Emerging Approaches in Parkinson's Disease

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Objectives

- Identify the hallmark clinical features of parkinsonism
- Understand the basic approach to medical management of motor symptoms in Parkinson's disease
- Recognize motor complications and the strategies that exist to address them
- Learn more about advanced therapies for Parkinson's disease and when to make a referral

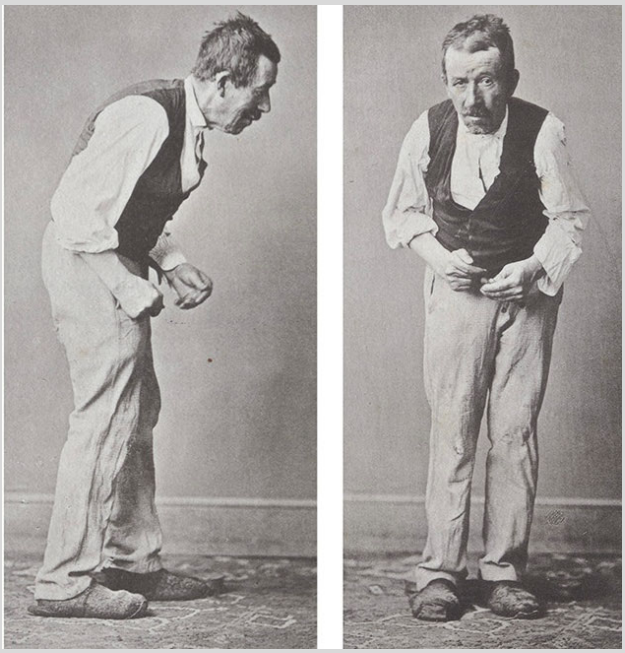
Disclosures

- Nothing to disclose

Parkinsonism

A clinical syndrome of that can include a number of 6 cardinal features

1. **Bradykinesia**
2. **Tremor at Rest**
3. **Rigidity**
4. Loss of postural reflexes
5. Flexed posture
6. Freezing of gait (motor blocks)

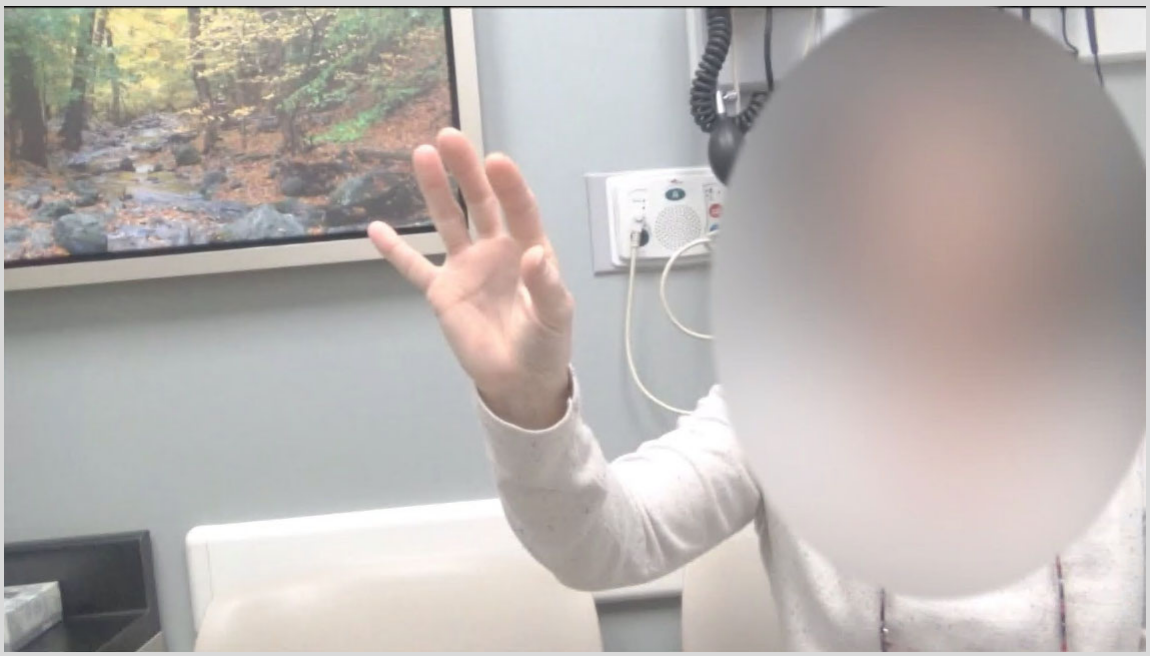


Bradykinesia

Literally: “slow movement”

