - Association studies: TREM2, GABA-A
  - GWAS
    - LINGO1 (1.2-1.7)
    - SLC1A2 (OR 1.4)

Clark and Lewis, Handb Clin Neurol. 2018 ; 147: 229-239

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### Pathophysiology of Essential Tremor

- Pathways thought to be involved
  - Thalamus (Vim), Sensorimotor Cortex, Olivary nucleus, Cerebellum
  - Ablation/lesions in these areas can reduce tremor
- Postmortem studies have demonstrated a heterogeneous pathology, clustered into 2 groups:
  - Cerebellar degenerative changes
  - Brainstem Lewy bodies ('Lewy body variant of ET')
- Environmental toxicant link?
  - harmaline and lead

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### ET Pathophysiology

- Interconnected oscillatory loops
  - olivo-cerebello-rubral loop
  - Central oscillator
    - Inferior Olivary Nucleus, Corticothalamic
  - Sensory feedback from muscle
- Peripheral contribution
  - Beta adrenergic blockers attenuate ET (β2 and/or β3 antagonists)
  - Peripheral injuries or severe neuropathy can cause tremor
  - IV or IA administration to isolated forearm
    - Epinephrine- increases tremor
    - Beta antagonists reduce tremor and can block the ability of epinephrine to cause tremor
- GABA Deficit Hypothesis
- T-Type Calcium Channel Oscillator

Milly J, et al., J Neural Transm. 1996; 103(5):555-60.  
Boecker et al., J Neurol Med. 2010  
Girolini, et al., Park Relat Disord. 2012  
Paris-Robbes, et al. Brain. 2012

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### Diagnostic Criteria for Essential Tremor

<p><b>Inclusion Criteria</b></p> <p><input type="checkbox"/> <u>Core Criteria</u></p> <ul style="list-style-type: none"> <li>Bilateral action tremor of the hands and forearms</li> <li>no resting tremor</li> <li>Absence of other neurological signs</li> <li>May have isolated head tremor</li> <li>No abnormal (dystonic) posture</li> </ul> <p><input type="checkbox"/> <u>Secondary Criteria</u></p> <ul style="list-style-type: none"> <li>Long Duration (&gt;3 years)</li> <li>Family History</li> <li>Improvement with alcohol</li> </ul>	<p><b>Exclusion Criteria</b></p> <p><input type="checkbox"/> Other abnormal neurological signs</p> <ul style="list-style-type: none"> <li>e.g., rigidity, bradykinesia, dysmetria, fixed posturing</li> </ul> <p><input type="checkbox"/> Known causes for enhanced physiological tremor</p> <p><input type="checkbox"/> Historical or clinical evidence for psychogenic tremor</p> <p><input type="checkbox"/> Sudden onset or stepwise progression</p> <p><input type="checkbox"/> Tremor in isolated position or location</p> <ul style="list-style-type: none"> <li>Voice</li> <li>Unilateral leg*</li> <li>Tongue/chin</li> <li>Postural/orthostatic</li> <li>Specific task (e.g., writing)</li> </ul>
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**Other Causes of Action/Postural Tremor**

- **Enhanced physiologic tremor**
  - Occurs during stressful or fear-provoking times
- **Medication induced tremor**
  - Over the counter, herbal and prescription medications
  - Steroids, Depakote, Lithium, TCA's, Amiodarone, dopamine antagonists, Cyclosporin, stimulants
- **Drug & alcohol withdrawal**
- **Trauma**
  - Closed head injury
  - Peripheral Injury
- **Metabolic: Hyperthyroid, hypercalcemia**
- **Other Hereditary Disorders (e.g., Wilson Disease)**
- **Psychogenic tremor**

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**Table 2. Selected Medications and Substances That May Exacerbate Tremor**

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

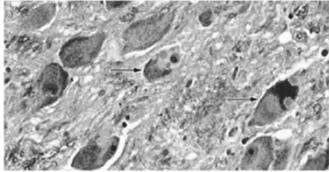
**Table 3. Characteristics of Psychogenic Tremor**

