



Parkinson's Disease (PD)

The Latest Advances in Treatment and Research

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BIO AND DISCLOSURES



- Board-certified neurologist with subspecialty fellowship training in Movement Disorders.
- Education:
 - Medical school – Royal College of Surgeons in Ireland
 - Residency – Northwestern University
 - Fellowship - UCLA
- Director of Movement Disorders Clinic at PNI/Providence Little Company of Mary since 2019.
- Active clinical trials researcher in Parkinson’s disease for more than 10 years.
- **No current relationships to disclose**

LEARNING OBJECTIVES



- Provide an overview of the the clinical spectrum of Parkinson’s disease, its stages of progression and its impact on morbidity and mortality.
- Discuss young onset Parkinson’s disease and any variations in disease severity and progression.
- Provide an update on diagnostic trends including biomarkers (e.g., alpha-synuclein) and the use of genetic testing (e.g., LRRK2 and other genes).
- Discuss the use of newer therapies (subQ infusion, exercise, deep brain stimulation, focused ultrasound, etc. and their impact on morbidity and mortality.

OVERVIEW OF PARKINSON'S DISEASE (PD)



- A chronic and progressive degenerative disease of the central nervous system that spans decades with significant morbidity and healthcare burden.
- PD is the 2nd most common neurodegenerative disorder following Alzheimer's disease.
- Affects about 1.5 million Americans with 90,000 new cases diagnosed every year in the USA.
- Not a fatal condition but with an overall mortality ratio of 1.52 due to secondary complications.
- Number of people with PD is expected to more than double by year 2040*.

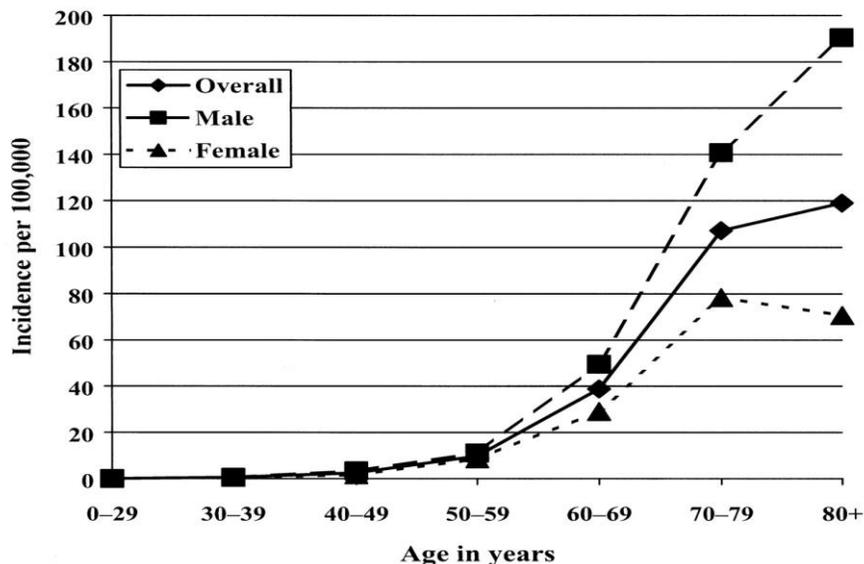
*Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. *J Parkinsons Dis*. 2018;8(s1):S3-S8.

*Su D, Cui Y et al. *BMJ* 2025;388:e080952 | doi: 10.1136/bmj-2024-080952

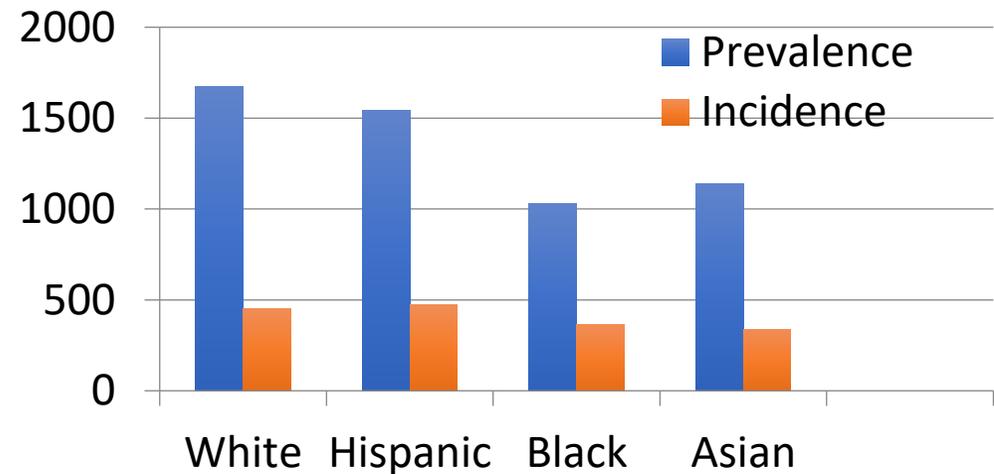
WHO IS AT RISK FOR PARKINSON'S DISEASE



- Mean age of onset 60, 10% patients with onset before the age of 50.
- Incidence increases with age.
- More common in males (2:1)
- Caucasian and Hispanic populations highest at risk



Van den Eeden SK et al. Amer J of Epidemil 2003



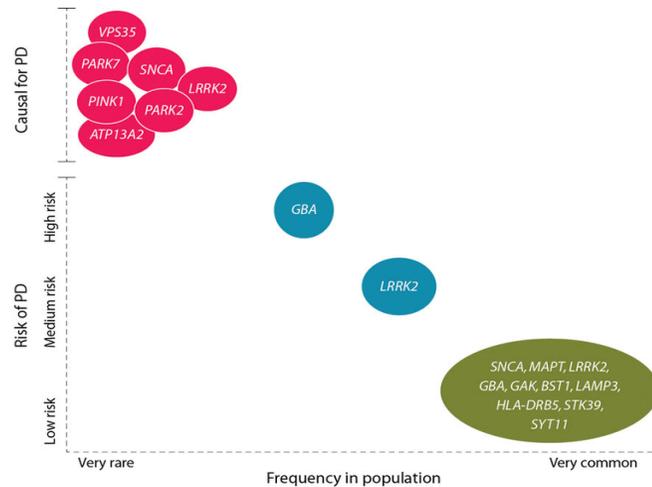
Age-adjusted Parkinson disease prevalence and annual incidence (per 100,000) by ethnic group. Taken from Neuroepidemiology, 2010;34:143-151

WHAT HAVE WE LEARNED IN THE LAST 25 YEARS



Genetics

Monogenic genes vs risk variants



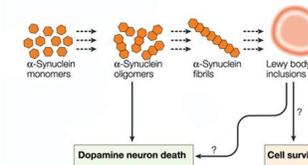
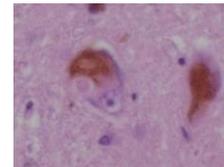
Marcel P. van der Brug *et al.* *Sci. Transl. Med.* 2015;7,305ps20-305ps20.