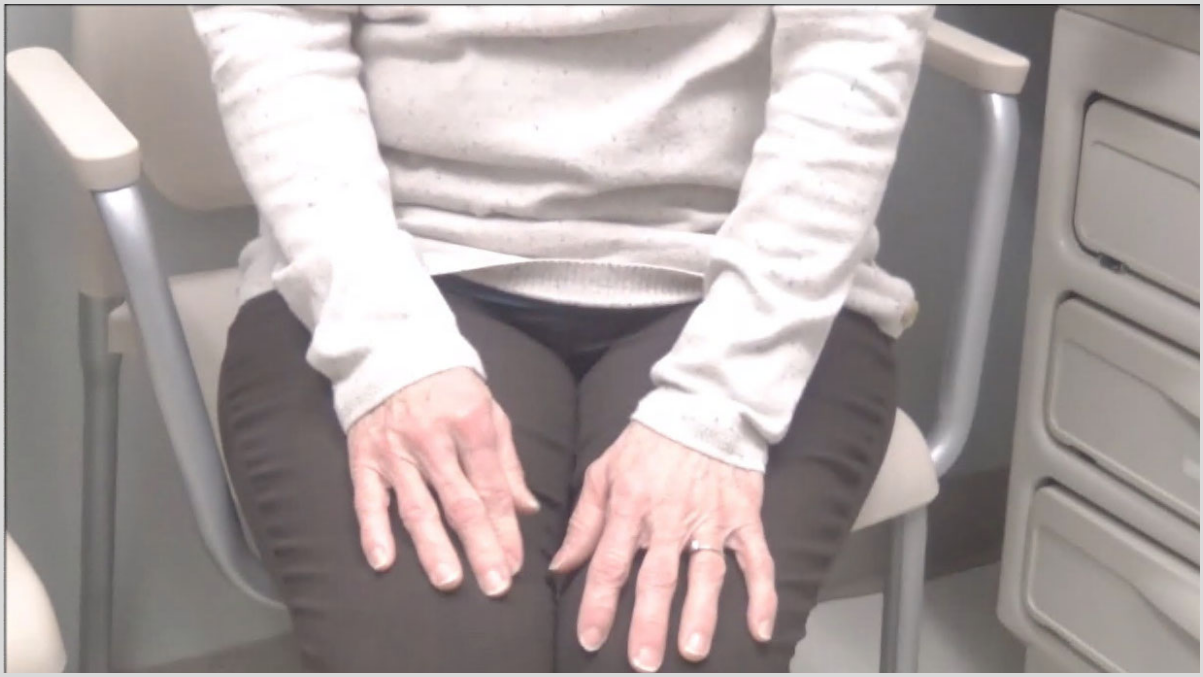
More specifically in the context of parkinsonism: reduction in frequency and amplitude with repeated movements

Also manifests as hypomimia (masked face), slow/shuffling gait, hypophonia (soft voice)



Rest Tremor

- Tremor that is prominent even when the affected part of the body is fully supported
- Accentuated (increased amplitude) with distraction
- 4-6Hz frequency
- Distribution of tremor:
  - Arms, legs, mouth
  - Uncommon to affect the neck
  - Axis typically very distal; fingers/wrists not shoulder



Rigidity

- Resistance with passive extremity movements
- The resistance is the same whether moving extremities fast or slow (as opposed to spasticity)
- May 'feel' the tremor when testing rigidity, "cogwheeling"

Parkinson's disease (PD) a clinical diagnosis

- Parkinsonism:
  1. Bradykinesia
  2. Rest tremor or Rigidity
- At least 2 supportive criteria
  - Dramatic levodopa responsiveness
  - Levodopa induced dyskinesia
  - Anosmia
- Absence of exclusion criteria or red flags:
  - Ataxia
  - Vertical gaze problems
  - Early falls (w/i 3 years)
  - Dopamine receptor blocker use
  - …

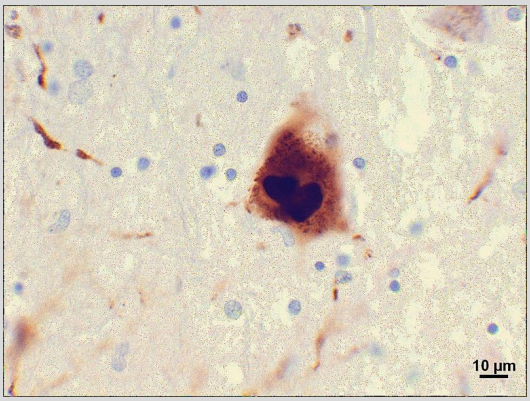
Postuma RB et. Al. 2015. MDS Clinical Diagnostic Criteria for Parkinson's Disease. *Movement Disorders*

