Treatment of Motor Symptoms of Parkinson's Disease

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UCI Health

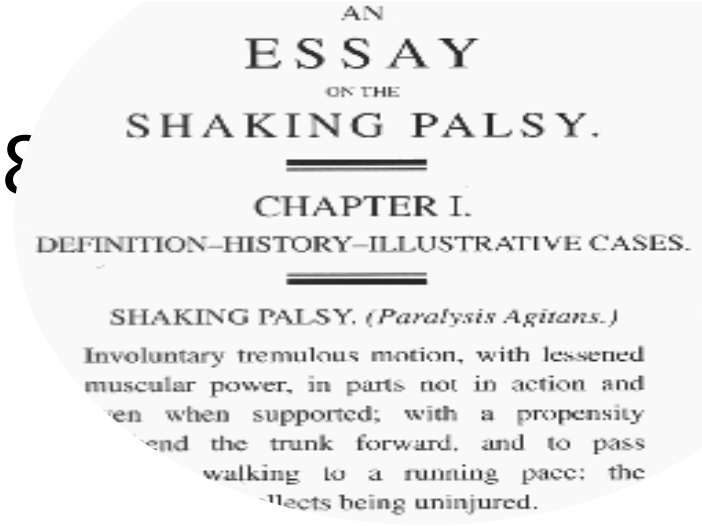
What is Parkinson's Disease (PD)?

-PD is a slowly progressive neurologic disease that primarily affects the movement

-Most symptoms due to loss of cells in the midbrain which produce dopamine

-It was first described by James Parkinson in 18

-"An Essay on the Shaking Palsy"



AN

ESSAY

ON THE

SHAKING PALSY.

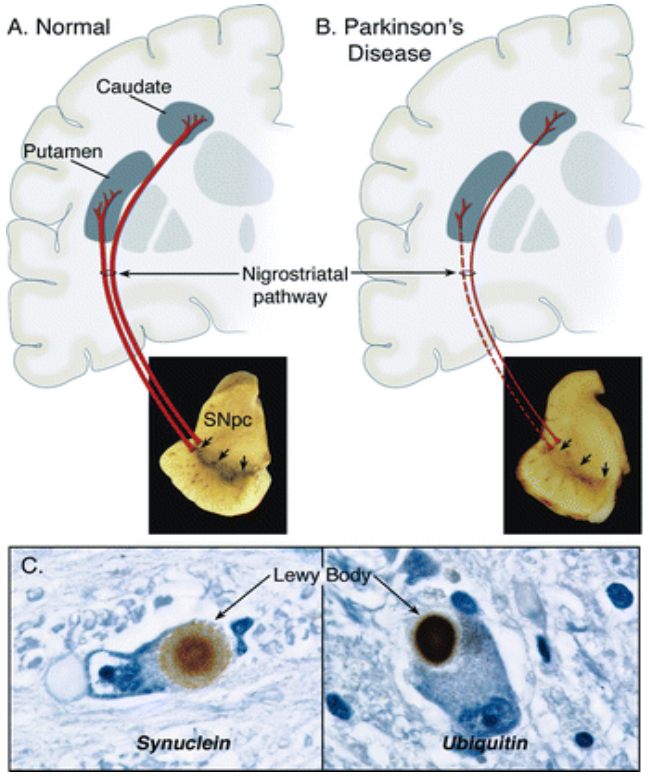
CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and
en when supported; with a propensity
nd the trunk forward, and to pass
walking to a running pace: the
lects being uninjured.

Anatomy


A. Normal
B. Parkinson's Disease
Caudate
Putamen
Nigrostriatal pathway
SNpc
C.
Lewy Body
Synuclein
Ubiquitin

What Causes PD?

-most cases are idiopathic

-genetic mutations have been linked to PD (probably less than 10% of cases)

-other risk factors:

--head injury

--exposure to metals (manganese, welding)