Genotype–clinical correlations

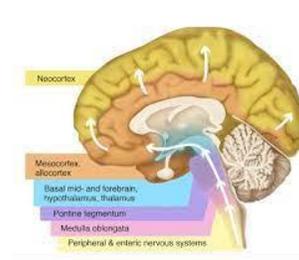
- Early vs late age onset
- Rate of progression
- Response to medication and DBS
- Cognitive and psychiatric decline

Pathology

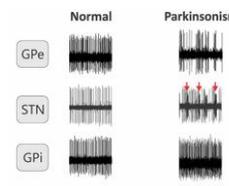
α -synuclein pathology



Braak Staging

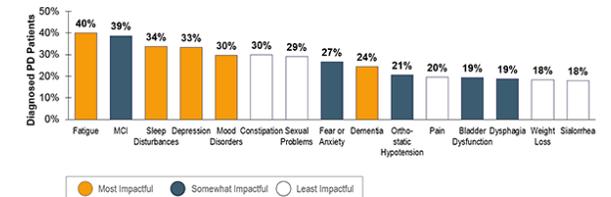


Changes in motor circuits and B-oscillations



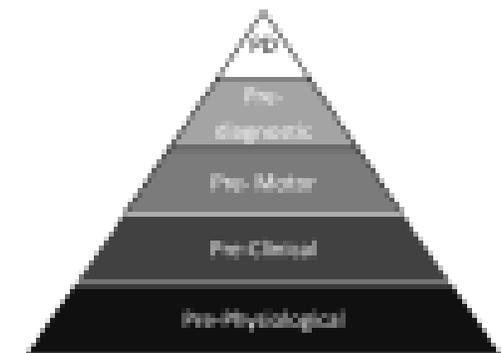
Clinical

Nonmotor spectrum of PD



PD gives rise to a spectrum of cognitive/neurobehavioral and other non-motor symptoms that highly impact quality of life of patients
The Michael J. Fox Foundation for Parkinson's Research

Prodromal PD and the search for biomarkers



OUR UNDERSTANDING OF PARKINSON'S DISEASE



Genetics



Single gene mutations
(autosomal and recessive
vs.
Risk gene variants

Brain aging

Cellular stress

Abnormal protein
accumulation and propagation

Loss of dopaminergic neurons
(and other neurotransmitters)

Parkinson's Disease

Environmental exposure



THE CLINICAL SPECTRUM OF PARKINSON'S DISEASE



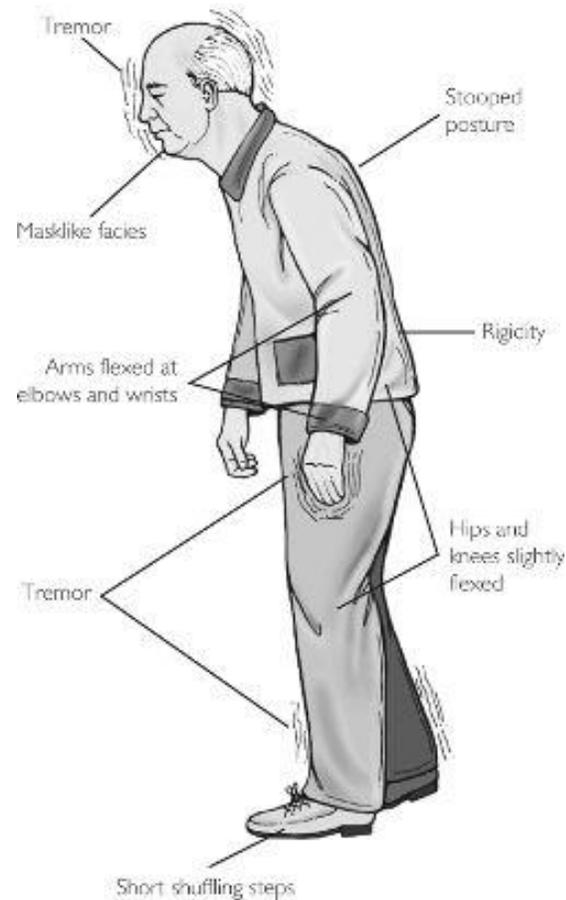
Motor Symptoms

Bradykinesia

Rest Tremor

Muscular rigidity

Changes in gait and balance



Non Motor Symptoms

Daytime fatigue and sleepiness

Reduced sense of smell

Constipation

Urinary, sexual dysfunction

Fluctuating blood pressure

Insomnia, REM sleep disorder

Mood disorders

Cognitive decline

Hallucinations and delusions

STAGES OF PARKINSON'S DISEASE



Early stage (Hoehn and Yahr 1, 2)

- Mild symptoms - One/both sides
- Independent with ADLs
- Walking independently
- Good medication response
- Some slight problems with attention and concentration

Mid- stage (Hoehn and Yahr 3)

- Moderate symptoms - bilateral
- Some assistance with ADLs
- May need cane or walker
- Increased frequency of medications
- Onset of dyskinesias (dance-like movements)
- Mild-moderate memory problems
- Susceptibility to psychosis

Advance stage (Hoehn & Yahr 4,5)

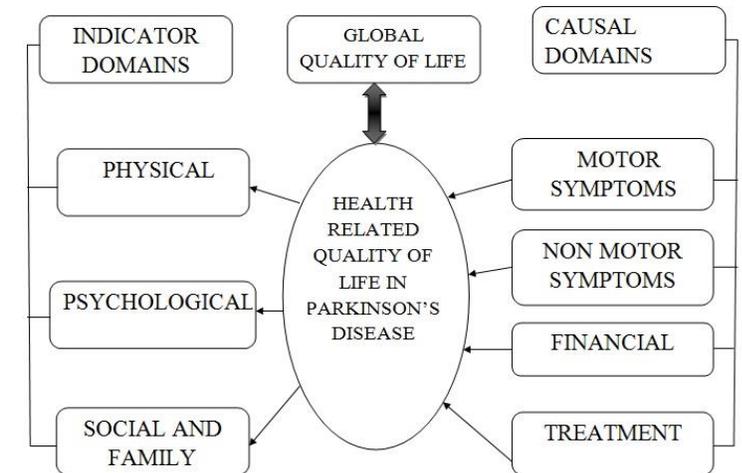
- Moderate -severe symptoms
- Needs assistance with most ADLs
- Walker or wheelchair dependent
- Frequent medication dosing.
- Prominent dyskinesias
- Swallowing difficulty
- Significant cognitive issues.
- +/- hallucinations, behavioral challenges

QUALITY OF LIFE IN PARKINSON'S DISEASE



Individuals with Parkinson's can face many challenges to their quality of life due to:

- Progressive motor disability and risk of falls with diminished ability to maintain independence over the years.
- Impact on employment, driving capabilities, traveling.
- Impact of emotional well-being and associated social stigma
- Personal financial cost of chronic illness—medical copays, hospitalizations, loss of employment, long-term care.



