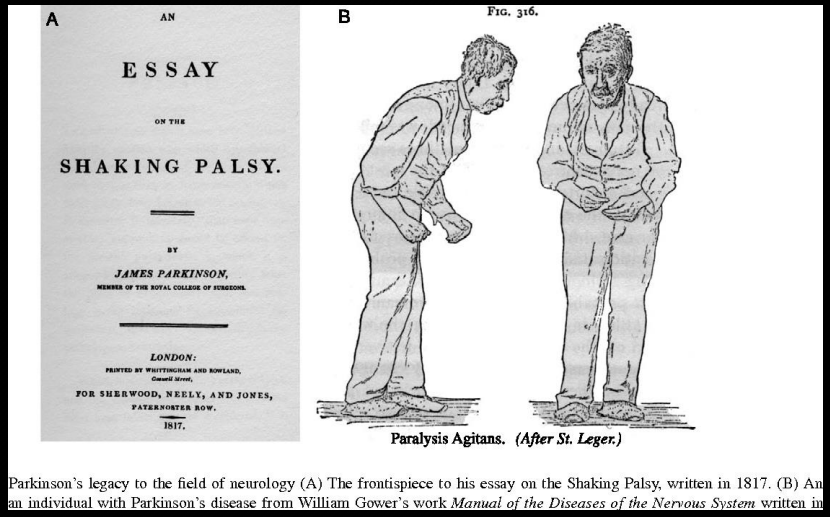
Parkinson's disease update

Jessica Hedeman DO

Trinity Health Mercy Neurosciences

PD History

- First described in 1817
- Based on 6 cases, 3 from a distance
- **James Parkinson**
- “involuntary tremulous motion, with lessened muscular power; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects uninjured”
- “kampavata” Indian medical system- Mucuna pruriens



Parkinson’s legacy to the field of neurology (A) The frontispiece to his essay on the Shaking Palsy, written in 1817. (B) An an individual with Parkinson’s disease from William Gower’s work *Manual of the Diseases of the Nervous System* written in

PD facts

Increasing prevalence worldwide

1-2 % of person's > 65

- 1,000,000 in US in 2020
- 10,000,000 worldwide

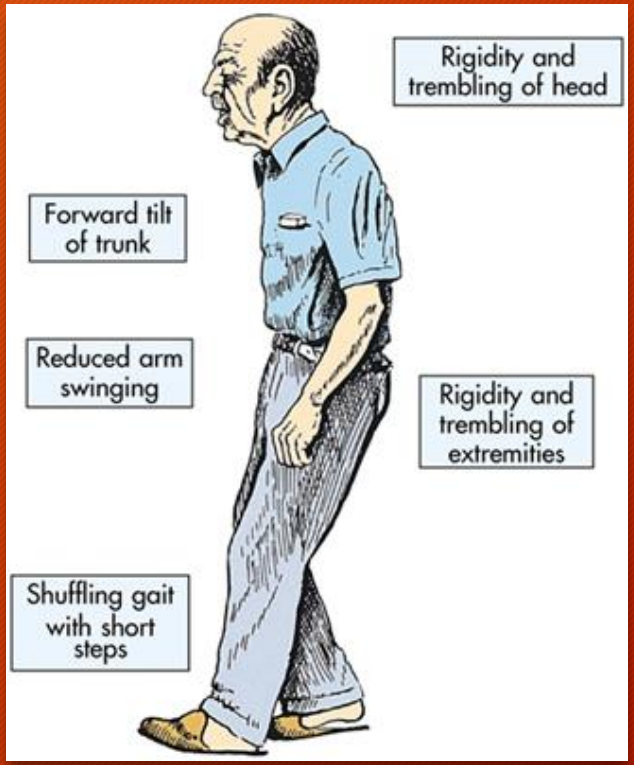
Relative mortality rate increase 2-5 times

Parkinson's prevalence increasing

- Aging
- Awareness
- Decline smoking rates?
- Environmental exposures (Industrialization)
- Refined diagnostic criteria

What is Parkinson's Disease?

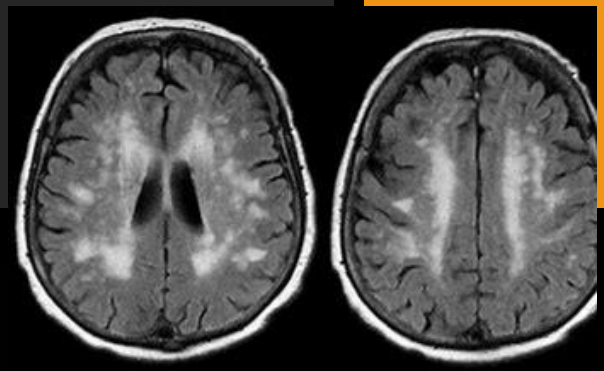
- PD is a progressive neurodegenerative movement disorder
  - **T**remor
  - **R**igidity
  - **A**kinesia or Bradykinesia (slowness of movement)
  - **P**ostural Instability