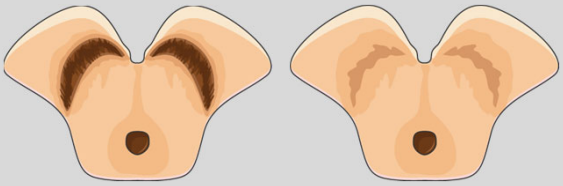
Pathogenesis of PD

Neurodegeneration of substantia nigra pars compacta (SNpc)

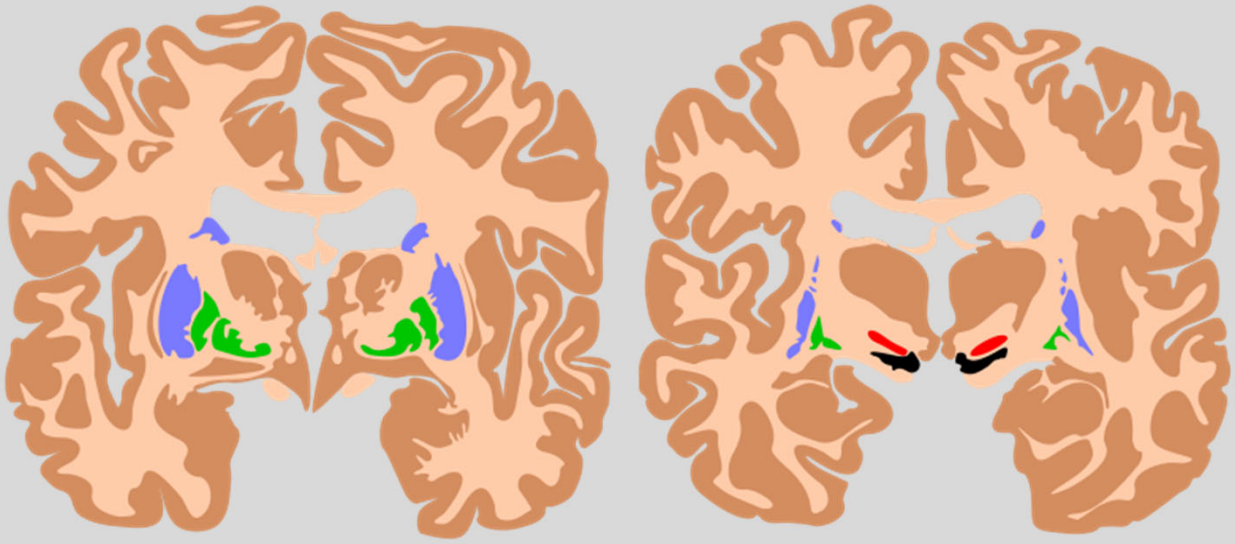
Presence of misfolded alpha-synuclein, aggregates called Lewy bodies (right)

Loss of dopaminergic input into the basal ganglia



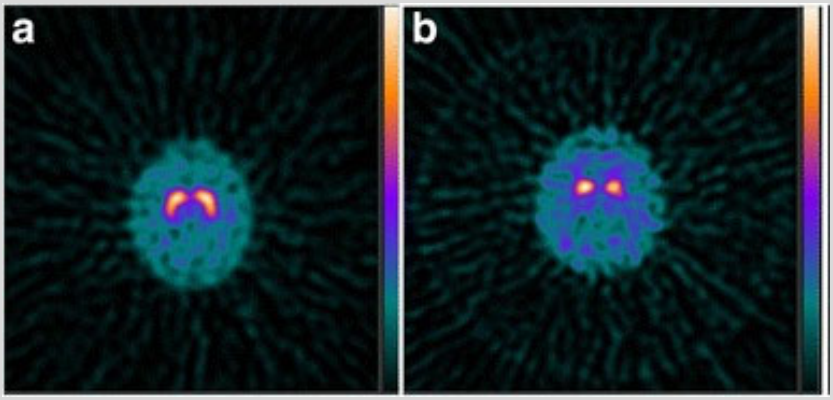


The Basal Ganglia



The Basal Ganglia

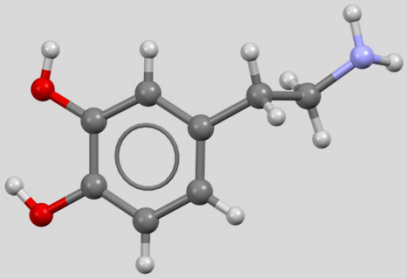
Loss of dopaminergic input to the basal ganglia can be visualized with a DAT scan