Aggarwal R, et al. Journal of Clinical and Diagnostic Research. 2016;10(9)©35-OC39

MORTALITY IN PARKINSON'S DISEASE



Most common causes of death in PD:

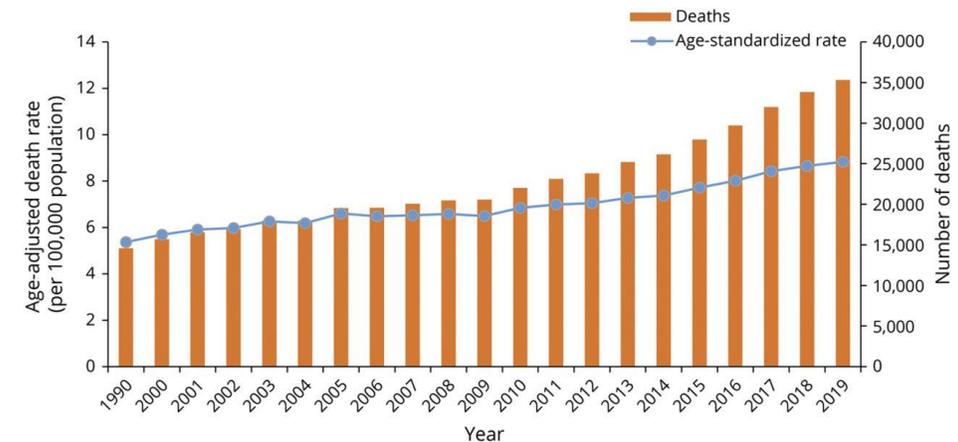
- Pneumonia – most commonly related to dysphagia and aspiration
- Falls – head injuries or fractures
- Other infections

Factors influencing risk of mortality:

- Advanced age
- Male sex
- Disease severity
- Presence of dementia and/or psychosis associated with PD

- Access to specialty and multidisciplinary care, access to surgical therapies such as DBS and lifestyle factors such as regular exercise, have been associated with increased survival.

Figure 1 Number of Deaths and Age-Adjusted Rate From Parkinson Disease: United States, 1999 to 2019



Rong S, Xu G et al. Neurology.2021;97 (20) e1986-e1993

PALLIATIVE CARE IN PARKINSON'S DISEASE

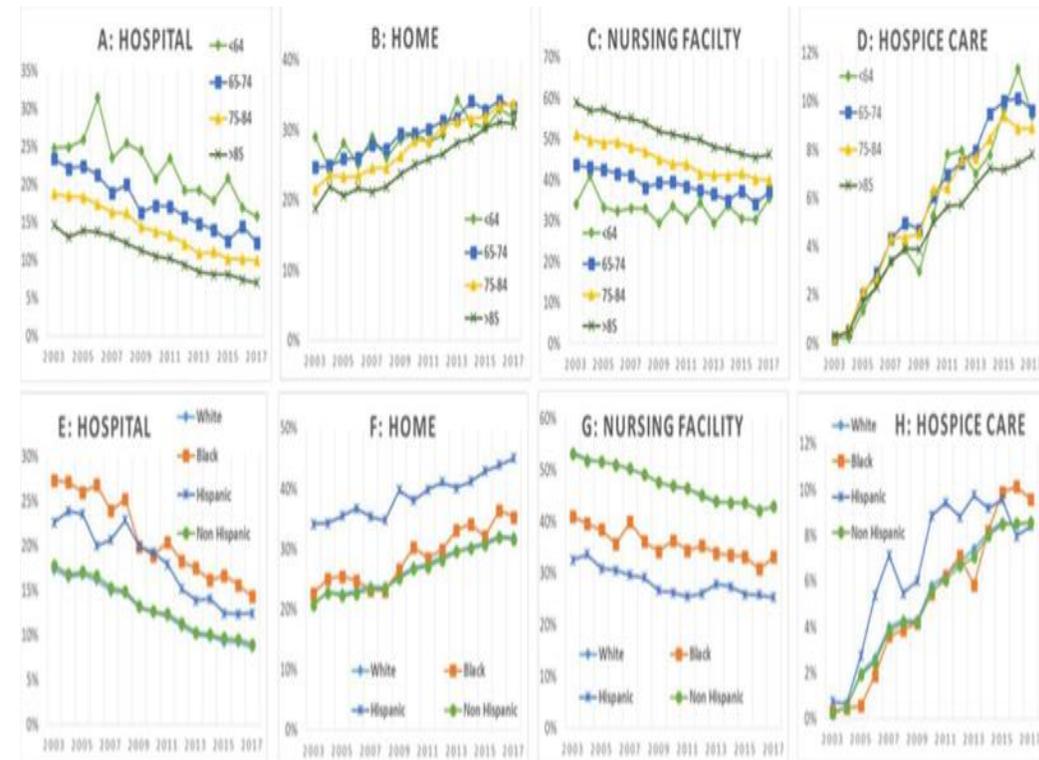


Palliative care – comprehensive approach to disease management with goal to improve QOL, not increase survival.

- Non motor symptom management
- Home supportive services
- Emotional and spiritual support
- Reduce caregiver stress
- Help with goals of care and advance care planning in later stages

Place of death in Parkinson's disease**

- Home and hospice facility deaths in PD patients are gradually increasing.
- Increased odds of hospital deaths in non-Caucasian populations with less access to advanced care.



Kluger BM, Katz M, et al. JAMA Neurol. 2024 Jan 1;81(1):39-49.PMID: 37955923

**Kumar P, Yasmin F, et al. BMJ Supportive & Palliative Care 2024;14:e1060-e1066.

YOUNG ONSET PARKINSON'S DISEASE (YOPD)



- Diagnosis before age 50
- 5-10% of people with PD.
- Diagnosis less recognized in this group and can be challenging – rule out secondary causes.
- Different clinical course vs. late onset PD (over age 50):
 - Prone to more muscular stiffness and dystonia (cramping and posturing), less early problems with gait and falls
 - Slower progression with longer period of preserved functional ability and less cognitive decline
 - Higher risk of mood disorders and neuropsychiatric side effects to therapy – depression/anxiety, compulsivity/impulsivity.
 - More sensitive to dopaminergic medications, higher risk of motor complications such as dyskinesias.
- Higher impact on professional and family life and quality of life.
- More commonly familial, genetic mutations may play a more prominent role as compared to late-onset PD.

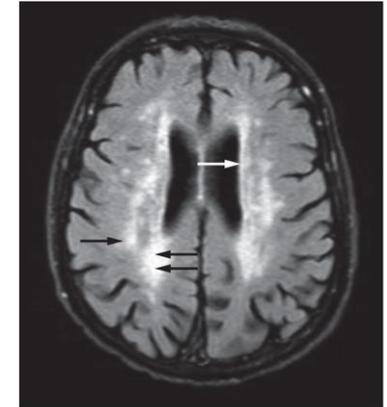


Mehanna R, Jankovic. Parkinsonism Relat Disord. 2019 Aug;65:39-48.