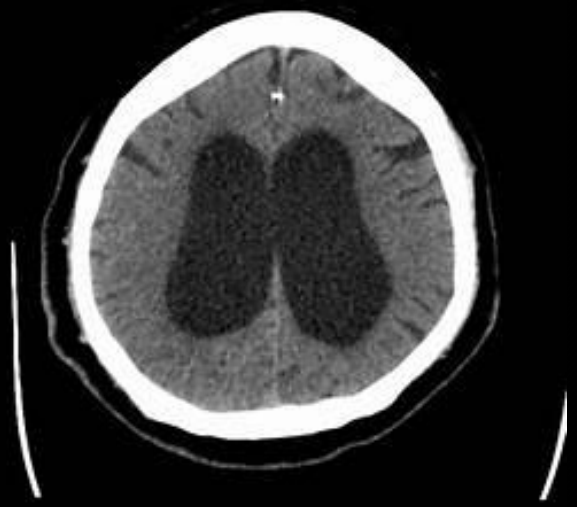
Early signs and symptoms

- Resting tremor
- Bradykinesia
- Rigidity
- Difficulty rising from a chair
- Difficulty turning in bed
- Hypophonic speech
- Sialorrhea
- Loss of sense of smell
- Micrographia
- Masked face
- Slowing of ADL's
- Stooped, shuffling gait
- Decreased arm swing
- Foot dystonia

Differential diagnosis of Primary PD

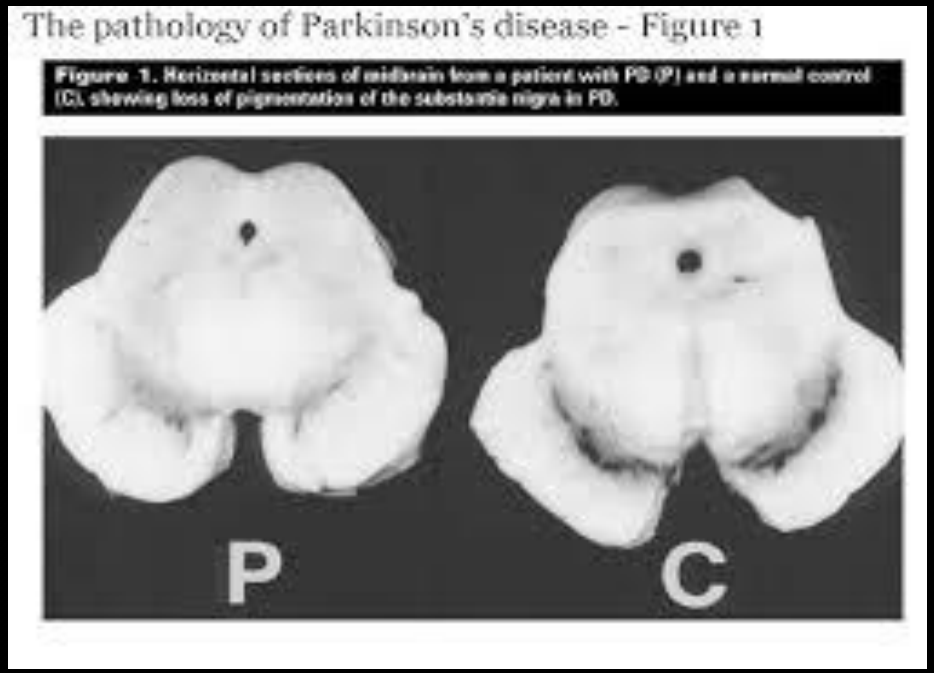


- Secondary Parkinsonism
  - **Drug induced (Reglan, anti-psychotics)**
  - **Vascular**
  - Hydrocephalus
  - Structural lesions
  - Toxin induced
  - Infectious
  - Neurodegenerative syndromes with parkinsonism
    - Multiple systems atrophy (MSA)
    - Progressive supranuclear palsy (PSP)
    - Cortico- basal degeneration (CBD)
    - Lewy body dementia (LBD)



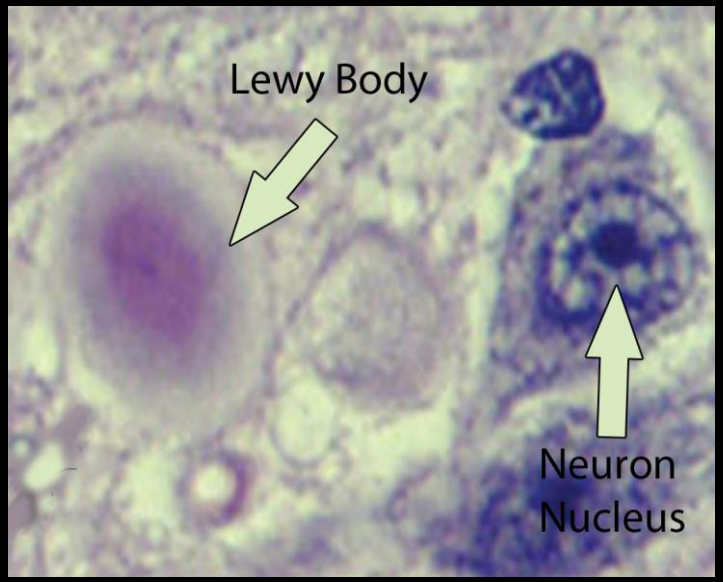
What is Parkinson's Disease?

- loss of dopaminergic neurons in the substantia nigra
- 60 % of the neurons in the SN have been lost
- Globus pallidus, tlalamic nuclei also affected
- Hippocampal atrophy on MRI



What is Parkinson's Disease?

