Hyperkinetic Movement Disorders

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Clinical Neurological Society of America

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Disclosures

Principal Investigator
- Roche
- Intracellular Therapy
- Biogen

Teaching Faculty
- Abbott

Advisor
- Orphalan

Objectives

Clinical Differentiation of Tremors and their management
Updates in HD
Updates in TD
Differential of chorea / ballism

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Tremor – Diagnostic Challenges

- Patient Challenges
- Poor awareness in patients and their affected family relatives (AFRs)
  - 1/3rd of the patients think that these are senile tremors
  - 1/4th unaware of extent of medication options
  - 38% not aware of brain surgery as a treatment option

Cristal AD, Chen KP, Hernandez NC, et al. Knowledge about Essential Tremor: A Study of Essential Tremor Families. Front Neurol. 2018;9:27.

- Clinical Challenges

Clinician Performance

- Randomly selected 50 patients diagnosed with ET, only 50 % were reported to have ET

Schrag A et al. Overdiagnosis of essential tremor . Lancet 1999 ; 353

- In NY Mov Dis Clinic, 1 in 3 patients were falsely diagnosed with Essential Tremor - Correct diagnoses - PD, dystonia, ET+PD

Jain S et al. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor Arch Neurol 2006 ; 63 (8): 1100 – 4

- Out of 104 consecutive patients in the Movement Disorders clinic, 55% were misdiagnosed as ET. Dystonia (27.9%) and other diagnoses (26.9%) including PD (5.8%) were missed the most.

Amlang, Christian J et al. "Essential Tremor as a "Waste Basket" Diagnosis: Diagnosing Essential Tremor Remains a Challenge." Frontiers in neurology vol. 11 172. 25 Mar. 2020, doi:10.3389/fneur.2020.00172

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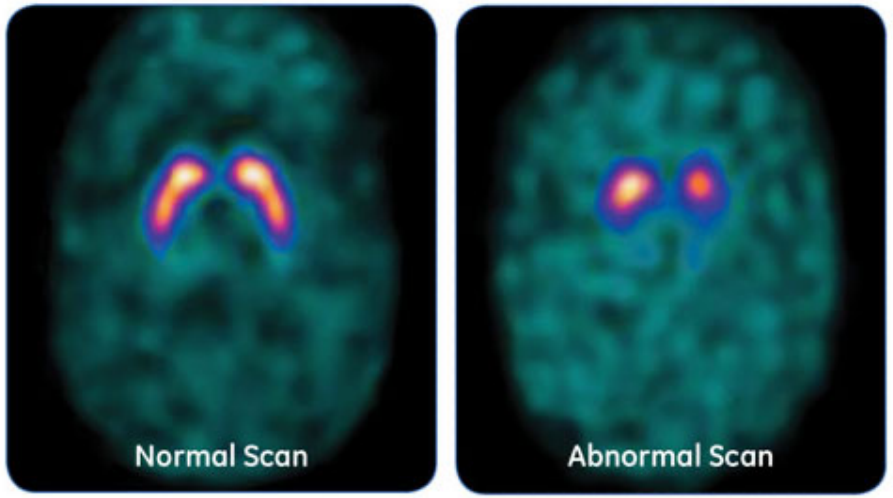
JAMA Internal Medicine
Formerly Archives of Internal Medicine

PERSPECTIVE

All My Husband Needed Was a Good Physical Examination

1. Two years of action tremors
2. PCP ordered a DAT scan
3. Two separate results
    1. Normal
    2. Abnormal scan consistent with Parkinson's disease
4. Data reconstruction by a colleague determined that patient's head was tilted
5. Overall impression of normal DAT scan but no conclusive diagnosis
6. Referral to a neurologist
7. THOROUGH clinical examination
8. Diagnosis of essential tremor
9. DAT scan was not necessary
10. Cost - $ 5700 !



"Comma"-shaped
Possible essential tremor

"Period"-shaped
Possible parkinsonian syndrome

In the end, all my husband needed was a good physical examination by a primary care physician.

AMA Intern Med. 2015;175(3):340. doi:10.1001/jamainternmed.2014.7183

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A. Rest tremors

1. **Parkinson disease (PD)**
2. **Other parkinsonian syndromes**
   a. Multiple system atrophies (SND, SDS, OPCA)
   b. Progressive supranuclear palsy
   c. Cortical-basal-ganglionic degeneration
   d. Parkinsonism–dementia–ALS of Guam
   e. Diffuse Lewy body disease
   f. Progressive pallidal atrophy
3. **Heredodegenerative disorders**
   a. Huntington disease
   b. Wilson disease
   c. Neuroacanthocytosis
   d. NBIA1 (Neurodegeneration with brain iron accumulation 1)
   e. Gerstmann–Sträussler–Scheinker disease
   f. Ceroid lipofuscinosis
4. **Secondary parkinsonism**
   a. Toxic: MPTP, CO, Mn, methanol, cyanide, CS_2
   b. Drug-induced: dopamine receptor blocking drugs neuroleptics ("rabbit syndrome"), dopamine-depleting drugs (reserpine, tetrabenazine), lithium, valproate, amiodarone, flunarizine, cinnarizine
   c. Vascular: multi-infarct, Binswanger disease, "lower body parkinsonism"
   d. Trauma: pugilistic encephalopathy, midbrain injury
   e. Tumor and paraneoplastic
   f. Infectious: postencephalitic, fungal, AIDS, subacute sclerosing panencephalitis, Creutzfeldt–Jakob disease
   g. Metabolic: hypoparathyroidism, chronic hepatic degeneration, mitochondrial cytopathies
   h. Normal pressure hydrocephalus
5. **Severe essential tremor (ET)**
6. **Midbrain (rubral) tremor**
7. **Tardive tremor**
8. **Myorhythmia**
9. **Spasmus nutans**

B. Action tremors

1. **Postural tremors**
   a. Physiologic tremor
   b. Enhanced physiologic tremor:
      (1) Stress-induced: emotion, exercise, fatigue, anxiety, fever
      (2) Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids
      (3) Drugs: β-agonists (e.g., theophylline, terbutaline, epinephrine), dopaminergic drugs (levodopa, dopamine agonists), stimulants (amphetamines), psychiatric drugs (lithium, neuroleptics, tricyclics), methylxanthines (coffee, tea), valproate, amiodarone, cyclosporine, interferon
      (4) Toxins: Hg, Pb, As, Bi, Br, alcohol withdrawal
   c. Essential tremor
      (1) Autosomal dominant
      (2) Sporadic
   d. Postural tremor associated with
      (1) Dystonia
      (2) Parkinsonism
      (3) Myoclonus
      (4) Hereditary motor-sensory neuropathy (Roussy–Levy)
      (5) Kennedy syndrome (X-linked spinobulbar atrophy)
   e. PD and other parkinsonian syndromes
   f. Tardive tremor
   g. Midbrain (rubral) tremor
   h. Cerebellar hypotonic tremor (titubation)
   i. Neuropathic tremor: motor neuron disease, peripheral neuropathy, peripheral nerve injury, reflex sympathetic dystrophy
2. **Kinetic (intention, dynamic, termination) tremors**
   a. Cerebellar disorders (cerebellar outflow): multiple sclerosis, trauma, stroke, Wilson disease, drugs and toxins
   b. Midbrain lesions
3. **Task- or position-specific tremors**
   a. Handwriting
   b. Orthostatic
   c. Other (e.g., occupational) task-specific tremors
4. **Isometric**
   a. Muscular contraction during sustained exertion