DIAGNOSIS OF PARKINSON'S DISEASE



- Clinical diagnostic criteria - 89.5% accuracy for early stages and 92.5% for later stages, based on neuropathological confirmation.*
- Diagnostic accuracy usually improves with later age of onset.
- Ancillary testing considered:
 - Younger age of onset – prognosis/planning and risk of exposure to PD medications
 - Mimics of Parkinson's disease – essential tremor, vascular parkinsonism, normal pressure hydrocephalus
 - Secondary causes of Parkinson's disease – medication or drug induced



Nature Reviews | Neurology



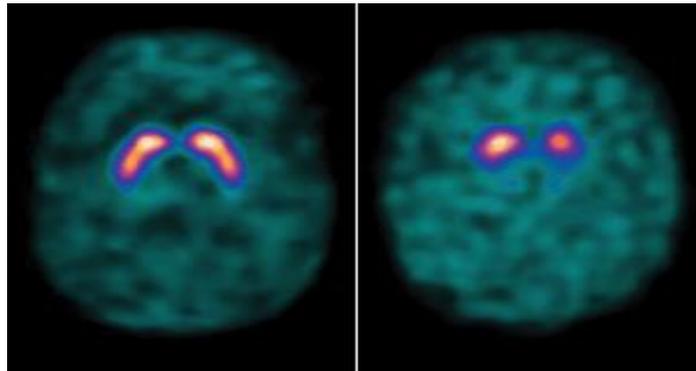
Wikipedia

* Virameteekul, S., et. Mov Disord. 2023; 38: 558-566.

DIAGNOSIS OF PARKINSON'S DISEASE

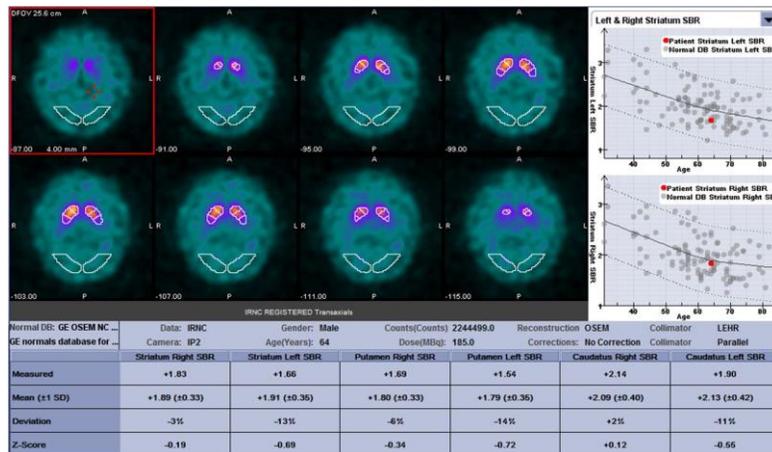


NM BRAIN DAT SCAN



Not PD

PD



- Nuclear medicine brain (SPECT) scan with Ioflupane I 123 injection - quantifies dopamine producing neurons
- Sensitivity 80-100%, specificity 97-98%
- The following medications may interfere with DaT imaging (false positive):
 - Amoxapine, amphetamine, benztropine, bupropion, buspirone, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, sertraline, citalopram and paroxetine
- Limitations:
 - Not quantitative – does not correlate with severity
 - Not used to monitor progression
 - Cannot distinguish between other parkinsonian syndrome

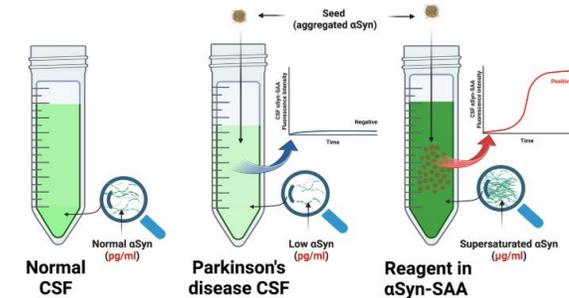
DIAGNOSIS OF PARKINSON'S DISEASE

Alpha-synuclein as a biomarker



SAAmplify- α SYN - (Mayo Clinic Labs and Amprion)

- Seed amplification assay to detect the seeding activity of misfolded alpha-synuclein in spinal fluid.
- 87% sensitivity and 97% specificity
- Requires lumbar puncture, risk of spinal headache

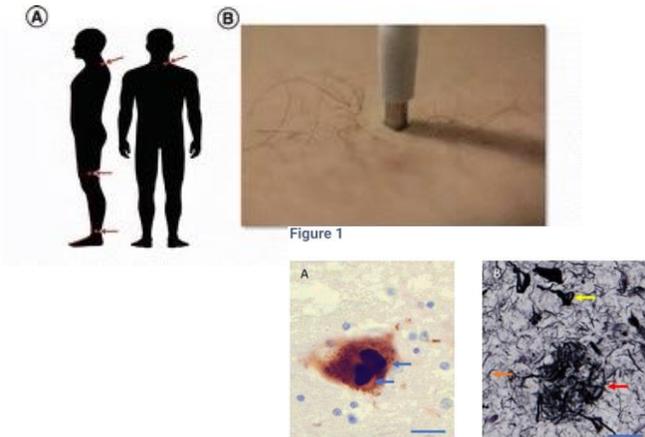


Espay AJ et al. Parkinsonism & Related Disorders, 2025; Vol 131:107256,

Syn-One (skin biopsy) test - (CND Lifesciences)

- Uses immunofluorescence to detect presence and distribution of phosphorylated alpha-synuclein within dermal nerves
- 95% sensitivity and 99% specificity in detecting synucleinopathies.
- In office procedure - three tiny skin biopsies on the upper back, lower thigh and lower leg under local anesthetic.

**Only diagnostic of alpha-synucleinopathy – does not predict disease onset or track progression and does not distinguish various types of synucleinopathy



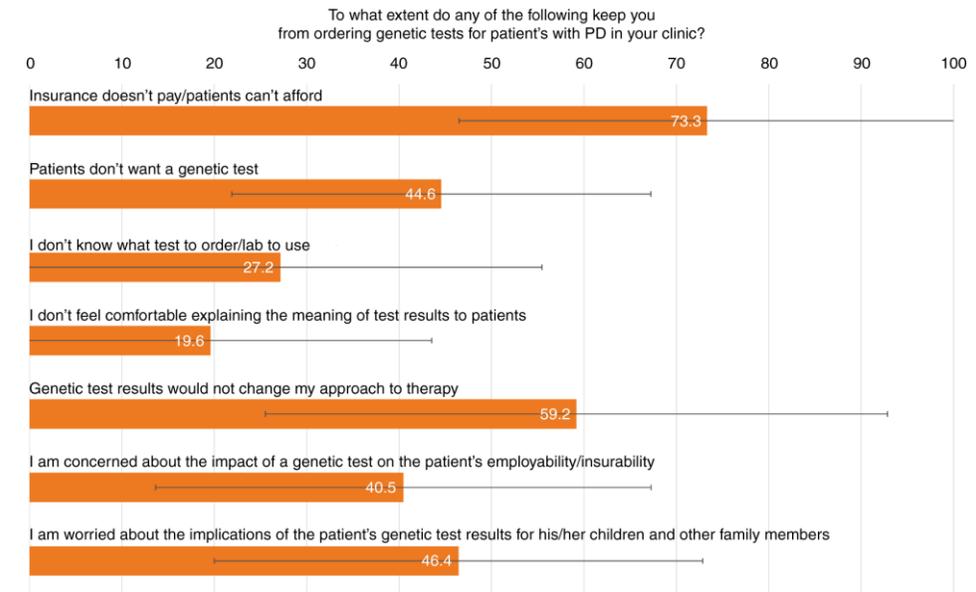
Courtesy of CND Lifesciences

GENETIC TESTING AND PARKINSON'S DISEASE



- Not common practice and relatively little guidance on genetic testing for physicians or patients.
- Generally considered in the following populations:
 - Young onset (<50) patient
 - Patients with strong family history
 - High-risk ethnicity groups such as Ashkenazi Jewish or North African ancestry (high risk of GBA and LRRK2 gene variants)
- Challenges in genetic testing:
 - Available tests vary—single gene, gene panels, exome sequencing.
 - Not diagnostic – test does not mean patient will develop disease
 - Limited access to genetic counseling
 - Significance of a negative test
- Free testing available through research groups – PD Generation, PPMI
- Targeted therapeutics are being studied for LRRKS and GBA variants.