- PD is characterized by the presence of **Lewy bodies** in the remaining dopamine producing neurons.
- Lewy Bodies are made of several proteins including **alpha synuclein and found**
  - **SN, locus ceruleus, the cerebral cortex, sympathetic ganglia, vagal nucleus, myenertic plexus of the intestines, and cardiac sympathetic plexus,**



Risk factors for PD

- Aging
- Male gender
- FH PD
- Farming
- Pesticides
- Herbicides
- Industrial agents (solvents)
- Metals
- Dietary lipid and milk intake
- High caloric intake
- Encephalitis
- Chronic inflammation
- Head trauma

High Parkinson's areas

Global increase 156 % since 2019

Largest increasing percentages were in Qatar, United Arab Emirates ,and East Asia (China) (800 % increase)

What about genes?

- 1st gene associated with PD was discovered in 1997
- Genetic
  - 2-3 % of all cases of Parkinson's (90-95 % considered sporadic)
    - Alpha-synuclein(SNCA)
    - Parkin
    - PTEN-induced kinase 1 (PINK 1)- AR
    - Leucine-rich repeat kinase 2 (LRRK2)
    - Glucocerebrosidase (GBA)

Global Parkinson's Genetics Program GP2

- Dozens of high risk PD genes but very rare incidence overall
- Global Parkinson's Genetics Program
  - Analyze genetic samples from a diverse group of more than 150,000
  - Discovery of GBA1 gene variant-novel genetic risk factor-published in Lancet Neurology August 2023

Genetics overall

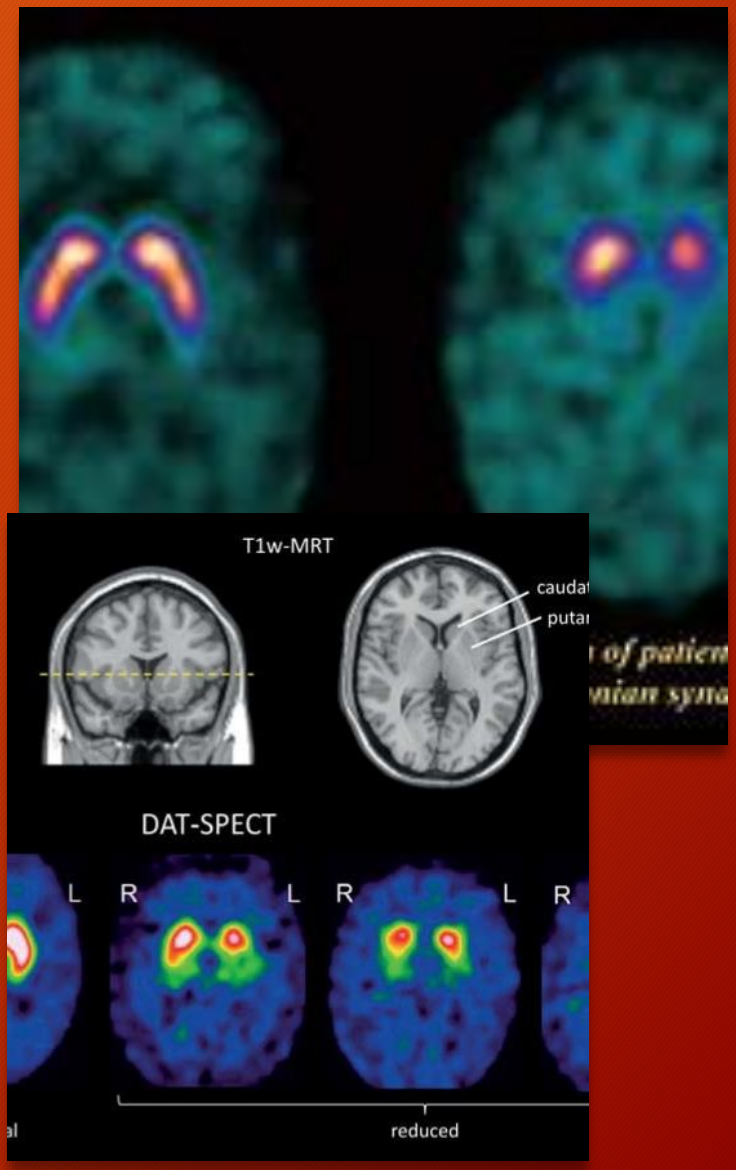
- Any person with PD, about **25 % can be attributed to genes**
- Accumulation of **many low risk variants** is the most likely explanation for most PD
- More than 200 genes that are potential drivers for the development of PD.

Protective factors

- Smoking
- Caffeine
- Exercise
- Ibuprofen
- Mediterranean diet

Pitfalls in diagnosis

- Diagnosis is clinical
- No laboratory or imaging confirmation
- loss of nigrostriatial dopamine transporters (DaT).
- Low sensitivity in detecting early PD