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

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**Relationship of Essential Tremor (ET) and Parkinson Disease (PD)? – both are common**

- Some (but not all) studies show a higher risk of PD in ET patients
- 2-19% of patients with ET have subtle parkinsonism
- 10% of patients with ET have a family history of PD
- PD is more common in ET kindreds than expected
- Striatonigral degeneration observed in ET
- Lewy bodies found in the locus coeruleus in a few ET patients



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**Essential Tremor: Diagnosis**

**Clinical history**

- careful attention to functional disability
- alcohol responsiveness
- onset and progression
- alcohol responsiveness
- family history

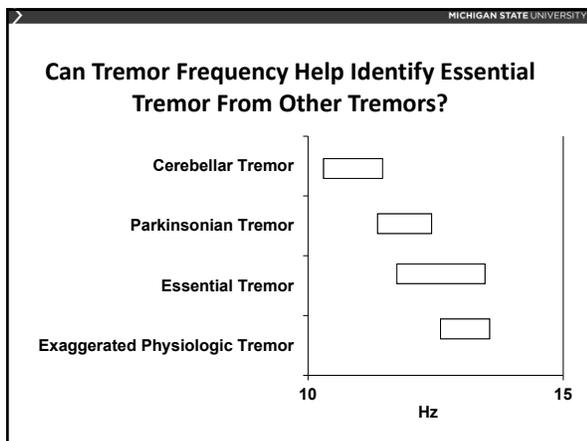
**Physical examination**

- Affected body part
- Rest vs posture
- Walking and distraction
- Absence of parkinsonism, dystonia, cerebellar dysfunction

**Objective/Function Assessment Tools**

- Spiral drawing, handwriting samples
- Water pour test, Cerebell bowl, Grooved Peg Board
- Electrophysiology, Accelerometry

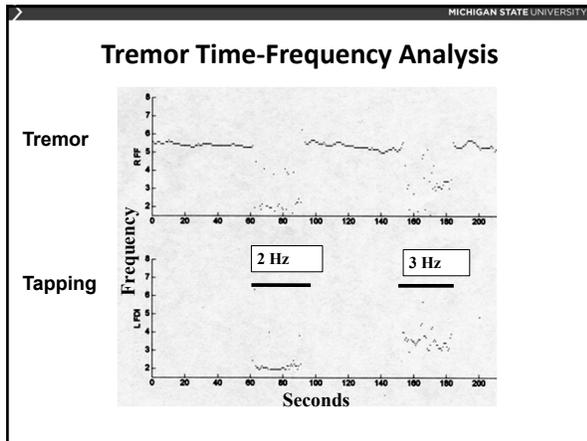
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Characteristic	Parkinson disease	Essential Tremor
<b>Family History</b>	Usually negative	Positive in ≥50%
<b>Improved with alcohol</b>	Postural tremor	Marked reduction in most
<b>Maximum tremor</b>	Resting and Postural	Posture, kinetic >> resting
<b>Symmetry</b>	No	Yes
<b>Affected body part</b>	Hands, Leg, Oral-buccal-lingual	Hands, Head, Voice
<b>Age at onset</b>	62.4	All ages
<b>Treatment sought</b>	Early	Often late
<b>Disease Course</b>	Slowly Progressive	Very Slowly Progressive
<b>Associated conditions</b>	Bradykinesia, rigidity, postural instability	Spasmodic dysphonia, Spasmodic torticollis

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### Essential Tremor: Diagnostic Testing

- Laboratory Studies**
  - TSH, calcium
  - Ceruloplasmin/24 hr urine copper
    - Screen for Wilson disease
      - if younger than 50yrs or other atypical features
- MRI Brain Imaging**
  - if Atypical Presentation
    - e.g.- unilateral postural/k
- DaTScan™**
  - SPECT imaging with dopaminergic ligand
  - Approved by FDA for differential diagnosis of tremor of parkinsonism

Two axial SPECT brain scans are shown. The left scan is labeled 'DaTScan of normal patient' and shows normal dopamine transporter binding. The right scan is labeled 'DaTScan of patient with Parkinsonian syndrome' and shows significantly reduced binding in the striatum.