C. Miscellaneous tremors and other rhythmic movements

1. **Myoclonus: rhythmical segmental myoclonus (e.g., palatal), oscillatory myoclonus, asterixis, mini-polymyoclonus**
2. **Dystonic tremors**
3. **Cortical tremors**
4. **Epilepsia partialis continua**
5. **Nystagmus**

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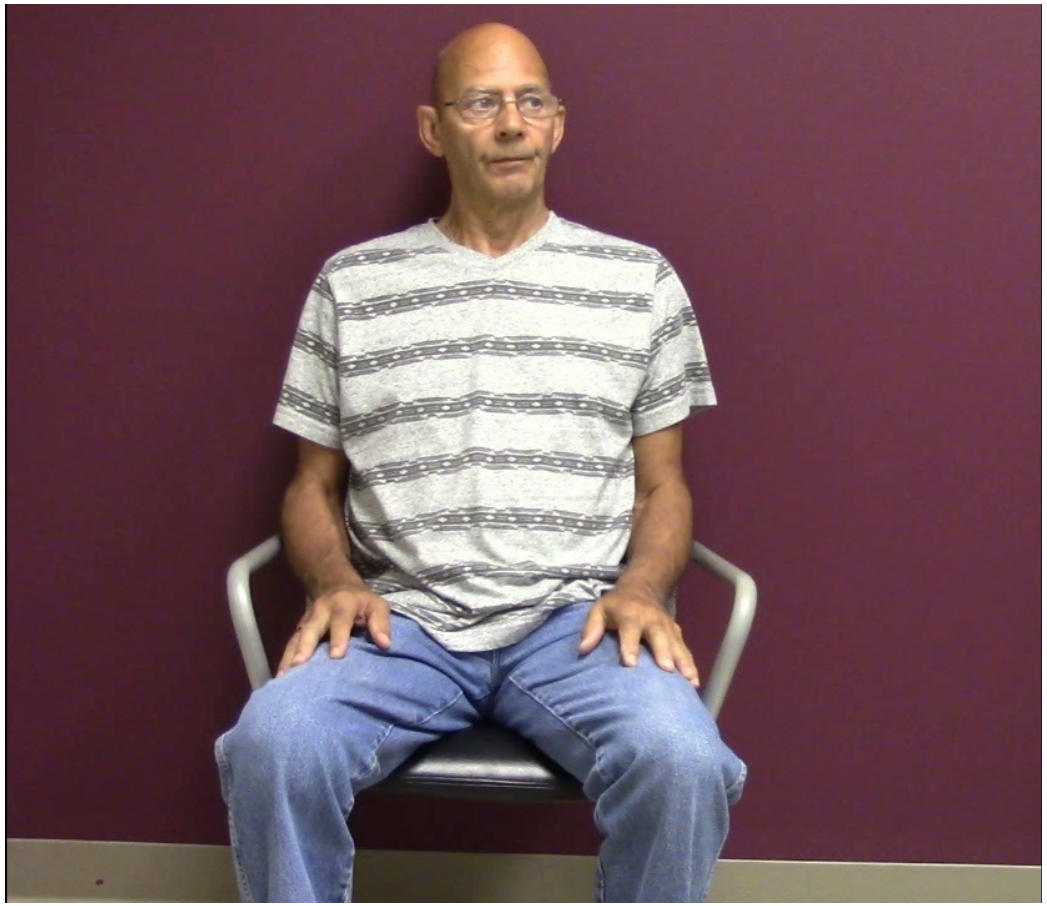
REST Tremors



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REST vs ACTION Tremors

- REST TREMOR

- Body part is fully supported against gravity and not contracting
- Diminishes with voluntary movement
- Most Common causes
  - Parkinson's disease (PD)
  - Wilson's disease
  - Drug induced parkinsonism
  - Dystonic tremor
  - Severe and chronic essential tremor

- ACTION TREMOR

- Occurs with voluntary contraction of the muscles
- Postural, Kinetic, Task specific, position specific and isometric tremors
- Most Common Causes
  - Enhanced physiologic tremor
  - Essential Tremor (ET)
  - Dystonic tremor
  - PD and parkinsonism
  - Drug induced tremor

POSTURAL TREMOR

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KINETIC TREMOR

ACTION TREMOR

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MOTOR FEATURES

- PD
  - ✓Rest tremor
  - ✓Unilateral at onset in 90% cases
  - ✓Postural tremor may be present
    - Metacarpal joints > wrist,
  - ✓Pronation-supination
  - ✓Kinetic tremor < postural tremor
  - ✓Presence of other tremors
    - Chin, leg tremors
  - ✓Rigidity
  - ✓Bradykinesia
  - ✓Reduced Arm swing
  - ✓Shuffling gait, reduced stride length, freezing

Sternberg EJ, Alcalay RN, Levy OA, Louis ED. Postural and Intention Tremors: A Detailed Clinical Study of Essential Tremor vs. Parkinson's Disease. Front Neurol. 2013;4:51.

- ET
  - ✓Postural Tremor
  - ✓Can be asymmetric but <10% cases unilateral
  - ✓Wrist > metacarpal joints
  - ✓Flexion – extension
  - ✓Kinetic Tremor > postural tremor
  - ✓Presence of other tremors
    - Head, voice, truncal
  - ✓ Rest tremor, rigidity and mild slowness and gait ataxia may be observed with chronic severe tremors

Louis E, Twelve clinical pearls to help distinguish ET from other tremors Expert rev neurotherapeutics. 9/2014, 1057 - 1065

NON-MOTOR SYMPTOMS

- PD
  - Autonomic symptoms
  - Postural hypotension, OAB, constipation
  - Anosmia
  - REM behavior disorder
  - Cognitive impairment
  - Visual hallucinations

- ET
  - Hearing Loss – sensory neuronal deficits
  - Cognitive impairment
  - Depression, apathy, anxiety and personality characteristics
  - Sleep dysregulation