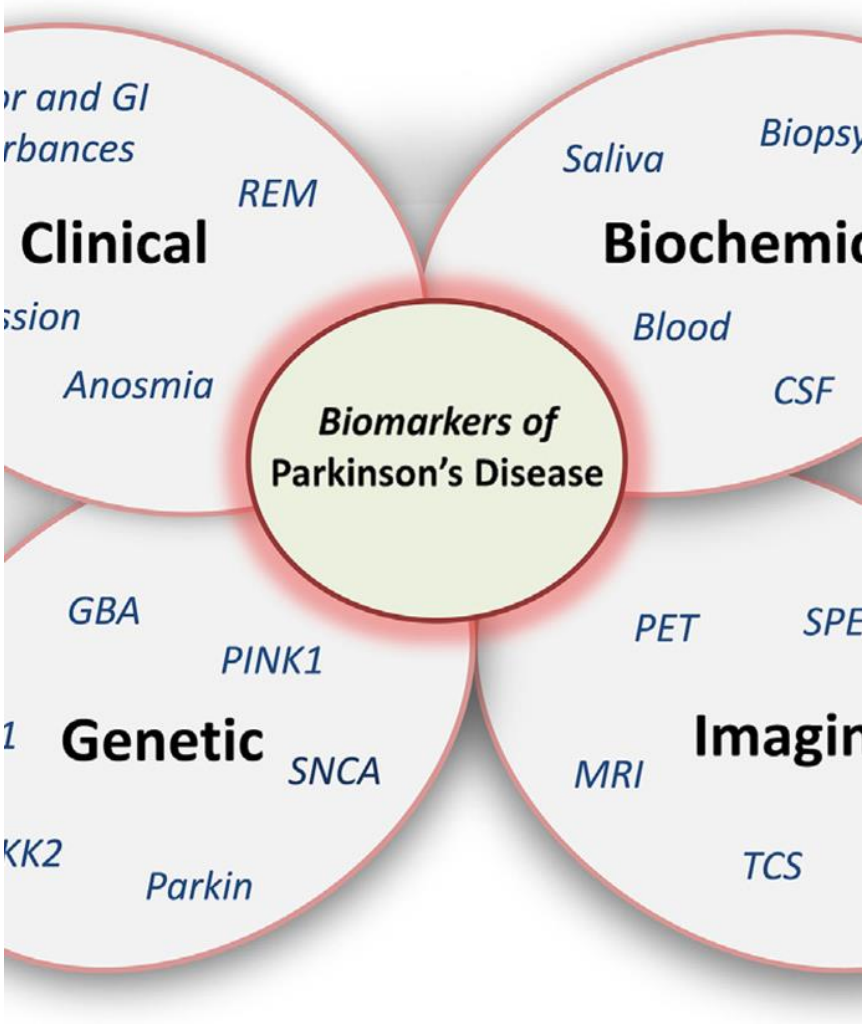
The woman who can smell Parkinson's disease

Biomarker

- Identify patients at risk for PD
- Motor deficits when neurodegeneration is advanced:
  - 50-60 % dopamine neurons lost
- Limits the effectiveness of potential neuroprotective therapies
- Identify alpha-synuclein in peripheral tissues
- Neuropathological changes the peripheral tissues
  - skin
  - olfactory bulb
  - GI tract

2 Emerging biomarkers

- Skin Biopsy
- RT QuIC



Journal of Clinical Neurology
thejcn.com

Alpha-Synuclein in Skin Nerve Fibers as a Biomarker for Alpha-Synucleinopathies

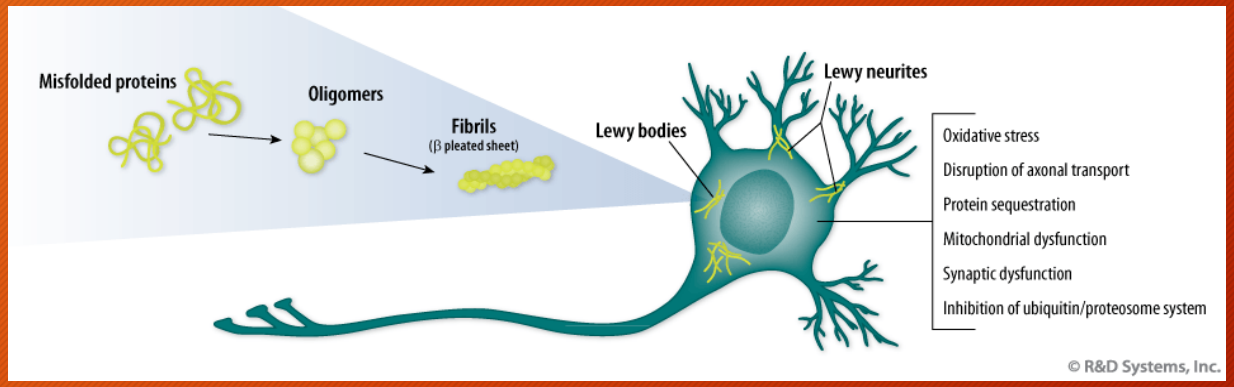
-**High specificity** and **good sensitivity** for detection of synucleinopathies