Genetic testing for Parkinson disease: current practice, knowledge, and attitudes among US and Canadian movement disorders specialists



Alcalay, R.N., Kehoe, C., *et al.* *Genet Med.* 2020; 22, 574–580).

FDA APPROVED MEDICATIONS FOR PARKINSON'S DISEASE



Levodopa

1. Sinemet (carbidopa/Levodopa) IR and CR
2. Parcopa (Carbidopa/levodopa disintegrating tab)
3. Dhivy (quartered tab)
4. Inbrija (levodopa inhaler)
5. Rytary (Carbidopa/levodopa ER caps)
6. Crexont (Carbidopa/levodopa ER caps)
7. Duopa (levodopa intestinal infusion)
8. Vyalev – levodopa SC infusion)

Dopamine Agonists:

9. Pramipexole (mirapex) IR and ER
10. Ropinirole (requip) – IR and ER
11. Rotigotine (Neupro) patch
12. Apomorphine injectable (Apokyn)
13. Onapgo - apomorphine SC infusion

Anticholinergic:

14. Trihexylphenidyl (Artane)
15. Benztropine (Cogentin)

MAO-B Inhibitors

16. Selegiline (Eldepryl)
17. Rasagiline (Azilect)
18. Safinamide (Xadago)

COMT Inhibitors

19. Entacapone (Comtan)
20. Tolcapone (Tasmar)
21. Opicapone (Ongentys)

Other

22. Amantadine IR
23. Amantadine XR (Gocovri)
24. Istradefylline (Nourianz)

MEDICAL THERAPY FOR PARKINSON'S DISEASE



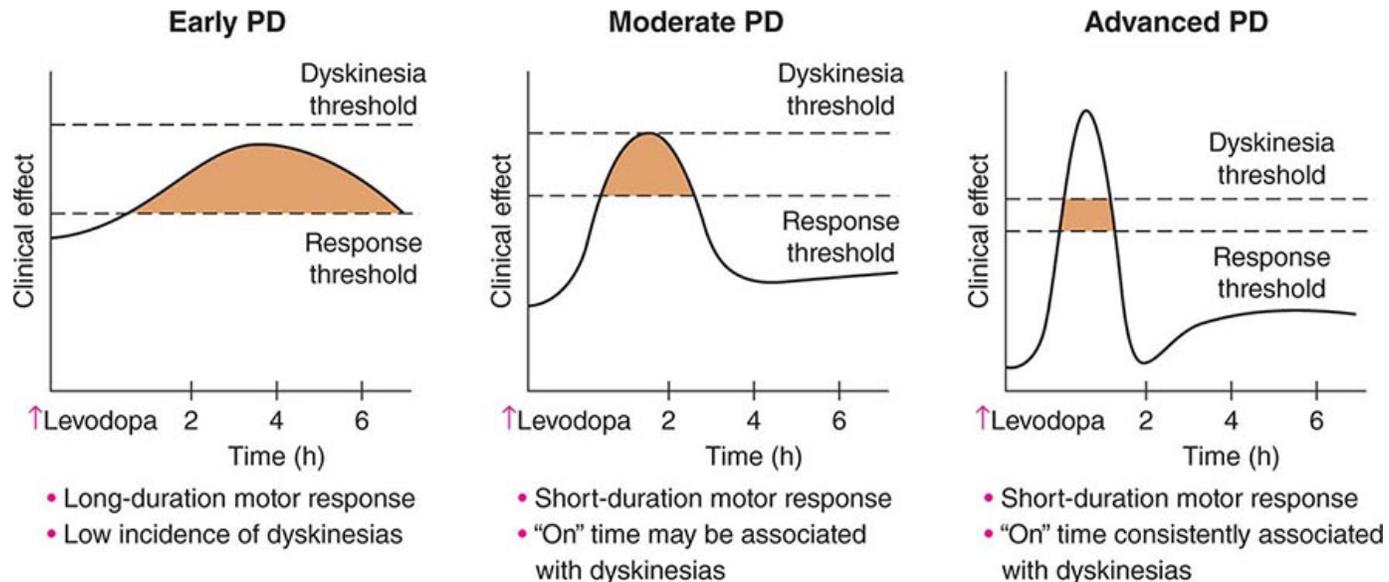
- Medical therapy treats symptoms only, not curative or disease modifying.
- Goal of treatment is to improve function, prolong independence and improve QOL and decrease caregiving burden.
- Treatment in early stages tailored to the individual – age of onset, main symptoms, comorbid conditions and non motor symptoms, judgement of long-term risks
- Treatment in advanced disease:
 - Management of medication-related motor complications
 - Emergence of less-responsive symptoms: dysphagia, worsening gait and balance, dementia and psychiatric symptoms



ADVANCED PARKINSON'S DISEASE - MOTOR COMPLICATIONS



Change in dopaminergic treatment response over time



Motor Complications:

- Fluctuation in medication effect:
 - predictable – end of dose
 - unpredictable
- Dyskinesias

Risk Factors

- Younger age at disease onset
- Higher levodopa dosage
- Severity disease on initiation of levodopa

Schapira AH et al. Eur J Neurol. 2009;16:982-989

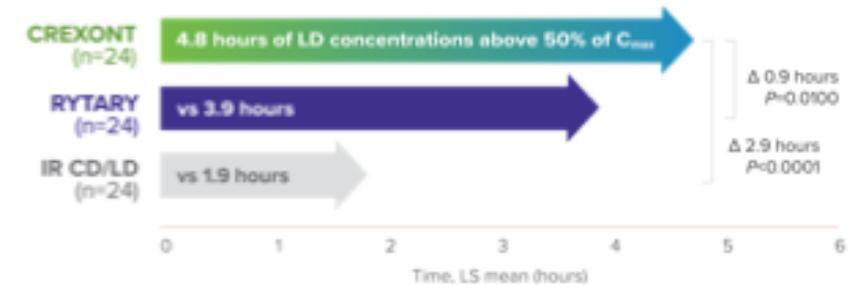
NEW UPDATES IN PARKINSON'S TREATMENT



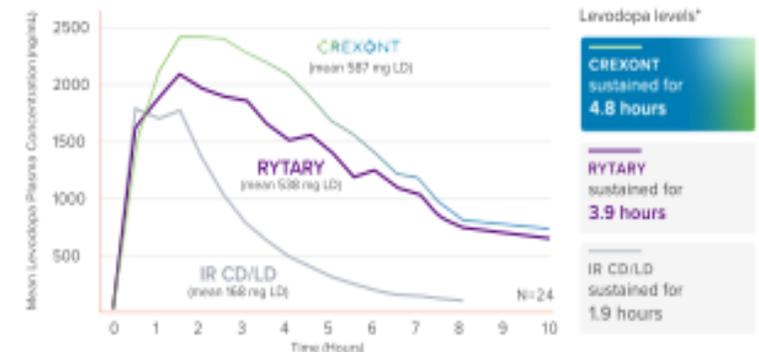
EXTENDED RELEASE FORMULATIONS OF ORAL LEVODOPA

☐ Crexont (ER carbidopa/levodopa) – 2024

- ¼ immediate-release granules and ¾ extended-release pellets
- Novel mucoadhesive polymer to maximize intestinal absorption
- Minimize dosing (i.e 5 times daily vs. 3 times daily)
- **Rise-PD study**
 - Nearly 2 hours additional on-time per dose of Crexont vs IR levodopa
 - 0.5 hours more “on” time with Crexont 3 times daily vs. IR levodopa 5 times daily.