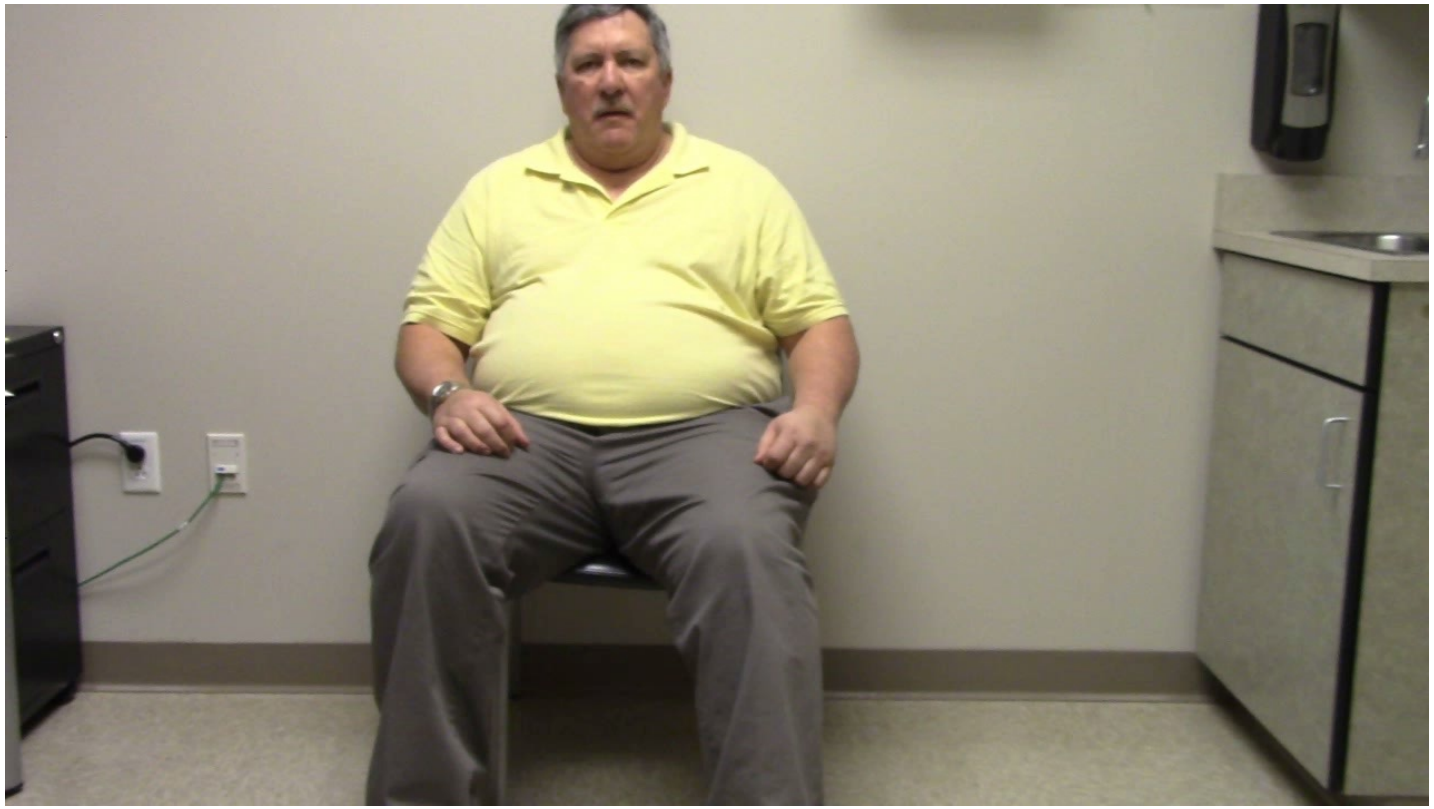
Ghika A, Kyrozis A, Potagas C, Louis ED. Motor and Non-motor Features: Differences between Patients with Isolated Essential Tremor and Patients with Both Essential Tremor and Parkinson's Disease. Tremor Other Hyperkinet Mov (N Y). 2015;5:335.

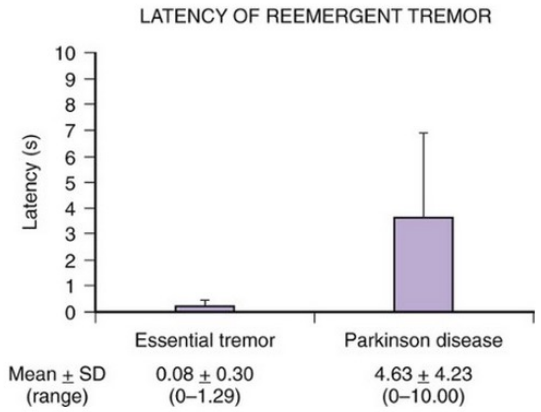
Non-motor symptoms in essential tremor: A review of the current data and state of the field. Louis E, Parkinson and Rel, 2016, Volume 22, Pages S115-S118

GAIT EVALUATION

RE-EMERGENT TREMOR

- Typically seen in patients with parkinsonism
- Re-emerge in a postural position
- First occurs after a “resetting” latency of >5 seconds
- The frequency is same as rest tremor (3-6 Hz)
- The amplitude correlates well with that of the rest tremor
- Usually improves with dopaminergic therapy





TREATMENT

- Treatment depends solely on severity
- Some patients require simple reassurance
- Most patients referred to Neurologist – have troublesome tremors
- Most Anti-tremor exert their effects by reducing tremor amplitude
- Limitations in effective therapeutic trials
  - Marked intra-individual and inter-individual variations
  - Diurnal variations
  - ET amplitude may vary 30-50% within in an hour even without external factors
  - Lack of uniform definition and therefore standardized rating scale
- Conservative approach
  - Weighted Utensils
  - Wrist weights

	Normal starting dose (mg/day)	Normal therapeutic dose (mg/day)	Side-effects
Propranolol	10	160–320	Fatigue, bradycardia, hypotension, depression, exercise intolerance
Primidone	62·5	62·5–1000	Sedation, nausea, vomiting, unsteadiness
Gabapentin	300	1200–3600	Drowsiness, nausea, dizziness, unsteadiness
Topiramate	25	200–400	Fatigue, dizziness, ataxia, weight loss, memory difficulties, paraesthesias
[illegible]			
Nimodipine	120	120	Orthostatic hypotension

Table 2: **Oral medications used in the treatment of ET**

SUMMARY OF ORAL MEDICATIONS FOR ET

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Botulinum toxin in essential hand tremor - A randomized double-blind placebo-controlled study with customized injection approach

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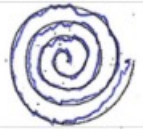
[b] Department of Neurology, Hartford Healthcare Ayer Neuroscience Institute, Hartford, CT, USA
[c] Department of Neurology, Columbia Asia Hospitals, Sarjapur Road, Bangalore, India
[d] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[e] Department of Neurology, Brigham and Women's Hospital, Massachusetts General Hospital, Boston, MA, USA