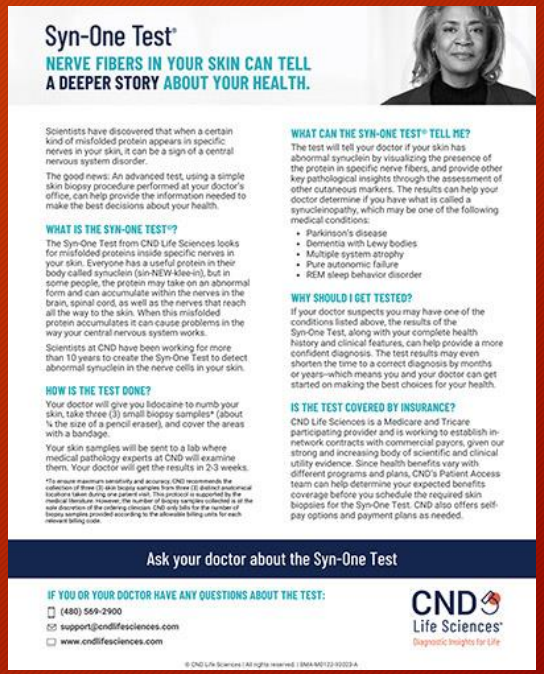
- **alpha- synuclein deposition in skin nerves in 75 %** of patients with idiopathic REM-sleep behavior disorder

J Clin Neurol. 2019 Apr; 15(2): 135–142.
Published online 2019 Jan
28. doi: 10.3988/jcn.2019.15.2.135
PMCID: PMC444158
PMID: 30938p06
Alpha-Synuclein in Skin Nerve Fibers as a Biomarker for Alpha-Synucleinopathies
Jee Young Kim, [a] Ben MW Illigens,[b] Michael P. McCormick,[b] Ningshan Wang,[b] and Christopher H. Gibbons[b]

Syn-One skin biopsy test

-Detects alpha synuclein in cutaneous nerves
-95-99% accurate detecting synucleinopathies



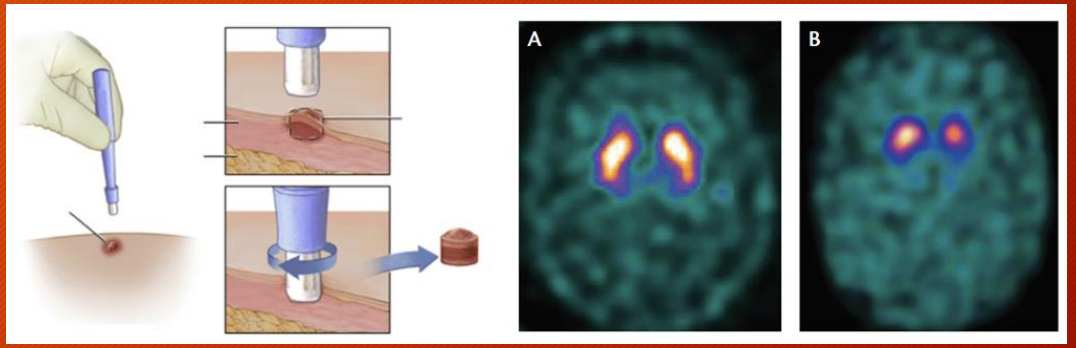


STUDY EXAMINES DIAGNOSTIC UTILITY OF SYN-ONE TEST® VS DATSCAN

- **Syn-One Test** versus **DaTscan** for diagnosing synucleinopathies.

- Syn-One Test may have higher diagnostic accuracy than DaTscan
  results matched suspected diagnosis in 65 % of cases
  versus 83 % for skin biopsy

- Less invasive and less costly



Reference: Urval N, Bortan E, Dagostine M, et al. Clinical utility of skin biopsy compared to DaTscan in diagnosing synucleinopathies. Poster presented at: American Academy of Neurology Annual Meeting; April 22-27, 2023; Boston, MA.

Seed amplification assay (clusters alpha synuclein)

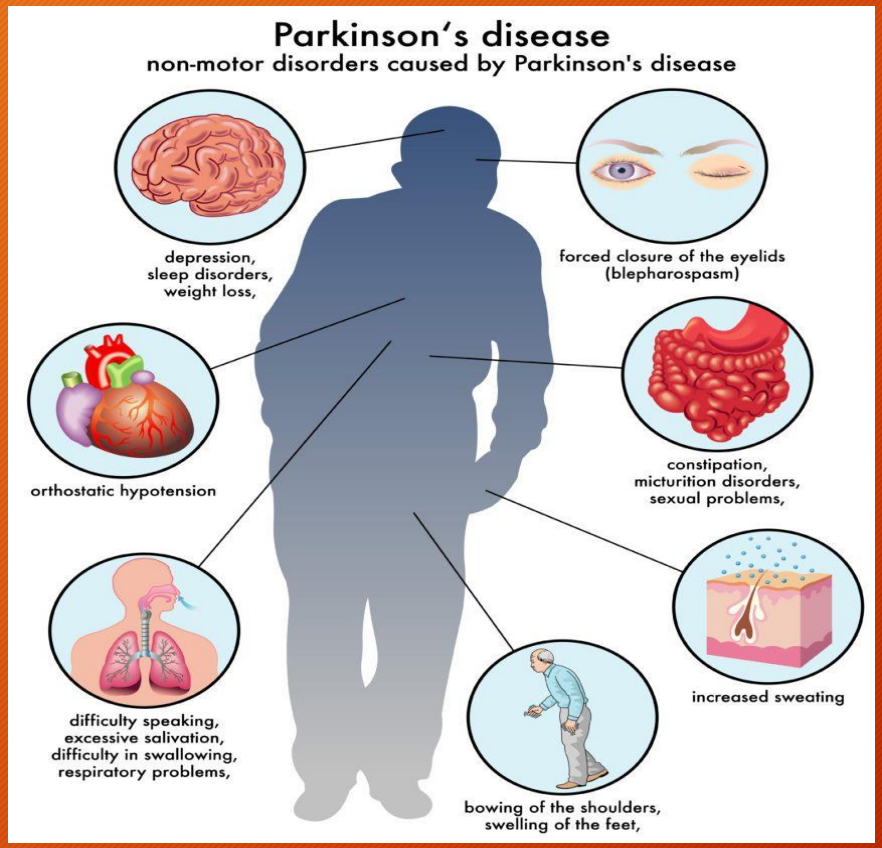
Seed amplification assay (RT- QuIC) – small amounts of aggregates , so called **seeds** (aggregation of alpha- synuclein)