Hauser RA et al. *JAMA Neurol.* 2023;80(10):1062-1069.
Modi NB et al. *Clin Neuropharmacol.* 2019;42(1):4-8.



Mean LD plasma level concentration-time profiles following a single dose of CREXONT, RYTARY, and IR CD/LD

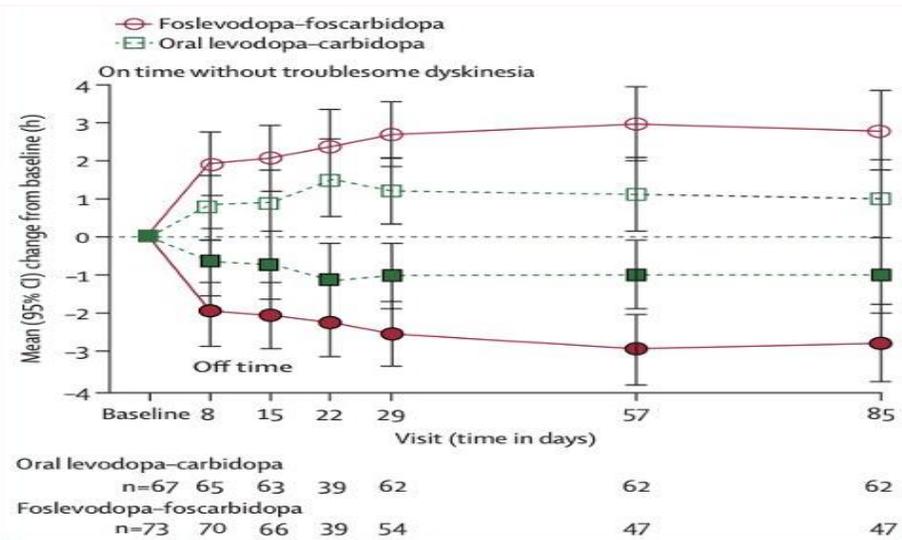
NEW INFUSION THERAPIES IN PARKINSON'S DISEASE



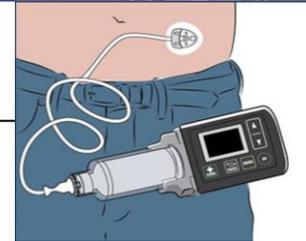
Vyalev



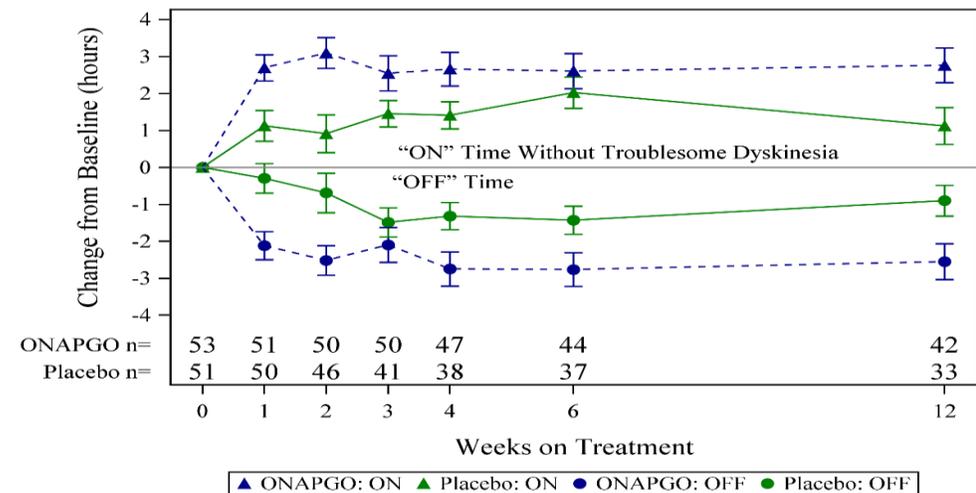
- Approved October 2024
- 25bhr SC infusion foslevodopa-foscarbidopa
- 1.75 hrs Increase in daily on-time and 1.79 hrs decrease in daily off-time (vs oral levodopa)
- 23% improvement in sleep disruptions
- 62% with mild-mod infusion site reactions



Onapgo



- Approved February 2024
- 16 hour SC apomorphine infusion
- 1.7 hrs increase in daily on-time and 1.7 hrs decrease in daily off-time (vs placebo)
- 44% mild-mod infusion site reactions



- **Allied therapies such as physical, occupational and speech / language therapy in combination medical therapy has been shown to:**
 - Improve endurance and mobility, improve balance and walking
 - Identify strategies to help patients complete daily tasks
 - Make home environments more safe and prevent caregiver injury
 - Improve communication and swallow function
 - May slow need for further medications in early disease*
- **Specialized therapy (vs. general therapy) is associated with**
 - More efficient – less treatment sessions needed
 - Fewer PD-related complications (orthopedic injury and pneumonia) and with lower costs of care**
 - Associated with a lower mortality rate***



Parkinson Foundation

*Frazzitta G, Maestri R, et al. *Neurorehabilitation and Neural Repair*. 2014;29(2):123-131.