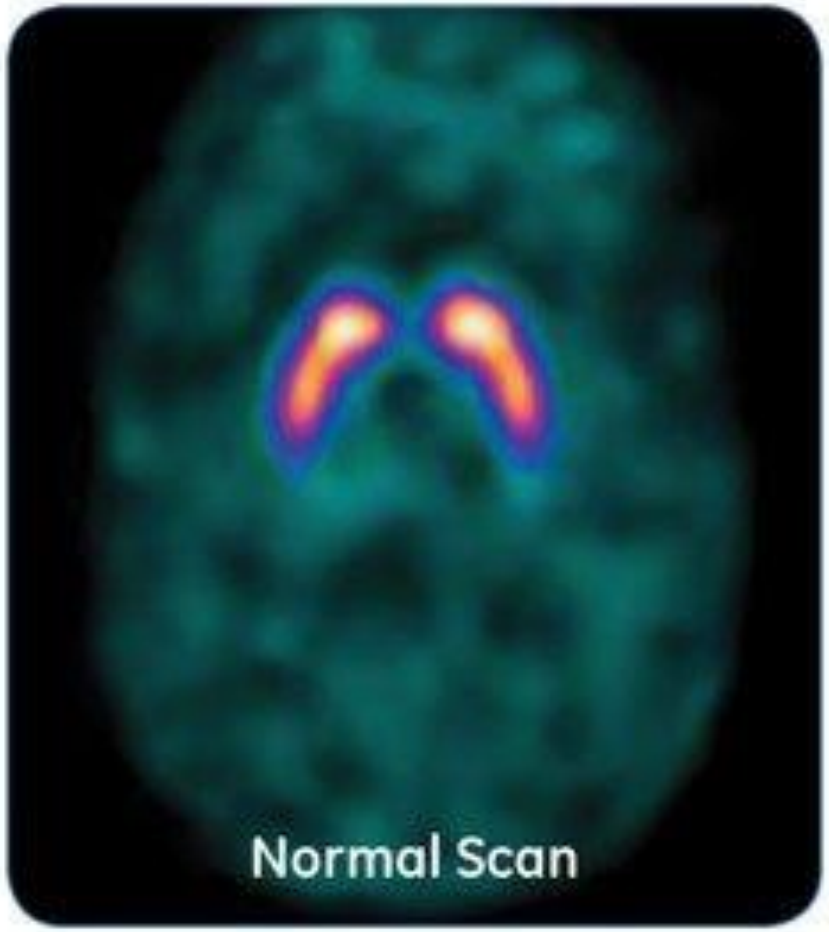
--solvent exposure

How is PD diagnosed?

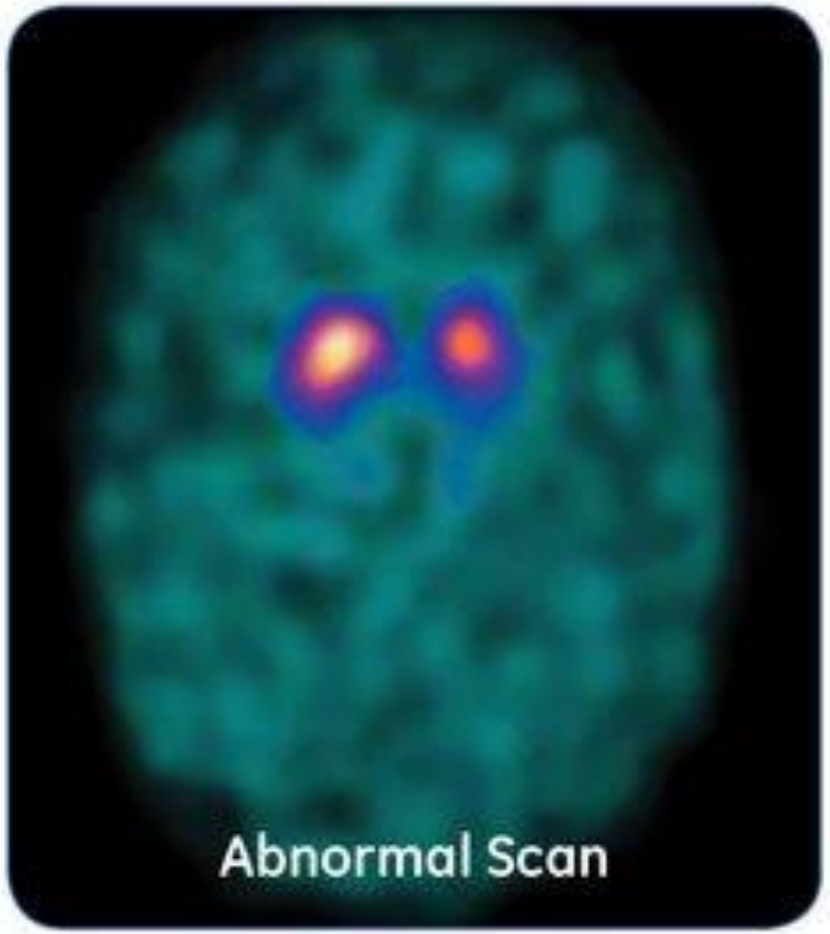
Usually by history and physical exam

DAT scan can be used in certain situations

-MRI spectroscopy



"Comma"-shaped
Possible essential tremor



"Period"-shaped
Possible parkinsonian syndrome

Diagnosis: Using Standardized Criteria

MDS Criteria for Parkinson's Disease

Parkinsonism - bradykinesia, in combination with at least one between rest tremor (4–6 Hz) and rigidity