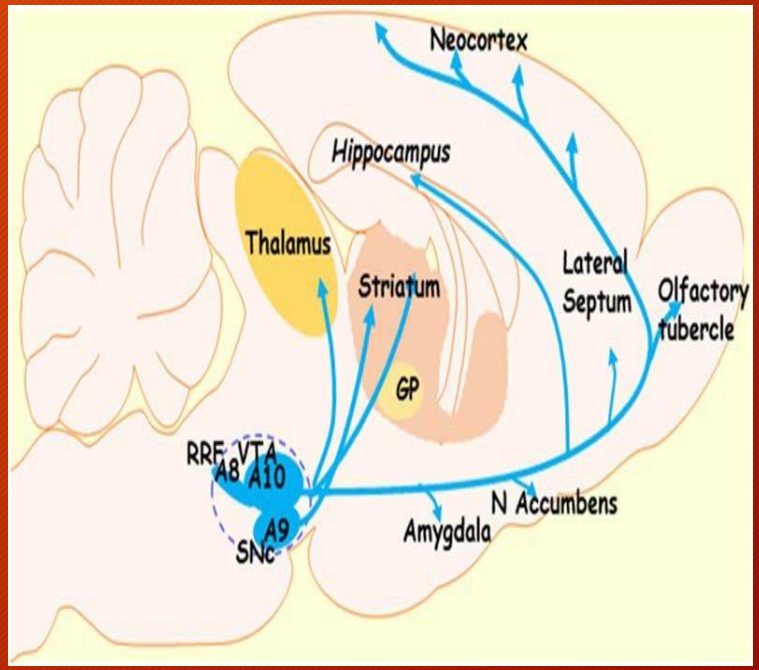
ultrasensitive detection of alpha-synuclein seeds in biosamples (CSF, serum, skin, tissues)

Promising- **high sensitivity/high specificity- in sporadic PD was 98.6 %**

can detect aggregates in prodromal states such as REM Sleep Behavior, hyposmia

More than just a motor disorder

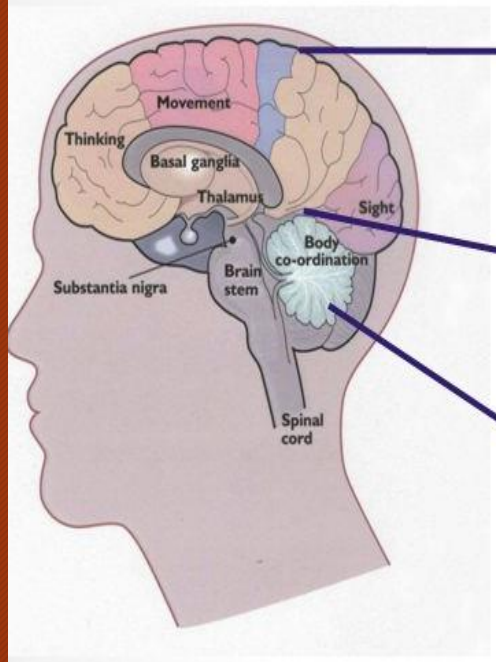




Pre-motor symptoms

- **Hyposmia**- occurs in up to 90% of PD patients and may predate diagnosis of PD by at least 4 years
- **Constipation**- occurs in up to 60-80% of PD patients and may predate PD by 10 years
- **RBD**- may predate motor symptoms by years, 80 % eventually develop PD or DLB
- **Depression**- may occur in 28% of patients with early stage PD

The 'Braak hypothesis'