**Ypinga, Jan H L et al. *Lancet Neurology*. 2018;;17(2) :153 – 161

***Ypinga, J.H.L., et al. . *npj Parkinsons Dis*.2025;11:214

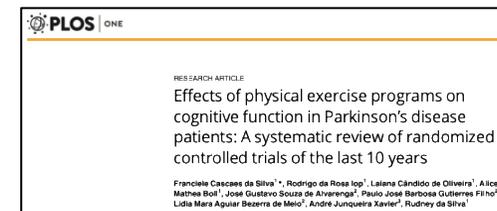
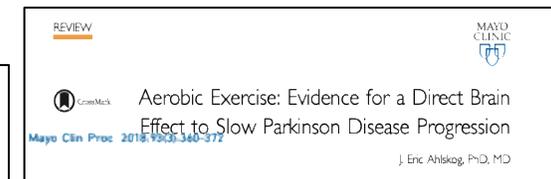
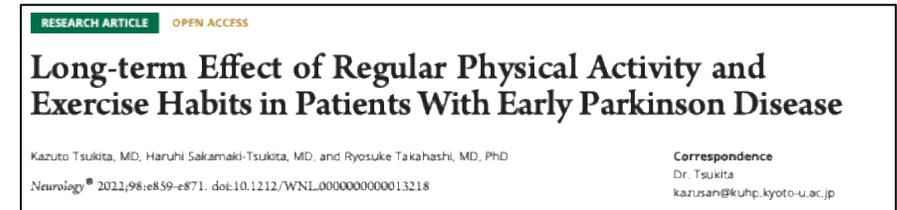
LIFESTYLE FACTORS IN THE TREATMENT OF PARKINSON'S DISEASE



Exercise

- Growing body of evidence to suggest that exercise clinically improves symptoms of PD, has neuroprotective effects, and should be recommended to patients with PD.
- Proven benefits:
 - Helps maintain strength, flexibility, endurance, balance
 - Helps alleviate depression, constipation and improves sleep
 - Accumulating evidence that those that exercise are able to maintain good QOL for longer, promotes brain health
 - Regular exercise during life reduces risk of developing PD
- Mechanisms:
 - induces expression of brain neurotrophic factors, - BDNF, GDNF
 - Reduce systemic inflammation
 - Improve mitochondrial function and reduce oxidative stress
 - increased cortical gray matter or hippocampal volumes

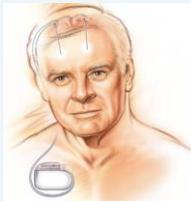
Exercise is now considered a treatment by many movement disorder specialists.



When to consider surgical options for PD:

- Confirmed diagnosis of Parkinson's disease in mid to later stages (\geq 4-5 years after diagnosis)
- Significant levodopa response with disabling medication wearing off periods or bothersome dyskinesias.
- Medically refractory tremor

Deep brain stimulation (DBS)



- Surgically implanted system.
- Delivers electrical stimulation to disrupt abnormal brain oscillations in specific brain targets.
- Nearly 20 years of clinical efficacy and safety data.
- Adjustable over lifetime and reversible if needed
- Continued neurological follow up and programming

Focused Ultrasound (MRlgFUS)



- Stereotactic thermal brain lesioning using high frequency ultrasound waves under MRI guidance.
- Incisionless, same-day procedure
- Staged procedure – unilateral to bilateral after 6-9 months
- Relatively new therapy for PD
- “One and done” – irreversible, no follow up needed.



Efficacy vs Best Medical Therapy

- Decrease in motor severity (UPDRS III) in off-meds state by 30-50%
- Increase in daily “on” time without dyskinesias by 2-5 hrs.
- Improvement in dyskinesia severity, ADLs and QOL.
- Continued efficacy with STN beyond 15 years**
- EARLYSTIM study - earlier intervention (> 4 yrs disease duration, <3 years motor complications) with significant long-term benefits in motor function and QOL.

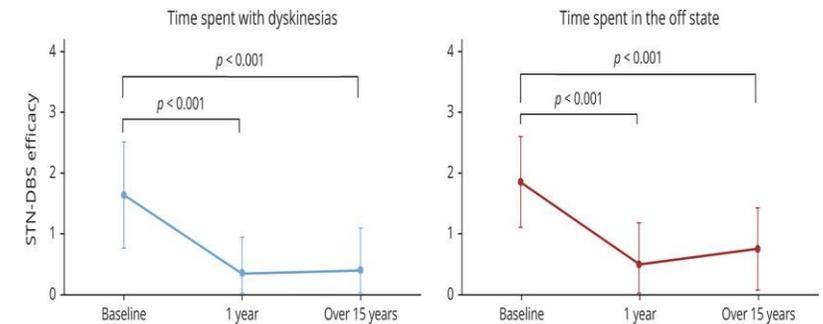
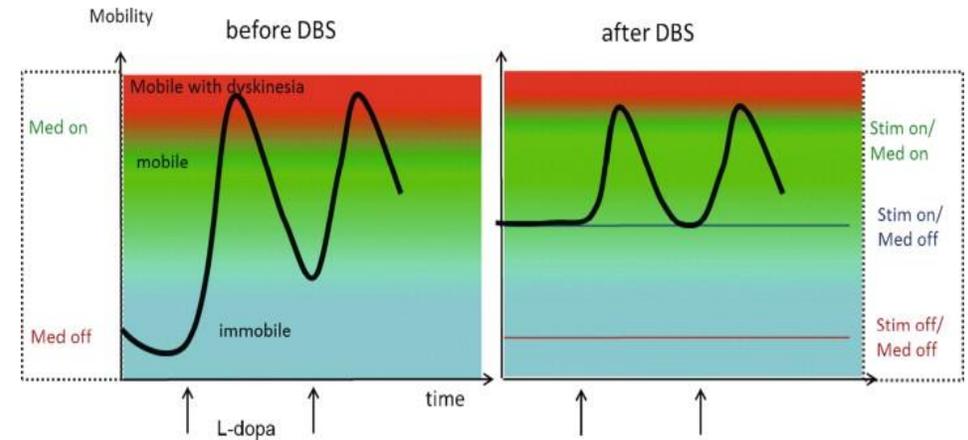


Figure 2 Long-term Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) Efficacy on Motor Complications.

****Francesco Bove et al. Neurology 2021;97:e254-e262**

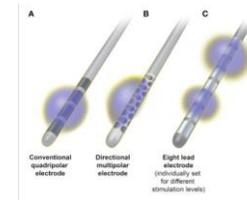
* Mahlkecht P et al. Movmt DO.2022;37(8):1581-92. **Schuepbade WMMM et al. NEJM.2013;368:610-22

ADVANCES IN DBS THERAPY FOR MOVEMENT DISORDERS



Advances in DBS systems

- Rechargeable battery – >15 years
- Newest models are all now MRI compatible
- Directional leads and independent current control allows current steering to maximize efficacy and lower side effects
- Virtual, remote programming available



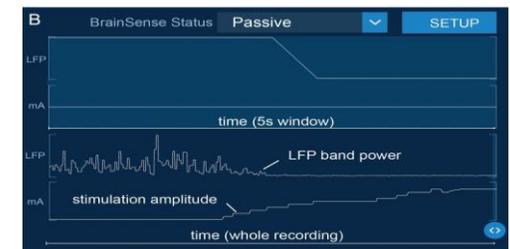
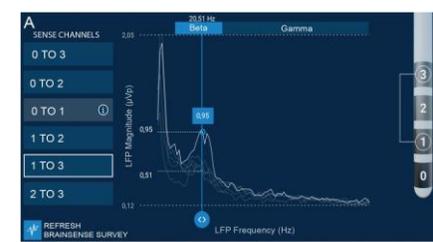
Courtesy of Abbott approved for media use



STIMVIEW XT – Boston Scientific

Advances in DBS Programming

- Image guided – recreation of patient's individual brain anatomy and lead placement
- LFP- guided – monitoring a patient's own brain signals to hone in stimulation and correlate to symptoms