non-motor manifestations, often dominating the clinical presentation of the disease, have now been incorporated into the diagnostic criteria

Supportive criteria

1. dramatic response to dopaminergic therapy
2. levodopa-induced dyskinesia
3. rest tremor of a limb
4. either olfactory loss or cardiac sympathetic denervation (MIBG)

Motor symptoms are due primarily to loss of dopamine producing cells in the basal ganglia

Most treatments are aimed at restoring or enhancing dopamine function

There are many types of receptors on dopamine cells

The most effective treatment for PD is levodopa

Levodopa enters the brain and is converted to dopamine

Most effective at improving bradykinesia

Associated with long term complications including wearing off (motor fluctuations) and dyskinesia

Carbidopa/levodopa formulations

Immediate release 10/100, 25/100, 25/250

Controlled release 25/100, 50/200

Rytary 95 mg,145 mg, 195 mg, 245 mg

Duodopa- carbidopa/levodopa gel

Inbrija- inhaled, faster acting

COMT inhibitors

Block the enzyme that metabolizes levodopa in the blood

Increase duration of effect of levodopa

Tolcapone, entacapone, opicapone

Stalevo

Dopamine agonists

Mimic the action of dopamine by stimulating dopamine receptors

Not as effective as dopamine

Lower risk of long term complications including wearing off and dyskinesia

Side effect include impulse control disorders, “sleep attacks”, hallucinations

Dopamine agonists

Pramipexole

` immediate release (3 times a day)

long acting (once a day)

Ropinirole

immediate release (3 times a day)

long acting (once a day)

Rotigotine patch

once a day

Apomorphine injection

3 times a day

Kynmobi sublingual

MAO-B inhibitors

Block enzyme that metabolizes dopamine in the brain

Rasagiline

Selegiline

Safinamide

NMDA receptor antagonists

Relieve symptoms of PD

Can improve dyskinesia

Side effects include hallucinations, confusion, leg swelling, nausea

Amantadine

3 times a day

Gocovri once a day

Adenosine A2A receptor antagonist

For off episodes in PD

Istradefylline (Nourianz)

Anticholinergics

Trihexyphendyl

Older drug, not used much for PD

May be better for tremor

Side effect include impaired memory, constipation, worsening of balance

Acetylcholinesterase inhibitors

Block the enzyme that metabolized acetylcholine

-acetylcholine is important is some balance pathways and memory pathways

-this class of medications has been shown to improve balance in some patients with PD

Acetylcholinesterase inhibitors

Donepezil (Aricept)

Rivastigmine (Exelon)

-available in patch and pill

New AAN guidelines for Dopaminergic Therapy

- Medications may help alleviate your motor symptoms.
- Studies do not show an advantage in delaying medical or drug treatment for motor symptoms.
- Choosing to start a medication is a collaborative decision between you, your doctor, and your family or care partners. The right medication for you will depend on your symptoms, age, and life circumstances.
- You are encouraged to discuss the potential benefits and adverse effects of your medication options with your doctor.

Disease Progression

May develop symptoms after many year

-cognitive decline/dementia

-gait and balance disorders

Complications of long term treatment

-motor fluctuations

-dyskinesia

What is the latest in Parkinson's disease treatment?

Motor Symptoms (surgical interventions)

<u>Deep Brain Stimulation</u>

(Dr Swope's and Hsu's talk!!).

- New leads

- Brain waves sensing technology

What is the latest in Parkinson's disease treatment?

Non Motor Symptoms

Symptomatic: Goal to address **quality of life** (patient and caregiver main role).

Behavioral difficulties and hallucinations or illusions.

Fatigue.

Mood difficulties. Depression and Anxiety.

Sleep Difficulties. Restless legs syndrome and REM sleep behavior disorder.

Cognitive/Memory difficulties.