Stage 5 and 6:
Changes spread to the cortex

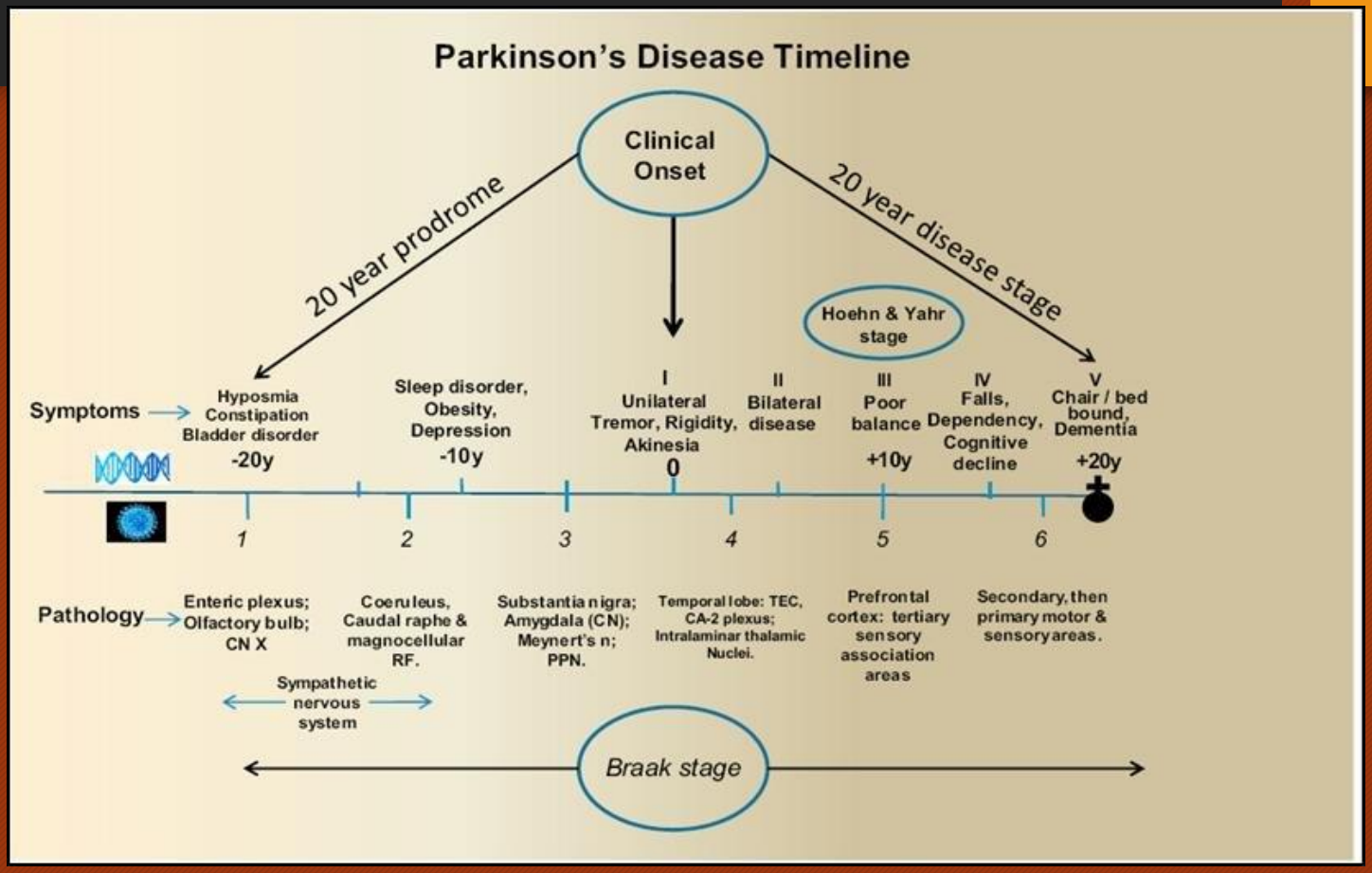
Stage 3 and 4:
Pathology spreads to the midbrain and basal ganglia

Stage 1 and 2:
Pathology confined to certain structures in the brain stem, not yet the substantia nigra

Where does Parkinson's disease begin?

Incidence of non-motor symptoms

- Olfactory dysfunction- 90%
- Depression- 40-50%
- Orthostatic hypotension- 50%
- Gastrointestinal symptoms- 50-95%
- Urogenital dysfunction- 57-83%
- Sleep disorders- 66 %
- Fatigue- 50 %
- Cognitive changes- 78 %