Normal "comma"

Neurodegenerative parkinsonism "period"

The rationale behind dopamine replacement therapy



Dopaminergic input can be normalized in several ways

1. Supplementing dopamine with levodopa
2. Dopamine receptor modulation with dopamine agonists
3. Decreasing break down of endogenous dopamine with MAO inhibitors

The overall effect is to improve **s**haking, **s**tiffness, **s**lowness

Approach to adjusting levodopa

- Typical formulation is carbidopa-levodopa 25-100
  - limited role for the 25-250, 10-100, CR, and ODT formulations
- Typical starting dose: ½ tablet 3-4x daily about every 4 hours
- If stiffness, slowness or shaking still bothersome, increase individual dose; typically by ½ tablet each dose
- If good clinical effect but short duration, can shorten dosing interval
- Most common side effects are nausea, lightheadedness, fatigue

Dyskinesia

- Dyskinesia refers to hyperkinetic (excessive) movements, including dystonia (patterned posturing) and chorea (dance like movements, think “choreography”)
- At peak levodopa dose, the dyskinesia most common in PD is chorea
- Incidence of dyskinesia is about 30% by 5 treatment years, 59% by 10 treatment years

Van Gerpen et. Al. 2006. *Levodopa-Associated Dyskineisa Risk Among Parkinson Disease Patients in Olmsted County, Minnesota, 1976-1990*. Arch Neurol

Initial therapy – dopamine agonist or levodopa?

056 Study, Rascol et. Al, 2000

- Prospective, randomized, double blind study, Parkinson's disease patients
- N=268, ropinirole:levodopa 2:1, treated for 5 years
- At 5 years of treatment, there was a 3 fold reduction in the risk of dyskinesia with the ropinirole group
- However, motor scores were also generally better in the levodopa group for the entirety of the study

Rascol O. et. Al. 2000. *A five year study of the incidence of dyskinesia in patients with early Parkinson's Disease who were treated with ropinirole or levodopa. NEJM.*

Initial therapy – dopamine agonist or levodopa?

LEAP study, Verschuur et al 2019

- Delayed start trial with levodopa in early/treatment-naïve PD patients
- N=445: 222 on levodopa for 80 weeks, 223 took placebo for 40 weeks then levodopa for 40 weeks
- At week 80, there was no difference in motor symptoms (MDS-UPDRS part 3 score)
- There was also no difference in the incidence of dyskinesia or motor fluctuations
- There was a significant difference in quality-of-life scores during the first phase of the trial, favoring the early start group

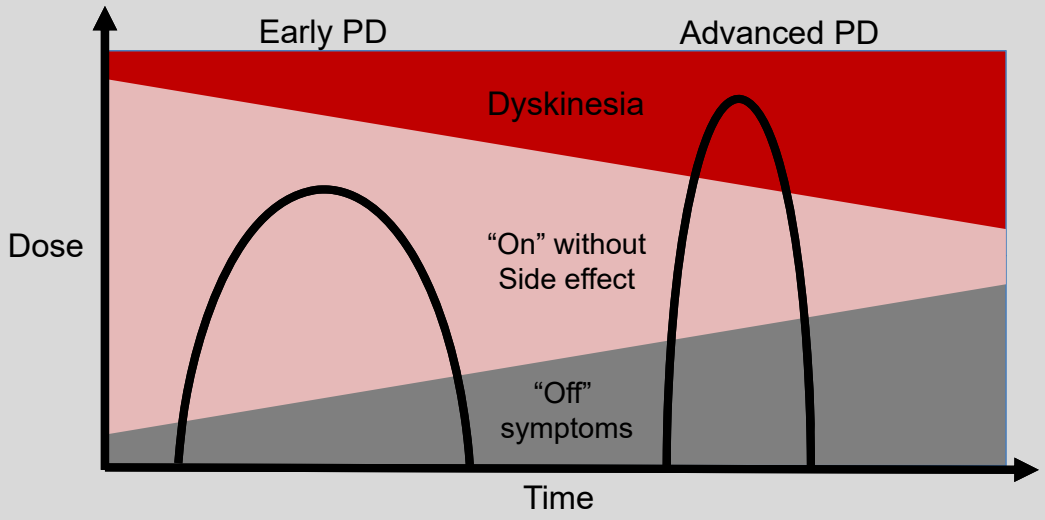
Verschuur et. Al 2019 *Randomized Delayed-Start Trial of Levodopa in Parkinson's Diseaese. NEJM*