Courtesy of Medtronic

NEW ADAPTIVE DBS FOR PARKINSON'S DISEASE



- Approved Feb 2025 (aDBS)
- Personalized therapy automatically adjusts stimulation based on a patient's own local brain activity in real-time.
- Delivers stimulation “on demand” rather than being continuous.
- Thresholds for stimulation set by clinician (single or dual thresholds)
- Adapt-PD Trial (aDBS vs cDBS)
 - Safe and well tolerated, no serious adverse events
 - Significant improved on time (+1.3 hrs) and decreased off time (-1.6 hrs) vs cDBS
 - Reduced battery power
 - 98% participants opted to continue with aDBS



Stanslaski, S et al. *npj Parkinsons Dis.* **10**, 174 (2024).. Bronte-Stewart HM, Beudel M, et al. *JAMA Neurol.* 2025. doi:10.1001/jamaneurol.2025.2781

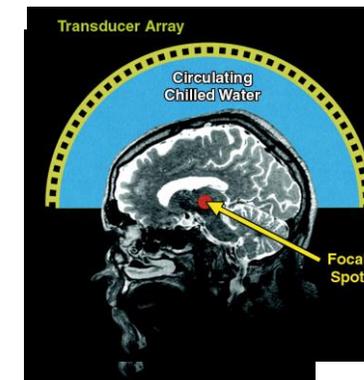
MRIgFUS FOR PARKINSON'S DISEASE



Advantages and disadvantages over DBS:

- Less invasive – incisionless, minimal risk of infection, no anesthesia
- Same- day procedure, no hospital stay
- Immediate effect – minimal follow up required
- Option for non-DBS or non-surgical candidates – cognitive or psych impairment, comorbid medical exclusions.

- Newer technology – less clinical and safety data
- Thus far, not as effective as DBS
- Staged procedure for bilateral treatment
- Head shave is mandatory
- MRI exclusions



MRIgFUS FOR PARKINSON'S DISEASE



Unilateral thalamotomy (tremor dominant PD - 2018)

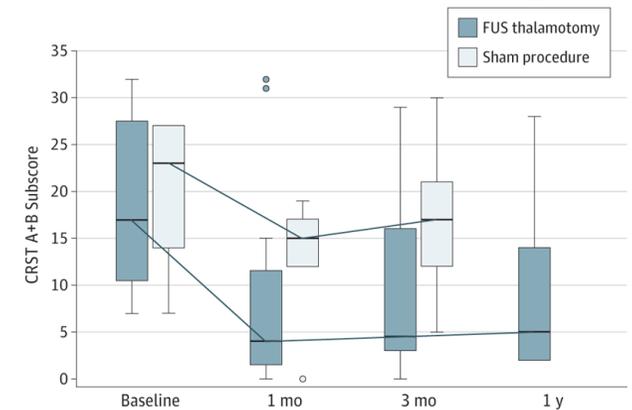
- 62% improvement in combined tremor (vs 22% in sham group)
- Sustained improvement out to 1 year.

Unilateral pallidotomy (advanced PD with motor complications - 2021)

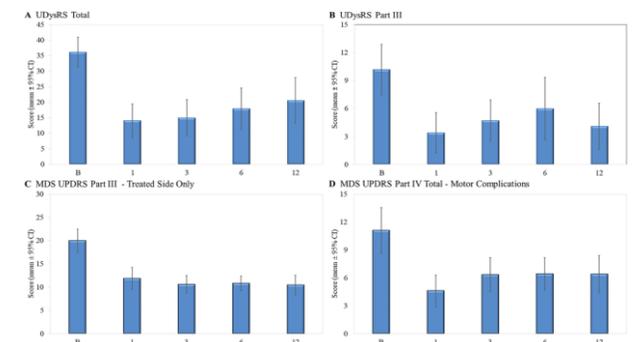
- 69% responders (threshold significant improvement in motor symptoms Effects sustained to 12 months)

New ** Staged (6 months) bilateral pallidothalamic tract (advanced PD with motor complications – 2025)

- Improvement in off-medication symptoms - 84% tremor reduction, 70% improvement rigidity, and 73% for bradykinesia,
- 100% suppression of on-medication dyskinesias
- 55% reduction in mean levodopa dose
- Sustained at 12 months



Bond A,E et al. JAMA Neurol. 74 (12) (2017) 1412–1418



Miller et al. J Neurosurg. 2023;134(4):1083-90

* Krishna V, et al. N Engl J Med 2023;388:683-693



Symptomatic therapies:

- ND0612 (FDA) – subcutaneous levodopa infusion
- Tavapadon (FDA)- first selective D1/D5 receptor partial agonist. Once daily oral monotherapy or adjunctive therapy.
- P2B001 (Phase III) – low dose extended release pramipexole (dopamine agonists) and rasagiline (MAO-B inhibitor)
- Solengepras (Phase III) - non-dopaminergic adjunctive therapy to improve OFF time

ON THE HORIZON FOR PARKINSON'S DISEASE TREATMENT



Disease modifying therapies

Alpha-synuclein and protein aggregation target therapies

- Prazinezumab - monoclonal antibody targeting alpha-synuclein
- Buntanetap - oral small molecule inhibiting neurotoxin protein formation

Targets of cellular stressors

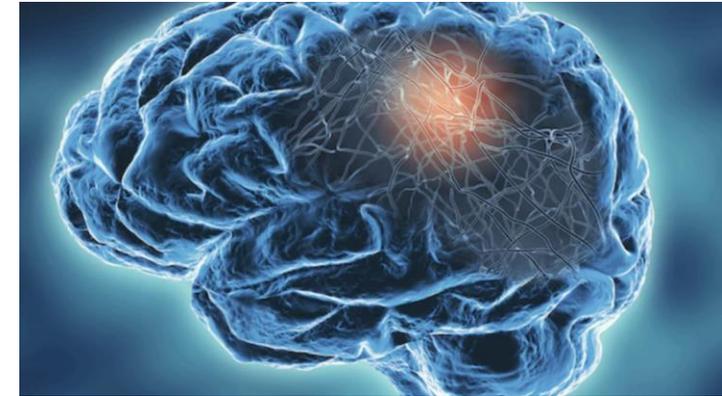
- GLP-1R agonists - lixisenatide
- Products for neuroinflammation, oxidative stress, and mitochondrial autophagy

Gene- based targeted therapies

- LRRK2 kinase inhibitors - to improve lysosomal dysfunction,
- Ambroxol and other therapies targeting GBA1 mutations to restore enzyme function

Cell and gene therapies

- Phase III trial bemdameprocel - dopaminergic neuron precursors are derived from pluripotent stem cells
- Phase II gene therapy AB-1005 – amplified gene for GDNF delivered by AAV vector
- NNI-362 - stimulates kinases to induce the creation of new neurons from neural progenitor cells in the brain



SUMMARY



- Parkinson's disease is a chronic neurodegenerative disease with progressive disability and morbidity from progressive motor and non-motor symptoms leading to reduced quality of life.
- PD is not considered a fatal condition but mortality is increased due to secondary complications and palliative care may help with advance care planning.
- Age of onset (young vs late) and genetics play a role in symptom presentation, progression in motor and non motor symptoms and response to medical and surgical therapies.
- Medical and surgical treatments for PD are tailored to the individual and research is developing more fine tuned treatments with exciting disease modifying therapies to slow progression in the works.

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