Autonomic difficulties. **Blood pressure,** urinary symptoms, constipation.

What is the latest in Parkinson's disease treatment?

Non Motor Symptoms

Behavioral difficulties and hallucinations or illusions.

- Clozapine.
- **Pimavanserine (Nuplazid)**. 4 to 6 weeks for effect.
- Quetiapine.

Black Box Warnings. Thanks to Terry Randall.

What is the latest in Parkinson's disease treatment?

Non Motor Symptoms

Blood pressure (Orthostatic hypotension). Falls, injuries.

- Fludrocortisone. Increases salt and water, increasing volume of fluids then raising blood pressure.
- Midodrine. Constricts blood vessels raising blood pressure
- **Droxidopa.** Constricts blood vessels raising blood pressure

Update on Treatment of Dystonia

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New 2013 Consensus Definition:

- Dystonia is a movement disorder characterized sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned, twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."
- Two Axis classification system (Axis I-- phenomenology and Axis II—possible causes)

- Albanese, Bhatia, Bressman, et al. "Phenomenology and Classification of Dystonia: a Consensus Update." Movement Disorders. 2013; 28: 863-873

Regions Affected

- **Focal.** Only one body region is affected. Typical examples of focal forms are blepharospasm, oro-mandibular dystonia, cervical dystonia, laryngeal dystonia, and writer's cramp. Cervical dystonia, is considered a form of focal dystonia, although by convention the shoulder can be included as well as the neck.
- **Segmental.** Two or more contiguous body regions are affected. Typical examples of segmental forms are: cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bi-brachial dystonia.
- **Multifocal.** Two non-contiguous or more (contiguous or not) body regions are involved.
- **Generalized.** The trunk and at least two other sites are involved. Generalized forms with leg involvement are distinguished from those without leg involvement.
- **Hemidystonia.** More body regions restricted to one body side are involved. Typical examples of hemidystonia are due to acquired brain lesions in the contralateral hemisphere.
-

Commonly used oral medications for dystonia

Class of medication	Examples
Anticholinergics	benztropine, biperidin, ethopropazine, ophenadrine, procyclidine, trihexyphenidyl
Dopaminergics	levodopa, pramipexole, ropinirole, tetrabenazine
GABAergics	alprazolam, baclofen, chlordiazepoxide, clonazepam, diazepam
Muscle “relaxants”	baclofen, benzodiazepines, carisoprodol, chlorzoxazone, cyclobenzeprine, metaxolone, methocarbamol, orphenadrine
Others	carbamazepine, cannabidiol, cyproheptidine, gabapentin, lithium, mexilitine, nabilone, riluzole, tizanidine, zolpidem

Neurol Clin. 2015 Feb; 33(1): 77–100.

Botulinum toxin is first line treatment for focal dystonia

- Most effective in reducing pain and motor sx
- 80% of patients with CD and Bleph report good response
- Repeated tx—sustained symptomatic benefit, reduced latency effect, and prolonged duration of response
- Risk of developing neutralizing antibodies with current preparations—1.2%
- Side effects: CD—dysphagia; Bleph—ptosis, diplopia

Comparison of the most common botulinum toxin formulations

	Onabotulinumtoxin A (Botox™)	**Abobotulinumtoxin A (Dysport™)**	**Incobotulinumtoxin A (Xeomin™)**	**Rimabotulinumtoxin B (Myobloc™)**
FDA-approved indications for dystonia	blepharospasm, cervical dystonia	cervical dystonia	blepharospasm, cervical dystonia	cervical dystonia
Preparation	vacuum dried	freeze dried	powder	liquid
Available dose sizes (units)	100, 200	300, 500	50, 100	1000, 2500, 5000
Storage	refrigerate	refrigerate	room temperature	refrigerate
Approximate dose equivalency*	1	2.5 – 3	1	40

Neurol Clin. 2015 Feb; 33(1): 77–100.