Dyskinesia – Approach to treatment

- Assess whether bothersome to patient
- Van Gerpen, 2006, study of PD patients with dyskinesia
  - 40% with bothersome dyskinesia, requiring adjustment
  - Only 10% could not be managed by medication adjustment
- Typical approach for medication adjustment:
  - Reduce dopaminergic medications
  - If reducing individual levodopa doses, may need to also shorten dosing interval
  - Amantadine can be used to directly reduce dyskinesia

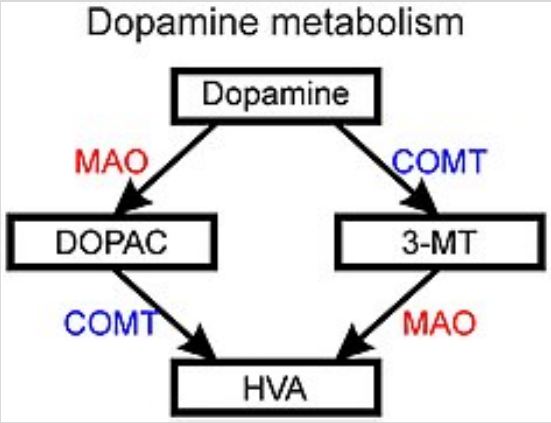
Van Gerpen et. Al. 2006. *Levodopa-Associated Dyskineisa Risk Among Parkinson Disease Patients in Olmsted County, Minnesota, 1976-1990*. Arch Neurol

Motor fluctuations in the progression of Parkinson's disease



Adapted from Hwang H, Norris S. 2021. Managing Advanced Parkinson Disease. *Journal of Geriatric Psychiatry and Neurology*

Motor fluctuations – strategies for treatment



Source: Puttonen HAJ, Sundvik M, Rozov S, Chen Y-C and Panula P (CC BY 3.0) No changes made. https://creativecommons.org/licenses/by/3.0/deed.en

Intervention	Reduction of off time (hours / day)
Entacapone	0.60
Istradefylline (Nourianz)	0.76
MAO-Bi (rasagiline, selegiline)	0.84
Opicapone (Ongentys)	1.00
Amantadine ER (Gocovri)	1.10
Add Dopamine agonist to levodopa	0.93 - 1.80
Rytary (1/3 IR, 2/3 ER levodopa)	1.17 - 2.30
Levodopa continuous intestinal gel (Duopa)	1.91 - 2.35
Deep brain stimulation (GPi or STN)	1.80 - 2.50

Adapted from Fabbri et al 2022. Off time Treatment Options for Parkinson's Disease. *Neurol Ther.*

Continuous levodopa infusion

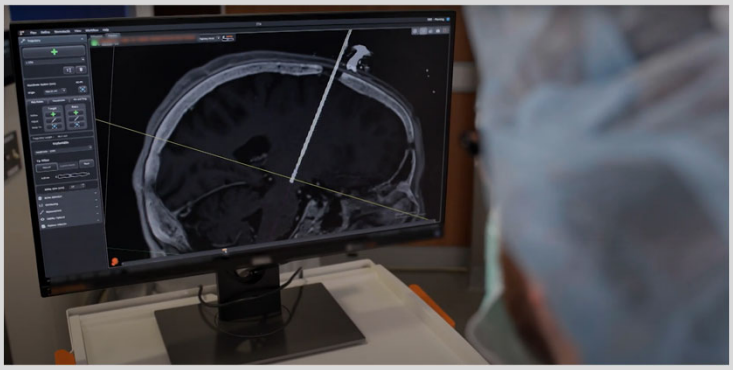
- Levodopa continuous intestinal gel (LCIG)
  - Jejunal tube is inserted, connected to external pump that must be carried/worn
  - Can make very fine-tuned adjustments to rate of levodopa per hour
  - Morning infusion, continuous infusion for 16 hours per day, extra dose pushes
  - LCIG Horizon study 2014 – double blind double dummy double titration study - significant reduction in off time: -4.04h LCIG vs -2.14h adjusting oral levodopa alone