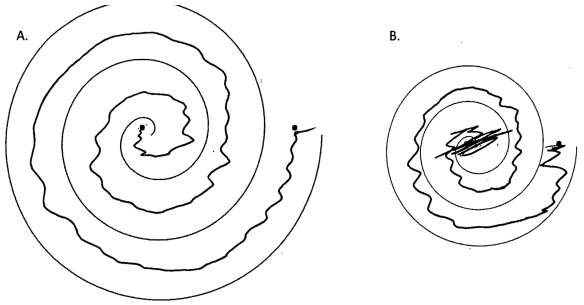
Total Dose and Muscle selection	Baseline Archimedes Spirals	4 Weeks Archimedes Spirals	8 Weeks Archimedes Spirals
Total 100 U. Biceps 15U (1),Triceps 20U (2), PT 10U (1), FCU 10U (1), FCR 10U (1), FDS 10U (2), Lumbricals 15U (3),ED 5U(1), ECR 5U (1)			
Total 90 U. Biceps 15U (1), PT 15U (1), FCU 15U (1), FCR 10U (1), FDS 10U (1), Lumbricals 15U (3), ED 5U (1), ECR 5U (1)			
Total 100 U. Biceps 10U (1), FCU 10U (1), FCR 10U (1), FDS 10U (1), FDP 10U (1), Lumbricals 10U (3), BR 10U (1), ED 10U (1), ECR 10U (1), ECU 10U (1)			
Total 100 U. PT 15U (1), FCU 15U (1), FCR 15U (1), FDS 20U (2), Lumbricals 15U (3), ED 10U (1), ECR 10U (1)			
Total 100 U. Biceps 10U (1), Triceps 10U (1), PT 10U (1), FCU 10U (1), FCR 10U (1), FDS 20U (2), Lumbricals 10U (3), ECU10U (1), ECR 10U (1)			

- 28 patients randomized to BoNT vs placebo and then crossed over
- Treatment efficacy at 4 and 8 weeks after each treatments
- Significant improvement in the rating score
- ~4% hand weakness

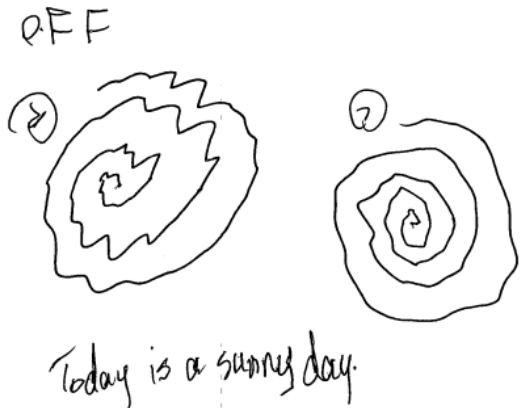
- A tailormade BoNT can be considered as a viable option before considering invasive brain surgery

Mitesh Lotia, MD; Joseph Jankovic, Botulinum Toxin for the Treatment of Tremor and Tics Semin Neurol. 2016;36(1):54-63

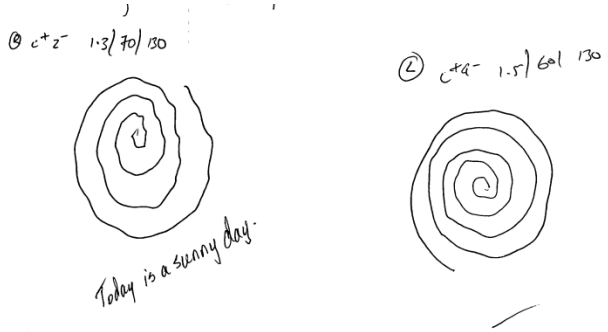
MDC PATIENT WITH ESSENTIAL TREMOR



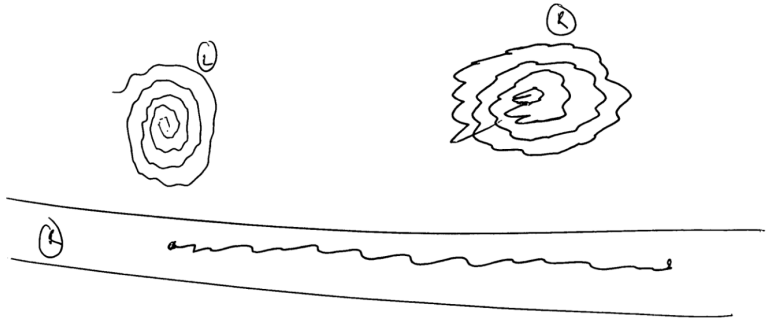
Pre – DBS Spirals



Post DBS OFF



Post DBS Programming

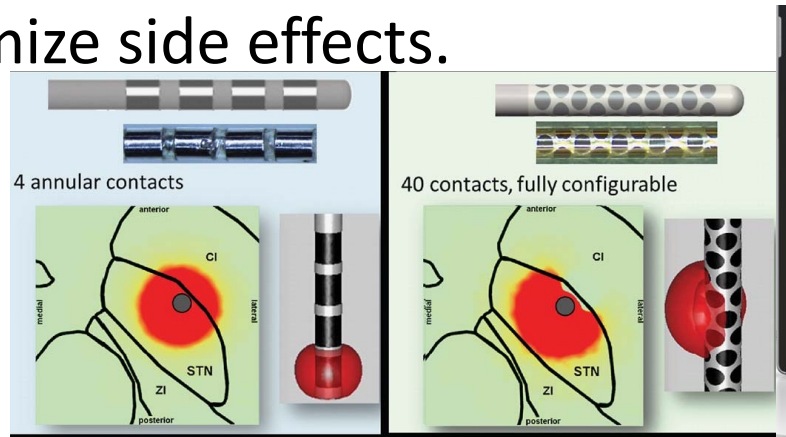


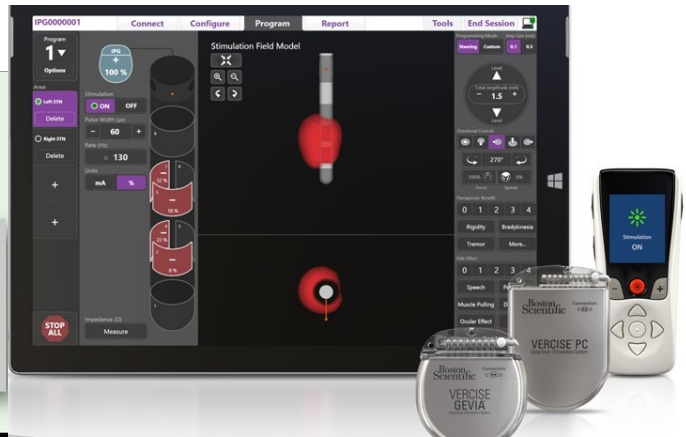
Post – DBS
Explantation

Post – Botox
1 year (No DBS)

SURGICAL TREATMENT FOR ET

- ~ 50% of ET patients cannot tolerate medications or have refractory tremors
- Patients are considered for
  - Lesional therapies – Thalamotomies
  - Deep brain stimulation
  - MR guided Ultrasound
- Continuous high frequency Ventro-intermedius(ViM) thalamic deep brain stimulation can alleviate tremor with fair risk / benefit ratio
- Significant tremor reduction with sustained benefits has been reported in 68 – 100%
- Three different systems - Omnidirectional, two-directional
- More targeted approach and minimize side effects.