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### ET Therapeutic Options

- No treatment**
  - Reassurance: none of the symptomatic treatments modify natural history
- Physical and psychological adaptation, lifestyle changes**
- Pharmacological**
  - Top Shelf (Best Evidence)
    - Beta-adrenergic antagonists
    - Primidone
  - Others
    - Benzodiazepines, topiramate, gabapentin, zonisamide
- Botulinum Toxin**
- Wearable Devices**
- Functional Neurosurgery**
- Research Studies** [www.clinicaltrials.gov](http://www.clinicaltrials.gov) [www.essentialtremor.org](http://www.essentialtremor.org)

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### Symptomatic ET Treatment: Beta Blockers

- Propranolol** (only FDA-approved drug indicated for ET)
  - 50-70% of patients obtain some symptomatic benefit
    - Tremor is rarely totally suppressed
    - Amplitude decreased, but frequency often is unaffected
  - Effects mediated by  $\beta_2$  and  $\beta_3$  Adrenergic Receptor
  - Wide dose range (60-240 mg/day)
  - Sustained Release = or > than immediate release
- Selective Other Beta Blockers: Timolol, Nadolol**
- Beta-1 Antagonists?**
  - Atenolol, Metoprolol.... May be less effective
- Use with CAUTION for patients with:**
  - Obstructive Lung Disease (Asthma, COPD)
  - Severe or poorly controlled depression
  - Insulin requiring diabetes mellitus
  - Advance age (higher risk of symptomatic bradycardia)

The chemical structure of Propranolol is shown as CC(N)C(O)COc1ccc2ccccc12. Below it is a photograph of several Propranolol tablets.

AAN Evidence-based guideline update: Treatment of essential tremor Zesiewicz, Neurology, 77(19), 1752-1755, 2011, 2022  
<https://www.aan.com/Guidelines/Home/GuidelineDetail/492>

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### Primidone (Mysoline)\*

- Primidone and propranolol have similar efficacy for ET
- 66% have improvement in placebo-controlled trials
- Up to 20% have acute adverse effects
  - Sedation most common
  - Associated with higher starting dose, advanced age
  - Over time, tolerance reduces side effects
- Initiation of therapy with low dose (Start= 25 mg at bedtime)
- Slow upward titration
  - 25 mg each week
- Divide dose BID or TID
- Average effective dose = 250 mg/day
- Maximum dose = 750 mg/day
- CBC prior to initiation and 6 & 12 months after starting

*\*Off label use*

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### Other Pharmacological Approaches\*

- Combination of Propranolol and Primidone**
  - Synergism? May reduce tremor more than either used alone
  - No worsening of adverse events when used in combination
- Benzodiazepines** (modulate synaptic GABA-A Receptor)
  - Clonazepam, diazepam, lorazepam, alprazolam
  - Tolerance, dependence, withdrawal
  - Can impair thinking and balance
  - May be helpful if anxiety drives tremor
- Anticonvulsants**
  - Gabapentin, Topiramate, Zonisamide
- Carbonic anhydrase inhibitors**
  - Acetazolamide, Neptazane
- Clozapine**
  - Small study, need to monitor for agranulocytosis

*\*Off label use*

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### What doesn't work or is unknown to work for limb tremor

*AAN Practice Parameter*

- Advises against the following agents for limb tremor:
  - Trazodone
  - Acetazolamide, isoniazid, and pindolol, methazolamide, mirtazapine, nifedipine, verapamil probably does not reduce limb tremor.
- Insufficient or conflicting data for ET limb tremor:
  - Amantadine, clonidine, glutethimide, L-tryptophan, pyridoxine, metoprolol, nicardipine, olanzapine, phenobarbital, quetiapine and theophylline

<https://www.aan.com/Guidelines/Home/GuidelineDetail/492>

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### Botulinum Toxin Chemodenervation for ET

- Botulinum toxin type A
- Effect on limb tremor is modest
- Associated with dose-dependent hand weakness
- May reduce head tremor and voice tremor, but data is limited
- Trading off weakness for tremor reduction, sometimes a hard balance to strike

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### Treatment of Essential Tremor with Alcohol ?