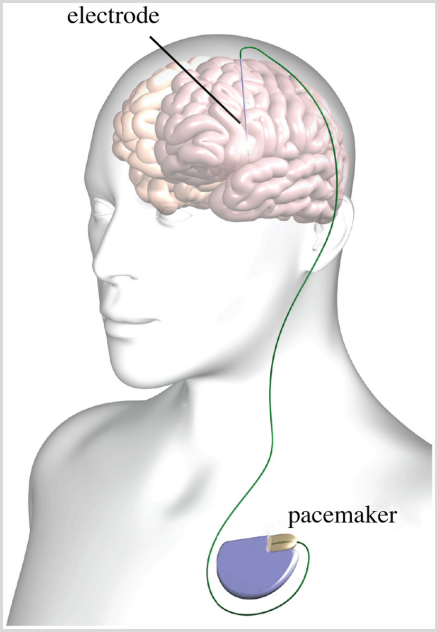
Olanow et al 2014 Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomized, controlled, double-blind, double-dummy study. *Lancet Neurology*

Deep Brain Stimulation

Stereotactic surgery with electrode placed in deep brain structures; pacemaker (IPG) placed in chest

Two main targets in Parkinson's disease are structures within the basal ganglia: STN and GPi





Source: Shamir R, Noecker A and McIntyre C (CC BY 3.0) No changes made. https://creativecommons.org/licenses/by/3.0/deed.en

Exact mechanism not known, likely multiple:

1. Inhibition of cell bodies

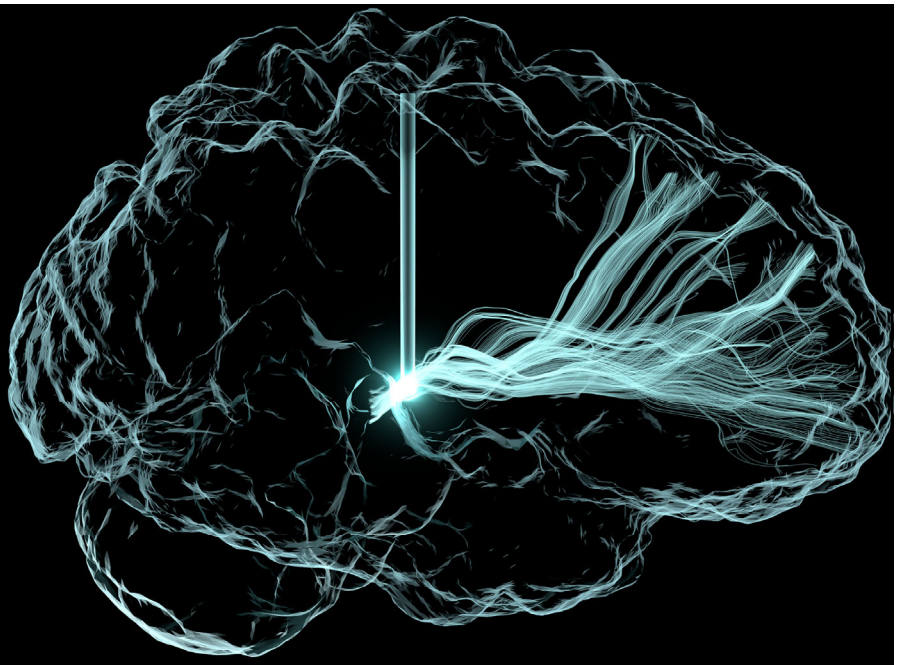
2. Excitation of neighboring axons and tracts