PATIENT SELECTION

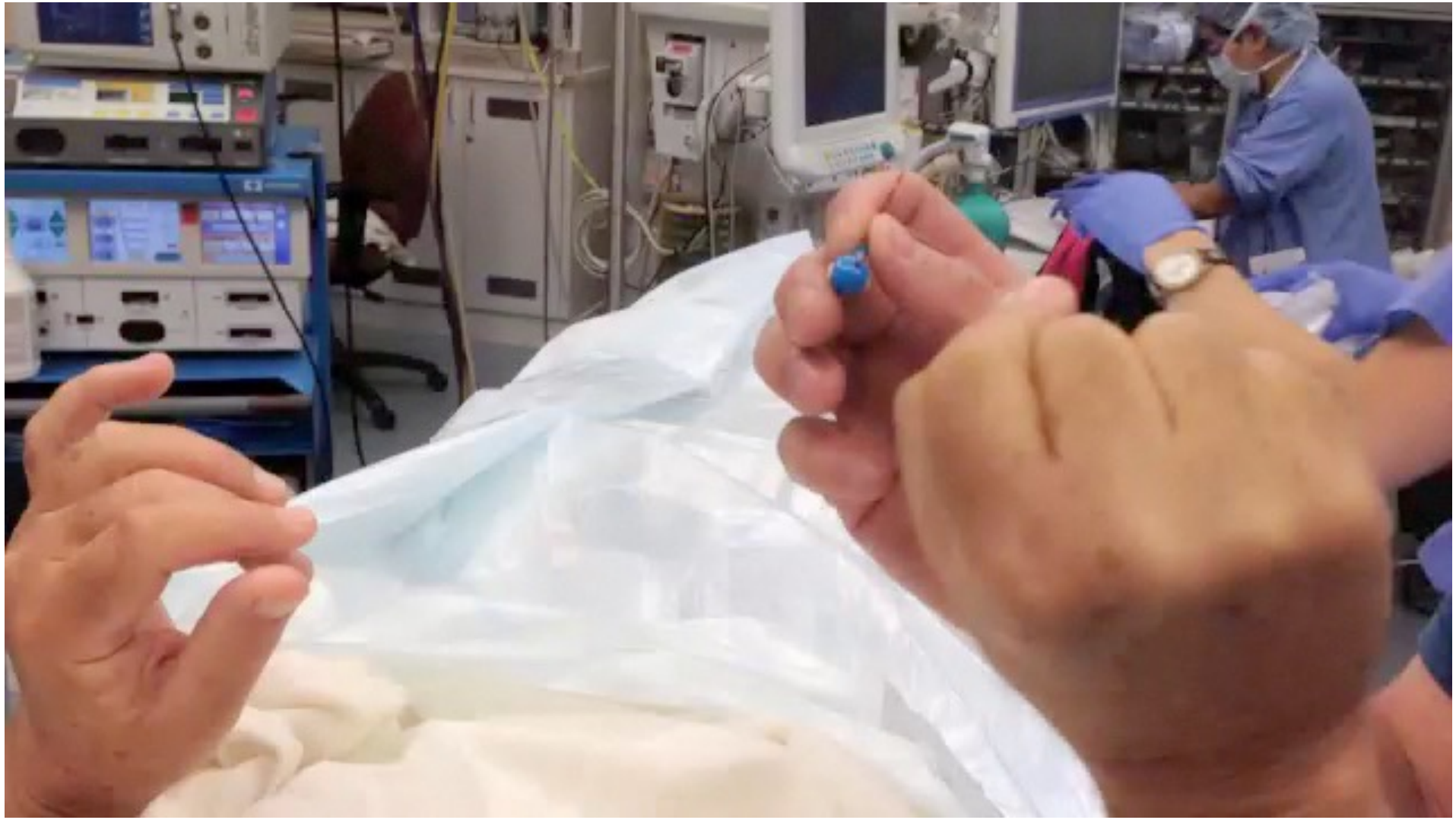
IDEAL CANDIDATES

- Failed medical management despite multiple medications
- Disabling tremors limiting ADLs
- Other factors – Annoying, anxiety provoking, Embarrassing, causing social isolation

PROCESS

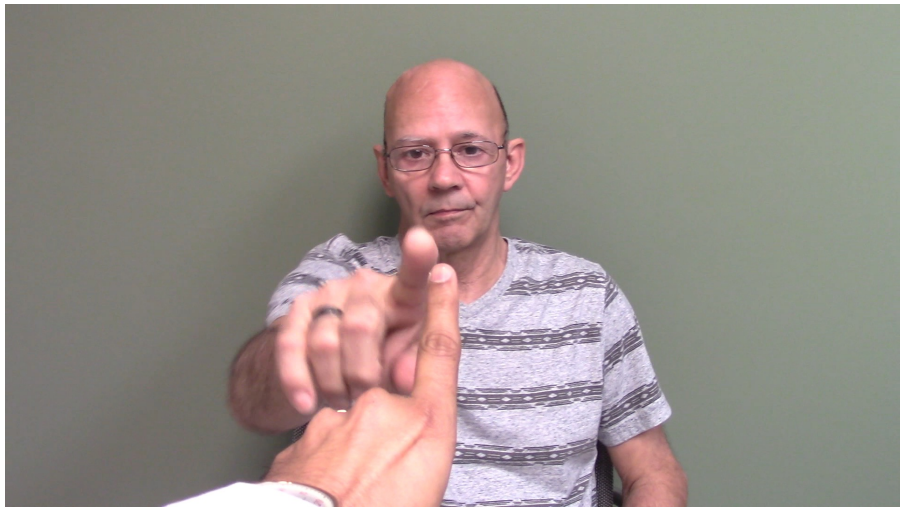
- Referral to Neurologist / movement disorder neurologist
- Medical optimization
- Neuropsychological evaluation
- Neuroimaging for stereotactic planning and safety
- Neurosurgeon input
- Multi-disciplinary approach
- Lead selection