TMS treatment of Cervical Dystonia

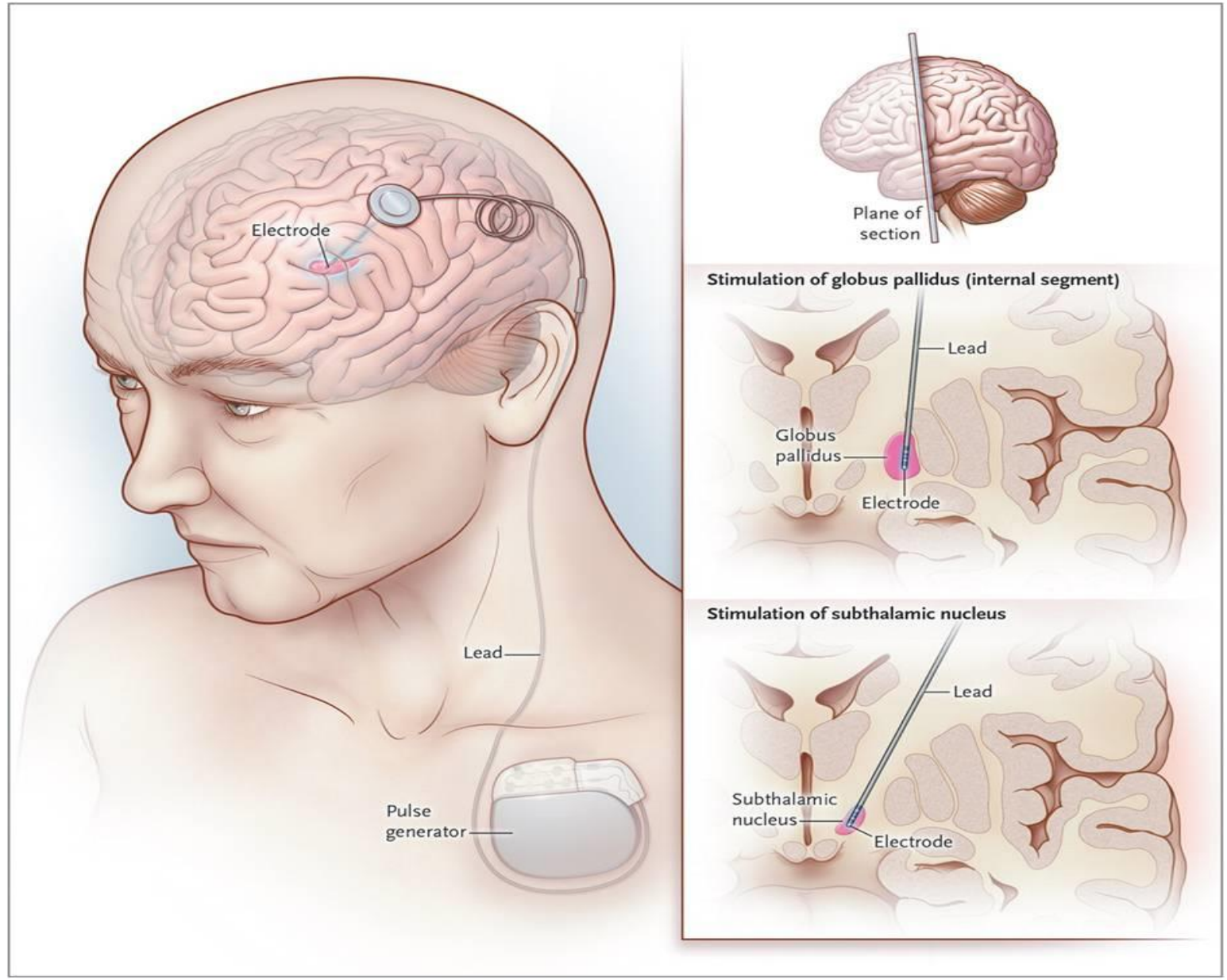
- 8 patients received 5 sessions of treatment with low frequency rTMS.
- Targets included primary motor cortex (MC), dorsal premotor cortex (dPM), supplementary motor area (SMA), anterior cingulate cortex (ACC), sham procedure.
- TWSTRS score improved with stimulation of dPM and MC between session 1 to session 5.

- Abnormal cerebellar connectivity and plasticity in isolated cervical dystonia
- PLoS One. 2015; 10(4): e0124937.
- Published online 2015 Apr 29. doi: 10.1371/journal.pone.0124937

DBS for Dystonia

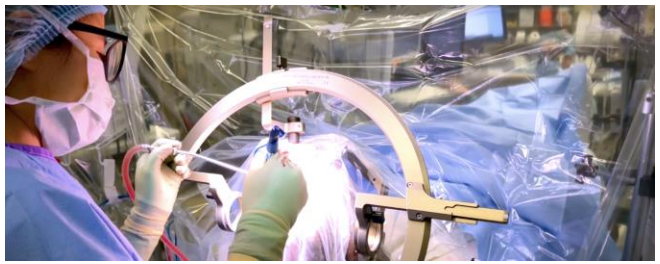
In general, the MAIN indications for surgery include:

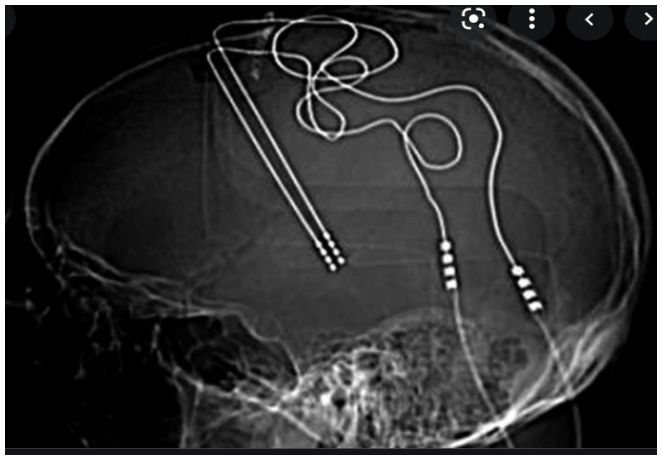
- Severe motor impairment
- Poor QOL,
- Severe pain
- Inability to perform ADL’s

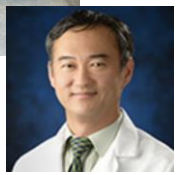

Electrode
Lead
Pulse generator
Plane of section
Stimulation of globus pallidus (internal segment)
Lead
Globus pallidus
Electrode
Stimulation of subthalamic nucleus
Lead
Subthalamic nucleus
Electrode

Augmenting the Good: Neuroplasticity and Surgical Treatment

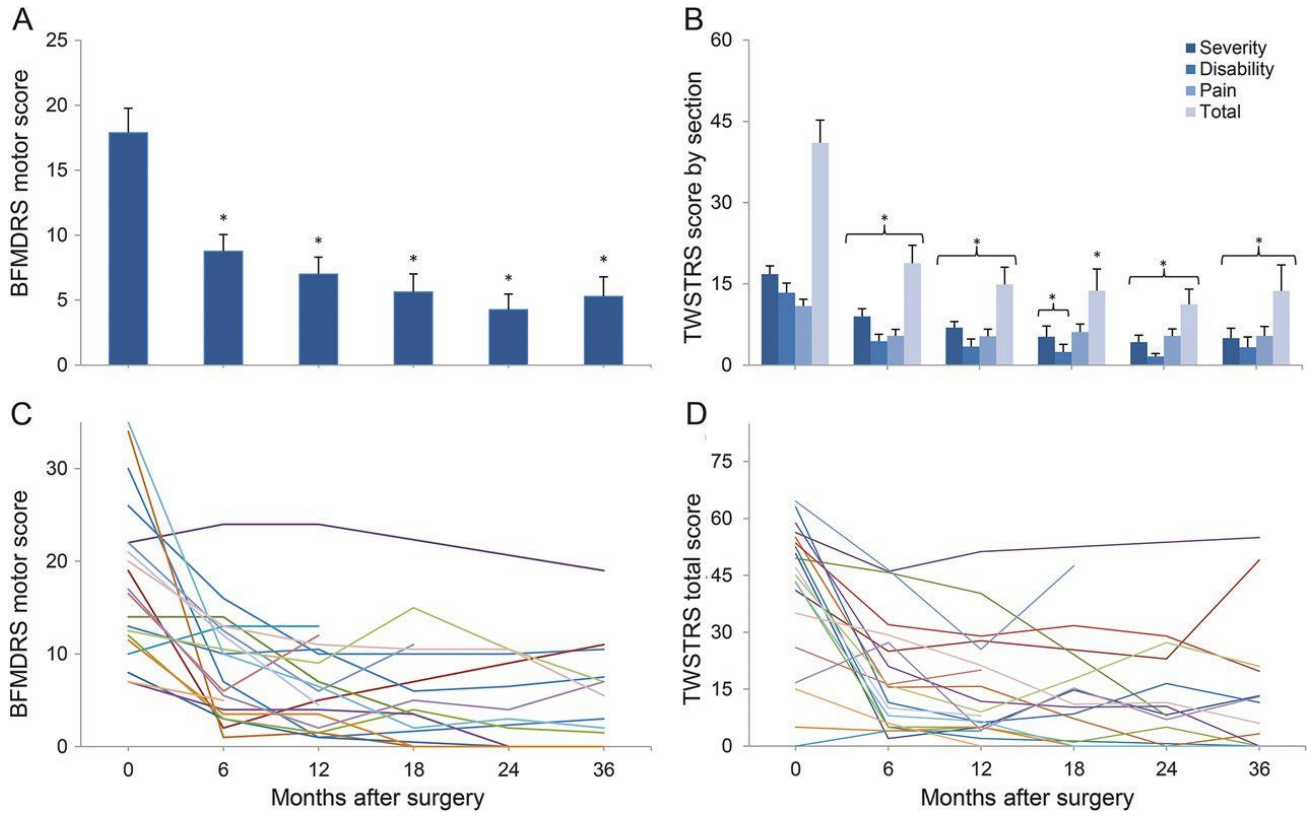
- ✓ Deep Brain Stimulation
  - ✓ Implantation of electrodes to deep structures of the brain treats Parkinson's disease and many more disorders