3. Astrocyte stimulation and calcium release

4. Glutamate and adenosine release

5. Increases in cerebral blood flow

6. Proliferation of neural precursor cells

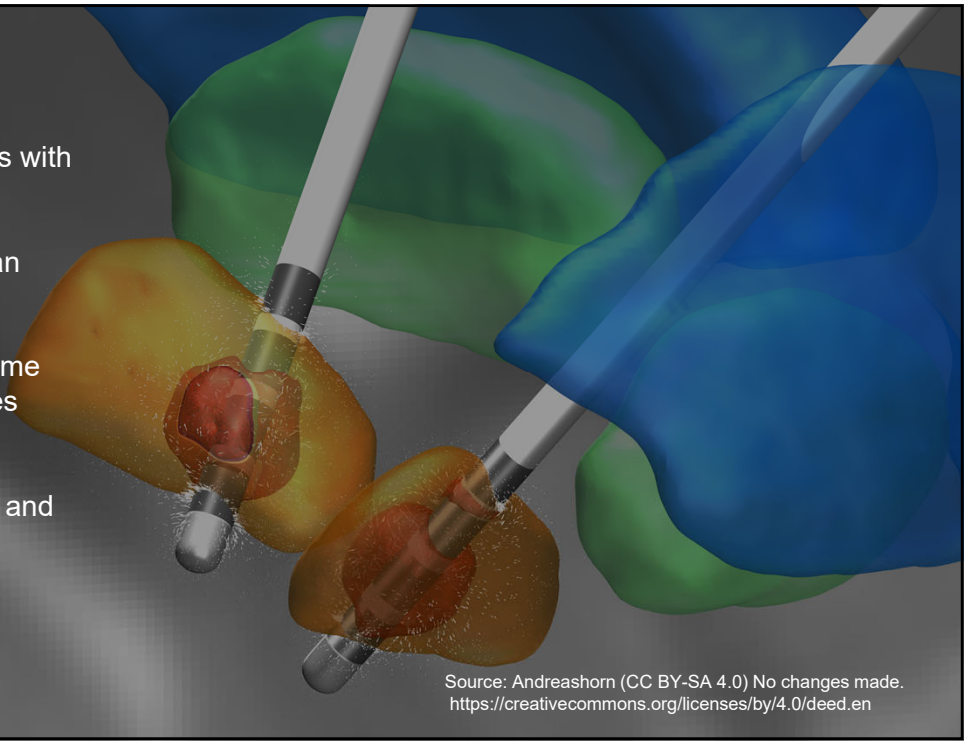


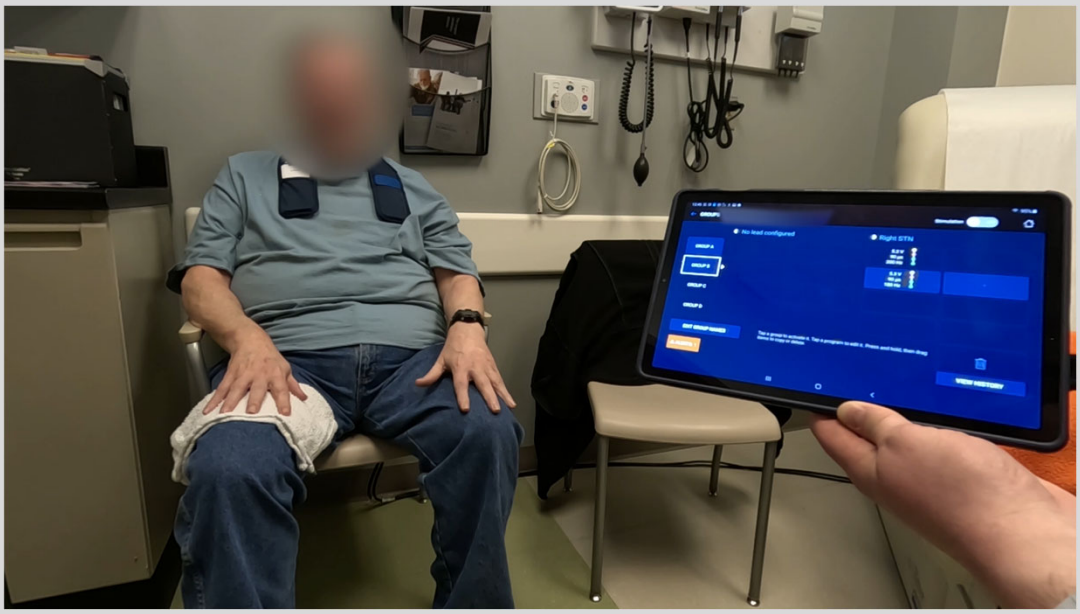
Improves motor symptoms with effect similar to levodopa

But not typically better than levodopa

Effect is adjustable over time with programming changes

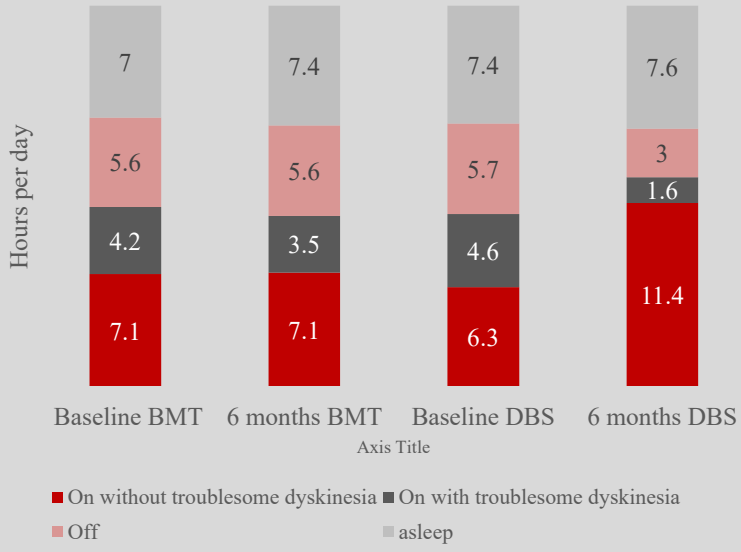
Tremor is the exception; suppresses tremor above and beyond medication