OR: Awake testing



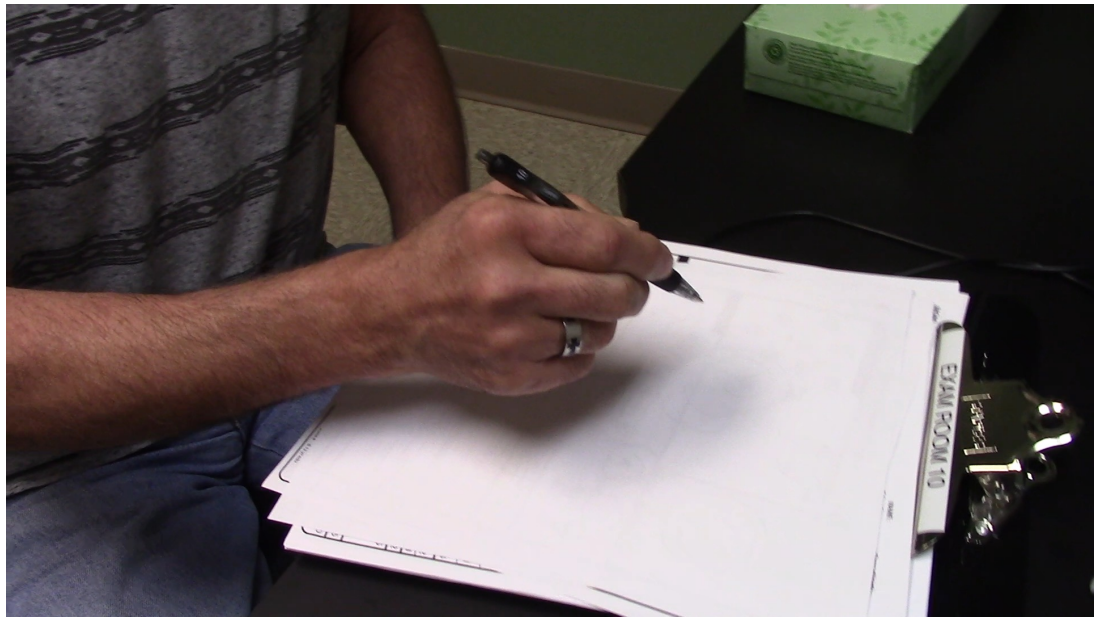
Pre DBS

Post DBS



Pre DBS

Post DBS



Pre DBS

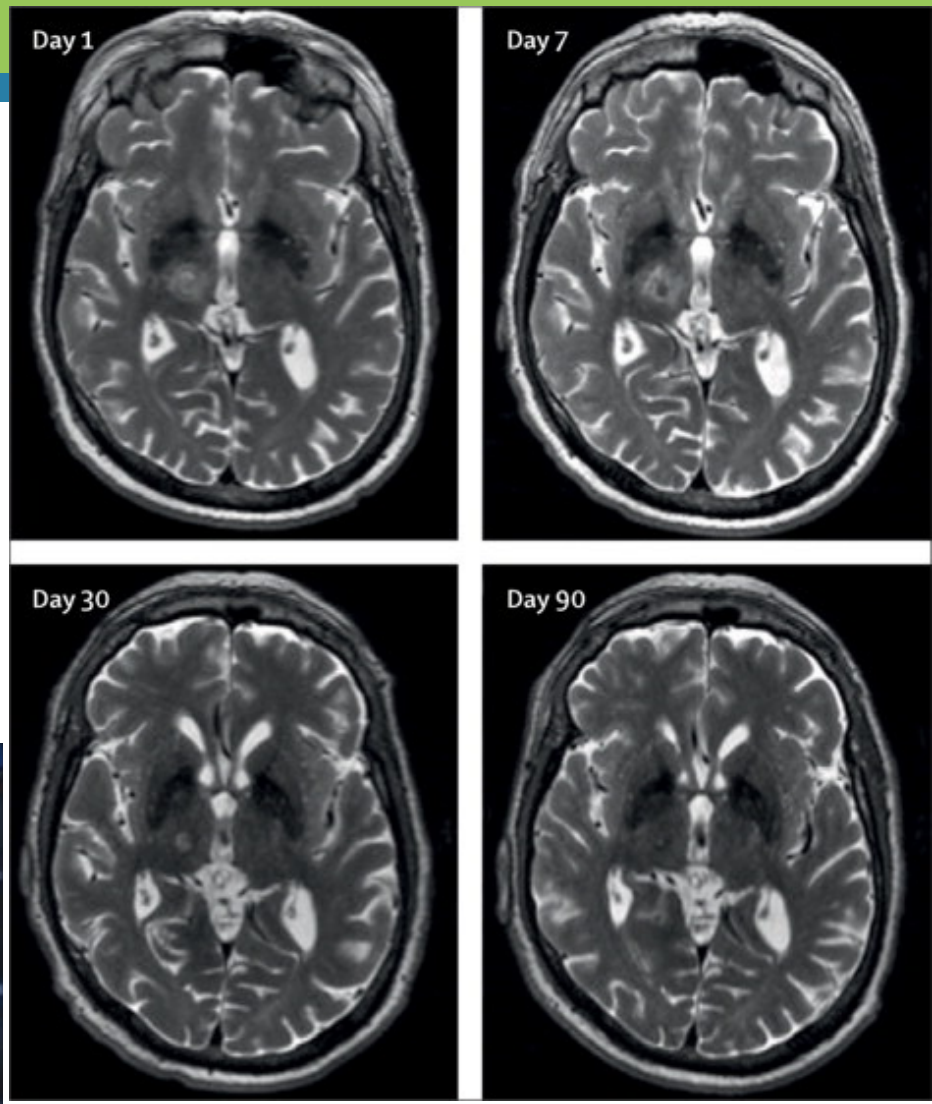
Post DBS

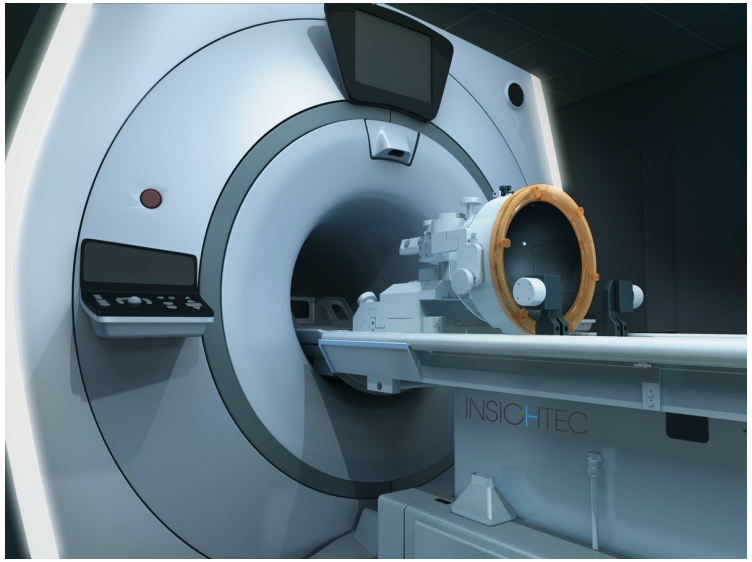
MRI Guided Ultrasound (MRgUS)

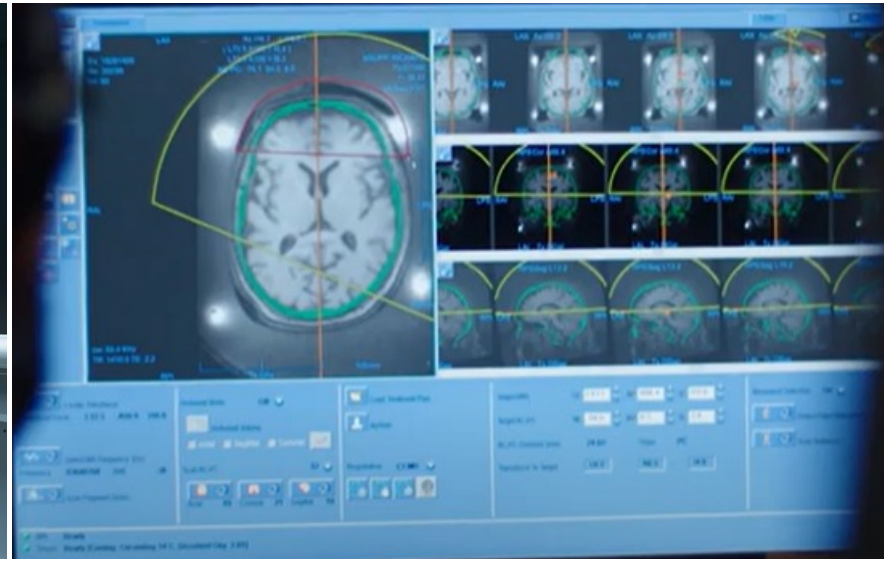
Incisionless lesional procedure to relieve tremor