- Alcohol reduces tremor in some patients
- Rebound tremor may occur after excessive alcohol intake
  - tremor can be temporarily more severe the next day
- Pre-treating prior to event ?
- Avoid excessive use of alcohol
- Do not drink and drive



**What about Cannabis Products?**

- No data from large RCT to support use
- CB1 and CB2 receptors found in brain areas associated with ET
- Synthetic CB1 agonist reduced tremor in harmaline rodent ET model
- Current trial- NCT03805750



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### Adaptive and Alternative Therapies

- Benefit is unconfirmed when using alternative therapies such as acupuncture, hypnosis, massage therapy, nutritional supplements, eye of newt, wing-o-bat...
- Biofeedback, Cognitive-Behavioral Therapy
  - May be helpful for people whose tremor worsens with stress
- Occupational therapy
  - Found helpful
  - Assistance with adaptive devices such as weighted utensils, plate guards, etc.






**The Tremadone Club**  
A monthly delivery of our powerful, all-natural tremor supplement



Sale Price: \$39.99 per month  
Shipping: Free Shipping in the US  
Supply: 60 capsules a month  
Guarantee: 60 Day Money Back Guarantee



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### Assistive Technologies:

[www.essentialtremor.org](http://www.essentialtremor.org)

Wearable weight, gyroscopic weighing, counter levering, exoskeleton



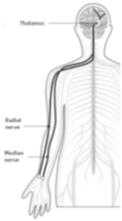





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### Transcutaneous Peripheral Nerve Stimulation





**Clinician-rated TETRAS Improvement or Clinic Visits**

Year	Pre	Post
Year 1	12.4	9.8
Year 2	11.9	9.7
Year 3	11.8	9.7

**Patient-rated ADL Improvement or Clinic Visits**

Year	Pre	Post
Year 1	18.4	14.5
Year 2	16.4	13.3
Year 3	15.8	13.4

\*p < 0.001

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### Essential Tremor Functional Neurosurgery

- Thalamotomy**
  - Stereotactic lesion of the Vim Thalamus for severe, refractory essential tremor
    - 78-100% show significant improvement
    - Bilateral thalamotomy increases risk for dysarthria
  - Gamma knife thalamotomy shows favorable outcomes in some studies, but:
    - Delayed complications have been reported
    - Delayed clinical effects (weeks to months)
- Deep Brain Stimulation**
  - Vim thalamus target approved in 1998
  - Unilateral or bilateral
- MRI Guided Focused Ultrasound**
  - Unilateral only



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### Deep Brain Stimulation (DBS) for Essential Tremor

- Consider DBS when:**
  - Medications fail to provide adequate relief
  - Dose-limiting medication side effects
  - Moderate to severe tremor
- DBS is an efficacious tremor treatment**
  - Tremor amplitude and frequency
    - 80-95% reduction in extremity tremor
    - 50-85% reduction in midline tremor (head, voice) with bilateral stimulation



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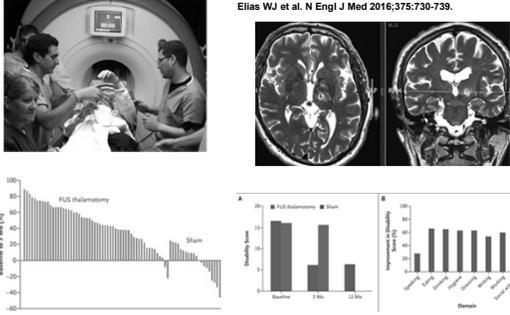
### Thalamic DBS for Essential Tremor



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### MRI Guided Focused Ultrasound for Essential Tremor

Elias WJ et al. N Engl J Med 2016;375:730-739.