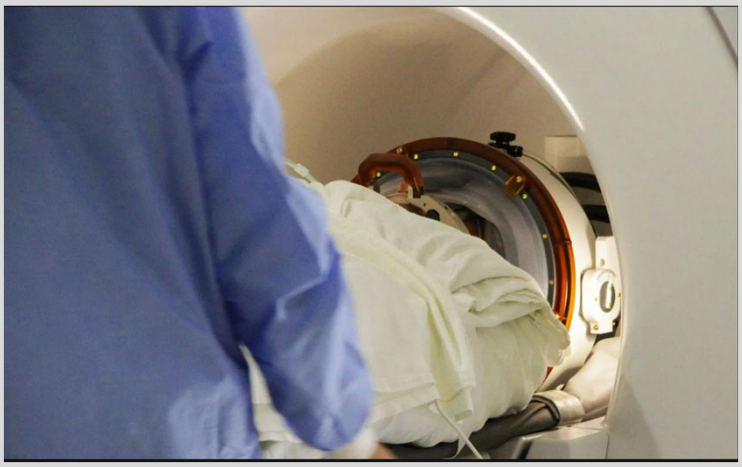
Deep Brain Stimulation in PD

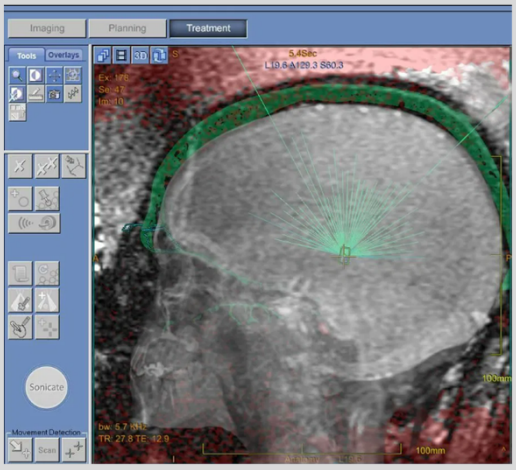
- Weaver et al 2009
- N = 255, 134 best medical treatment (BMT), 121 deep brain stimulation (DBS), 61 GPI/60 STN)
- Follow up at 6 months
- Motor diaries to keep track of symptoms
- Significant difference ($p<0.001$) in off time and on time with / without troublesome dyskinesia



Weaver et al. 2009 Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients with Advanced Parkinson Disease
Figure adapted from Jankovic J, Hallett M, Okun M, Comella C, and Fahn S. 2002 Principles and Practice of Movement Disorders. 3rd edition. Elsevier

Focused Ultrasound Ablation (FUSA)





Source: The Ohio State University Wexner Medical Center

Focused Ultrasound Ablation (FUSA)

	Thalamotomy (VIM)		Subthalamotomy (STN)		Pallidotomy (GPi)	
Improves	Tremor		Tremor, Rigidity		Dyskinesia, Dystonia	
Limitations	Does not improve other Parkinson symptoms Must wait 9 months for second side		Not currently FDA approved		Approved for unilateral procedure only	
Selected potential side effects	Paresth./Numb Gait dist. Weakness Dysarthria	8/56 at 12mo 5/56 at 12mo 1/56 at 12mo 1/56 at 6mo	Dyskinesia Weakness Dysarthria Gait dist.	2/27 at 12mo 2/27 at 12mo 1/27 at 12mo 1/27 at 12mo	Dysarthria Visual dist. Gait dist. Loss of taste	1/68 at 12mo 1/68 at 3mo 2/68 at 7d 2/68 at 7d

Elias W et al. 2016 A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *NEJM*
Martinez-Fernandez R et al. 2020 Randomized trial of Focused ultrasound Subthalamotomy for Parkinson's Disease. *NEJM*
Krishna V. et al. 2023 Trial of Globus Pallidus Focused Ultrasound Ablation in Parkinson's Disease *NEJM*

Conclusions

Parkinson's disease is a clinical diagnosis

Symptomatic therapy is adjusted based on clinical evaluation of motor symptoms

It is no longer necessary to avoid the use of levodopa in early PD

When medication adjustments are inadequate in managing motor complications, can consider advanced therapies