76% improvement in tremor
10% gait issues and ataxia

Approval of the Second side after 9 month from first procedure







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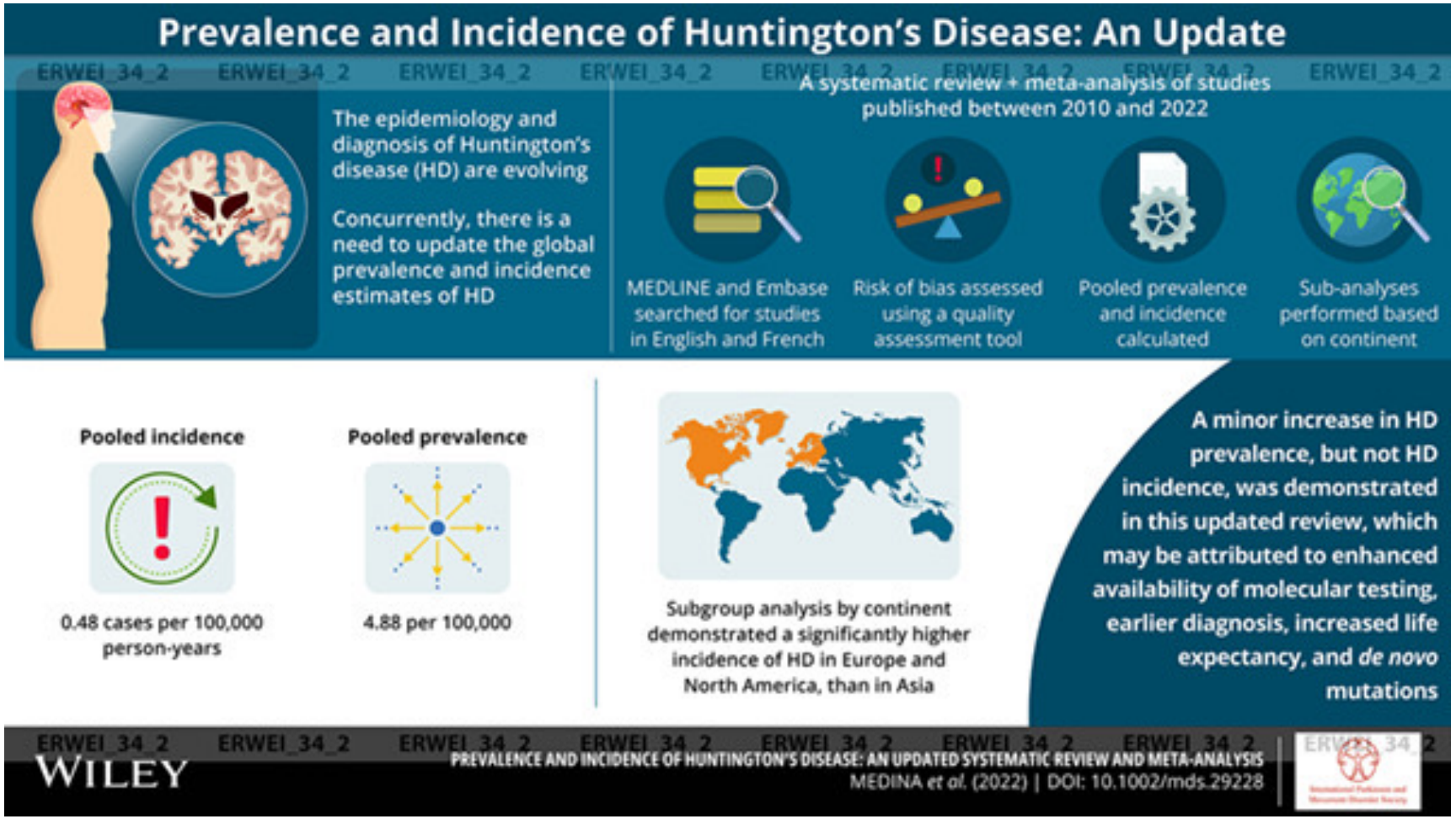
HD Incidence / Prevalence



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HD mimics

Autosomal dominant disorders			
HDL1	*PRNP*	Third and fourth decades	Seizures Truncal ataxia Quick progression (death within 10 years)
HDL2	*JPH3*	Third and fourth decades	South African ancestry Acanthocytosis Quick progression (Death within 15 years)
HDL4 (SCA17)	*TBP1*	Third to fifth decades (rare in childhood)	Cerebellar ataxia Dystonia Pyramidal features Family history of these features
C9orf72 hexanucleotide repeat expansion	*C9ORF72*	Fifth decade	Motor neurone disease/frontotemporal dementia overlap Pyramidal features Prominent early psychiatric symptoms
DRPLA	*ATN1*	Third and fourth decade	Japanese ancestry Seizures Quick progression (death within 15 years) Myoclonus prominent in juvenile cases
SCA8	*ATXN8OS*	Childhood to eighth decade	Ataxia Slow progression with normal life expectancy
Benign hereditary chorea	*TITF1*(also called *NKX2.1*)	Infancy and early childhood	Non-progressive/very slow progression Few cognitive deficits Thyroid/respiratory disease
Neuroferritinopathy	*FTL1*	Fourth to fifth decade	Orofacial dystonia Iron deposition in basal ganglia seen on MRI Low serum ferritin
ADCY5 mutations	*ADCY5*	First to second decade	Combined dystonia and myoclonus Paroxysmal chorea Worse during sleep

HD mimics

Recessive disorders			
HDL3	4p15.3 (gene unknown)	Childhood (3–4 years)	Autosomal recessive inheritance
Chorea-acanthocytosis	*VPS13A*	Fourth decade	Autosomal recessive inheritance Self-mutilating behaviour Acanthocytosis Peripheral neuropathy/areflexia Raised serum creatine kinase Prominent orolingual dystonia when eating Seizures
McLeod's syndrome	*XK*	Mid-adulthood Third to fifth decade	X-linked recessive inheritance Peripheral neuropathy Acanthocytosis Cardiomyopathy Skeletal myopathy and atrophy Raised serum creatine kinase Facial tics
Lesch-Nyhan syndrome	*HPRT1*	First and second decade	X-linked recessive inheritance Seizures Self-mutilating behaviour High uric acid
Wilson's disease	*ATP7B*	First and second decade	Autosomal recessive inheritance Liver dysfunction Kayser-Fleischer rings Risus sardonicus Low plasma caeruloplasmin/ raised urinary copper excretion MR brain scan showing T2 hyperintensity in putamen, globus pallidus, brainstem and cerebellum
Ataxia with oculomotor apraxia	*APTX* (AOA1) and *SETX* (AOA2)	First and second decade	Autosomal recessive inheritance Cerebellar ataxia Peripheral neuropathy Elevated α-fetoprotein (AOA2) Hypoalbuminaemia and Hypercholesterolaemia (AOA1)
Friedreich's ataxia	*FXN*	First and second decade	Autosomal recessive inheritance Ataxia Pyramidal signs Cardiomyopathy Skeletal abnormalities Optic atrophy Deafness Diabetes mellitus Peripheral neuropathy