DBS targeting STN in isolated dystonia
3 year follow up: significant and sustained improvement



Boston Scientific Website

Primary Author	Study Design	Sample Size	Follow Up	BFMDRS or TWSTERS	Change in Mean Scores BFMDRS or TWSTERS	% Improvement in BFMDRS and TWSTERS
Cersosimo et al, 2009[1]	Prospective Case Series	9	6 mos.	BFMDRS (Motor Scale)	• Baseline: 46.9 ± 24.3 • Post DBS: 24.1 ± 16.9	Not Reported
Houeto et al, 2007[2]	Prospective, Controlled, Multicenter	22	1 mo.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.1 • Post DBS*: 26.7 ± 14.9	Not Reported
Vidailhet et al, 2005[3]	Prospective, Controlled, Multicenter	22	12 mos.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.3 • Post DBS: 21 ± 14.1	51
Vidailhet at al, 2007[4]	Prospective, Controlled, Multicenter	22	36 mos.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.3 • Post DBS: 19.8 ± 17.4	58
Kiss et al, 2007[5]	Prospective, Single-Blind, Multicenter	10	12 mos.	TWSTERS (Severity Score)	• Baseline: 14.7 ± 4.2 • Post DBS: 8.4 ± 4.4	43
Kupsch et al, 2006[6]	Prospective, Controlled, Multi-center	40	6 mos.	BFMDRS (Motor Scale)	• Baseline: 36.4 ± 24.6 • Post DBS: 20.2 ± 18	46
Volkmann et al, 2012[7]	Prospective, Controlled, Multi-center	40	5 yrs.	BFMDRS (Motor Scale)	• Baseline: 43.4 ± 28.6 • Post DBS: 15.4 ± 16.3	60
Ostrem et al, 2011[8]	Prospective Pilot	9	12 mos.	TWSTERS (Total Score)	• Baseline: 53.1 ± 2.57 • Post DBS: 19.6 ± 5.48	62.9
Vidailhet et al, 2009[9]	Prospective	13	12 mos.	BFMDRS (Motor Scale)	• Baseline: 44.23 ± 21.12 • Post DBS: 34.69 ± 21.87	24.4

Long-term Outcomes of Pallidal Deep Brain Stimulation in X-linked Dystonia Parkinsonism (XDP): Up to 84 Months Follow-Up

- 11 patients implanted with bilateral GPi DBS between Oct. 2009 and Sept. 2018.
- BFMDRS mean score of 23.3 from mean baseline score of 36.3 one month after implant
- BFMDRS mean score or 13.7 at 12 months.
- 3 patients maintained benefit up to 72-84 months.

- Parkinsonism Relat Disord. 2019 Mar;60:81-86.doi: 10.1016/j.parkreldis.2018.09.022. Epub 2018 Sep 21. Joshua Emmanuel E Abejero [1], Roland Dominic G Jamora [2], Theodor S Vesagas [3], Rosalia A Teleg [4], Raymond L Rosales [5], Joseph P Anlacan [6], Monserrat S Velasquez [3], Jose A Aguilar

Summary

- Medical treatment of dystonia may be effective in some cases and can be used in conjunction with other treatments
- Botulinum toxin injections are treatment of choice for focal dystonia
- -very effective
- Transcranial magnetic stimulation still considered experimental
- Deep brain stimulation (DBS) can be effective in refractory cases

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