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### Table 1 A comparison of surgical outcomes for ET

	DBS	FUS	GKRS	RF
Experience	1093 patients since 1998	151 patients since 2013	360 patients since 2007	278 patients since 1986
Level of Evidence, (OCER)	Level 2	Level 1	Level 4	Levels 2-4
Tremor control, 12-month follow-up	Unilateral: 53.4%-62.8% Bilateral: 66%-78%	Unilateral: 35%-75% Bilateral: no data	Unilateral: 48%-63% Bilateral: no data	Unilateral: 74%-90% Bilateral: no data
Tremor control, long-term follow-up	Unilateral: 60%-75% Bilateral: 75%	Unilateral: 56% Bilateral: 37%-73%	Unilateral: 3%-63% Bilateral: 74%-90%	Unilateral: 74%-90% Bilateral: 47%
Quality of life improvements	57.9%-82%	37%-73%	65%	47%
Complications (range, transient and permanent)	Unilateral, bilateral			
Dysarthria	11%-39%, 22%-75%	3%	1%-3%	4.6%-29%
Ataxialgait	9%-17%, 56%-86%	23%	0%-17%	5%-27%
Paresthesia	5%, 5.9%	14%-25%	1%-9%	6%-42%
Hemiparesis	4.5%, 6.7%	2%-7%	0%-8%	0%-34%

ET, essential tremor; DBS, deep brain stimulation; FUS, focused ultrasound; GKRS, gamma knife radiosurgical thalamotomy; RF, radiofrequency.  
Dallapiazza, et al., J Neurol Neurosurg Psychiatry 2019

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### Essential Tremor Surgery Comparisons

	DBS	FUS	GKRS	RF
Frame application	Yes	Yes	Yes	Yes
Hair removal	Partial	*Can be performed framelessly	None	Partial
Craniotomies	Yes	No	No	Yes
Target confirmation	MER, electrical stimulation, procedural evaluation	MER, electrical stimulation, procedural evaluation	Test lesions, procedural evaluations	Indirect anatomical targeting
Treatment effects	Immediate	Immediate	Delayed (typical delay 4 months)	Immediate
Adjustable	Yes	No	No	No
Reversible	Yes	No	No	No
Bilateral treatment	Yes	No	Yes	No
Implanted devices	Yes	No	No	No
Other considerations	Device maintenance and programming	MRI guided Skull penetration	Radiation	Variable thermal dosing

ET, essential tremor; DBS, deep brain stimulation; FUS, focused ultrasound; GKRS, gamma knife radiosurgical thalamotomy; RF, radiofrequency.

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## Treatments Under Development

- Drug Treatments
  - GABA-A Receptor Allosteric Modulators
    - SAGE 324, KINETIC-2 Trial
  - T-type Calcium Channel Blocker
    - Suvcaltemide (JZP385)
    - Ulixaltamide (PRAX944, Essential1 Trial)
- Surgical Treatments
  - Posterior Subthalamic Nucleus Deep Brain Stimulation
  - Closed-Loop Deep Brain Stimulation
  - Bilateral MRI-Guided Focused Ultrasound and Gamma Knife
- How to Find Clinical Trials for Essential Tremor
  - [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
  - [www.essentialtremor.org](http://www.essentialtremor.org)



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## Summary: Essential Tremor

- Essential Tremor is the most common movement disorder
- Essential Tremor can be differentiated from other conditions like Parkinson disease (in most cases)
- Pharmacological treatment with beta-blockers or/and primidone can reduce tremor
- Functional neurosurgery is highly effective in treating Essential Tremor
- New Treatment Are Under Development !

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