Medications to Treat HD chorea

Pharmacological treatment options for chorea in Huntington's disease

Drug	Starting dose	Recommended titration interval	Usual dose
Tetrabenazine	12.5 mg once daily	1–2 weeks	12.5 mg three times daily (increase to 25–50 mg three times daily as required) Maximum dose 200 mg
Olanzapine	2.5–5 mg once daily	2–4 weeks	20–30 mg daily
Sulpride (or Amisulpride)	100–200 mg two times per day	2–4 weeks	400 mg two times daily Maximum dose 1200 mg two times pdaily
Risperidone	1 mg two times per day	1–2 weeks	2–3 mg two times daily Maximum dose 8 mg two times daily
Aripiprazole	2.5–5 mg once daily	2–4 weeks	20 mg daily
Quetiapine	25 mg two times per day	1–2 weeks	200 mg two times daily Maximum 400 mg two times daily
Amantadine	100 mg once daily	1–2 weeks	200 mg two times daily
Clonazepam	0.5 mg once daily	1–2 weeks	1–2 mg two to three times daily

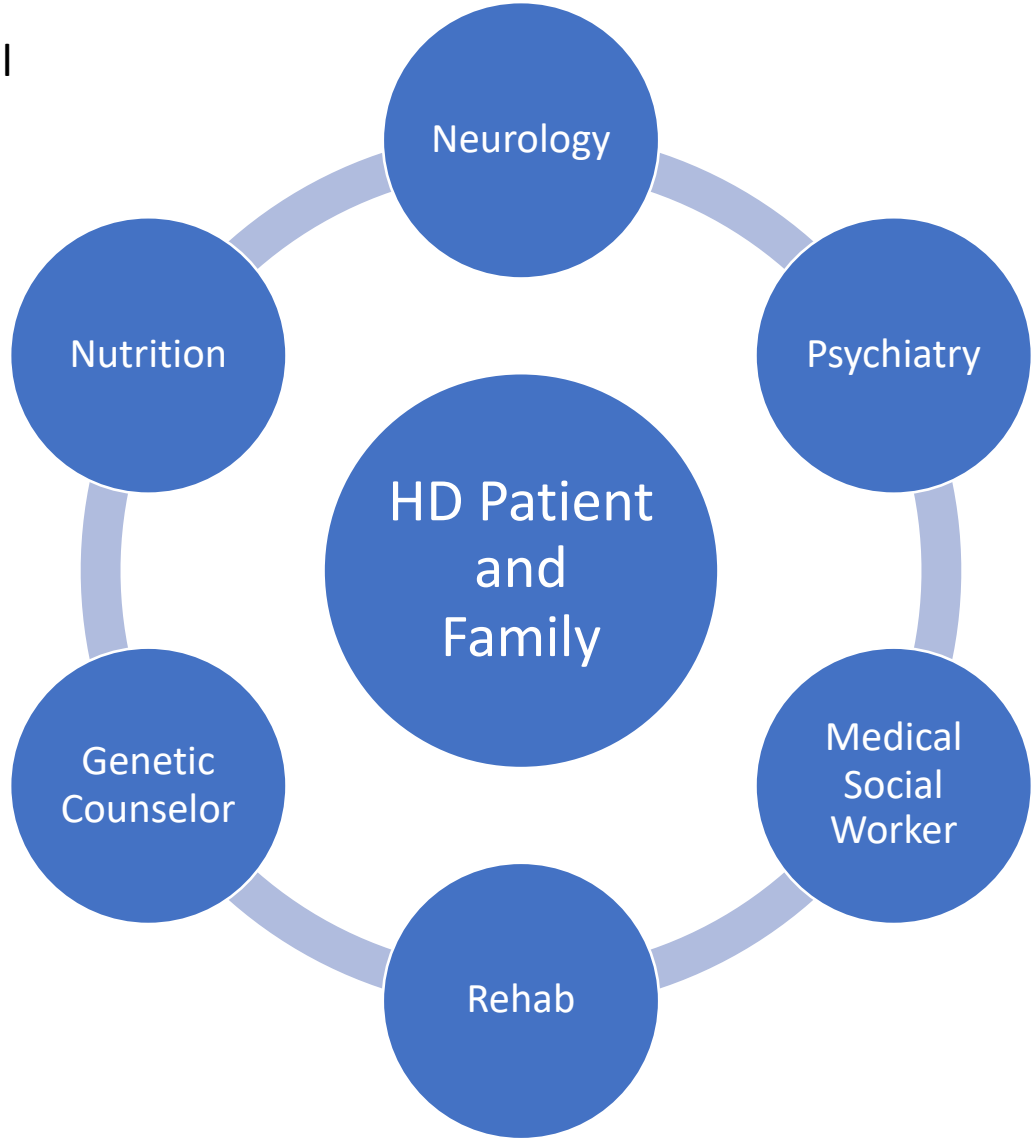
VMAT-2 Inhibitors

Deutetrabenzine
Valbenazine

Stoker, T. B., Mason, S. L., Greenland, J. C., Holden, S. T., Santini, H., & Barker, R. A. (2022). Huntington's disease: Diagnosis and management. *Practical Neurology, 22*(1), 32-41.

HD Management

Multi-disciplinary care model



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Hemichorea

Video

55-year-old female with no PMH

Presented with subacute onset of involuntary movements

Started on the left and then generalized

MRI showed Right temporal lobe cavernoma

No epileptiform discharges on EEG

Movement Consult

MRI review

Hemichorea

MRI Brain

Right Caudate / Putamen hyperintesity

No benefit from D2 antagonists

Trial Deutetrabenazine

Movements subsided

Lost access to the medication, readmitted to the hospital

Is it Tardive Dyskinesia ?

Patient Video

22 year old male with developmental delay

Episodes of disruptive outbursts since teengage years

”concussion injury” from abusive parent

Use of Neuroleptics for many years

New onset seizures

Worsening Movements

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Is it Tardive Dyskinesia ?

Patient Video

Worsening Movements

Generalized chorea

Abnormal mouth movements, especially when trying to eat

MRI brain – Caudate Atrophy

HD Negative

Peripheral blood – no acanthocytosis

WES – heterozygous mutation for Choreoacanthocytosis

Progressive chorea

Psychiatric Manifestations

Seizures

Clinical Neurological Society of America

50TH ANNIVERSARY

Questions