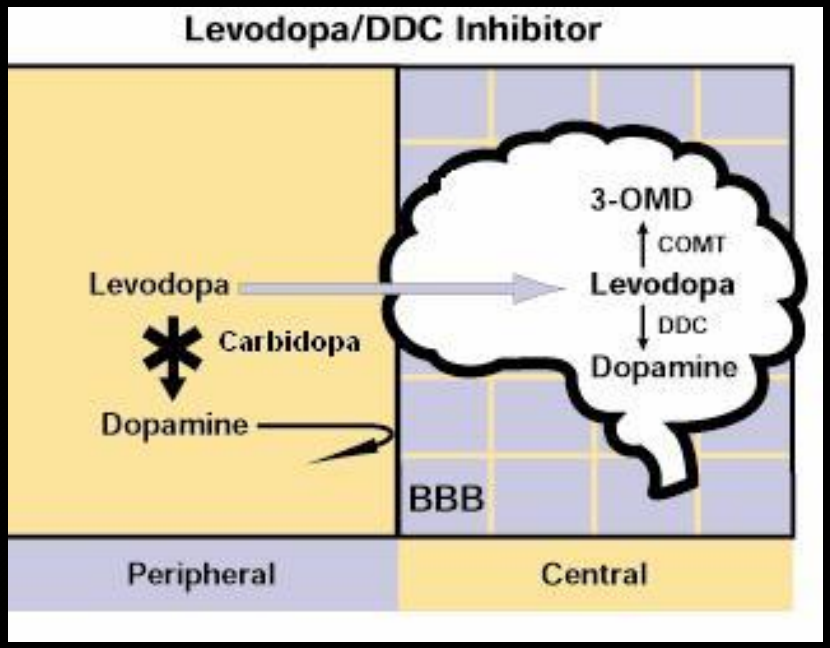

Parkinson's Disease Timeline
Clinical Onset
20 year prodrome
20 year disease stage
Hoehn & Yahr stage
Symptoms
Hyposmia
Constipation
Bladder disorder
-20y
Sleep disorder,
Obesity,
Depression
-10y
I
Unilateral
Tremor, Rigidity,
Akinesia
0
II
Bilateral
disease
III
Poor
balance
+10y
IV
Falls,
Dependency,
Cognitive
decline
V
Chair / bed
bound,
Dementia
+20y
1
2
3
4
5
6
Pathology
Enteric plexus;
Olfactory bulb;
CN X
Coeruleus,
Caudal raphe &
magnocellular
RF.
Substantia nigra;
Amygdala (CN);
Meynert's n;
PPN.
Temporal lobe: TEC,
CA-2 plexus;
Intralaminar thalamic
Nuclei.
Prefrontal
cortex: tertiary
sensory
association
areas
Secondary, then
primary motor &
sensory areas.
Sympathetic
nervous
system
Braak stage

Pharmacologic	Non-pharmacologic	Surgical
Levodopa	Education	Deep Brain Stimulation
Dopamine agonists	Exercise	Carbidopa/Levodopa Enteral Suspension
MAO-Inhibitors	Nutrition	High intensity focused ultrasound
COMT Inhibitors	OT/PT/Speech	
Anticholingergics	Psychologic	
Amantadine		

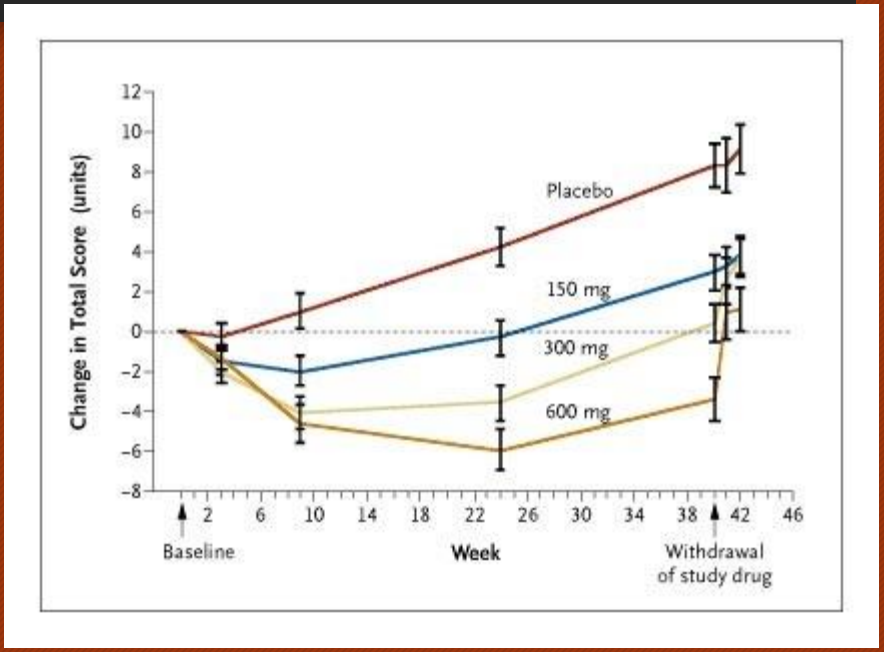
Treatment options in PD

Levodopa

- **Most effective agent for the treatment of PD**
- Virtually all patients with PD have significant benefit
- Almost all patients with PD require Levodopa at some point
- Levodopa remains effective, even in late stages of disease
- Half life of levodopa with carbidopa is 90 minutes
- Long term use contributes to dyskinesia
- Not all symptoms are responsive to levodopa such as falls, freezing of gait, dementia, speech, and swallowing



ELLDOPA (Earlier versus Later Levodopa *Therapy in Parkinson's disease)*



Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, Tanner C, Marek K; Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004 Dec 9;351(24):2498-508. doi: 10.1056/NEJMoa033447. PMID: 15590952.

Should I wait to start Levodopa?

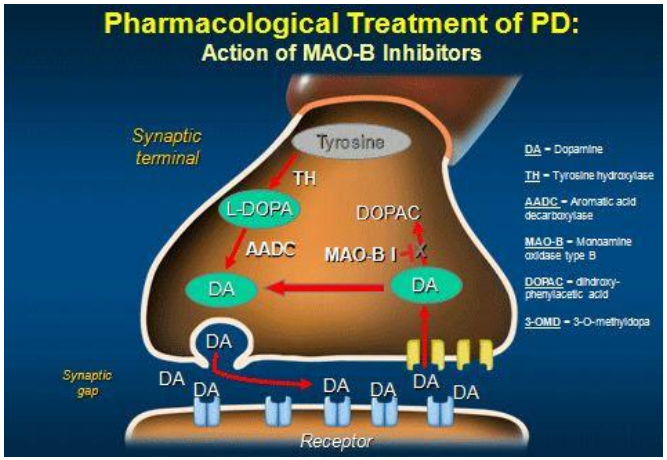
- No evidence to suggest waiting
- Rate of clinical progression to disability or death is reduced
- Life expectancy is substantially increased
- No worsening of progression with early use

Levodopa formulations

- Immediate release carbidopa/levodopa (Sinemet)
- Controlled release carbidopa/levodopa (Sinemet CR)
- Orally disintegrating (Parcopa)
- Extended release carbidopa/Levodopa (**Rytary)-2015**
- Scored tablet **(Dhivy) -2022**

Other medication

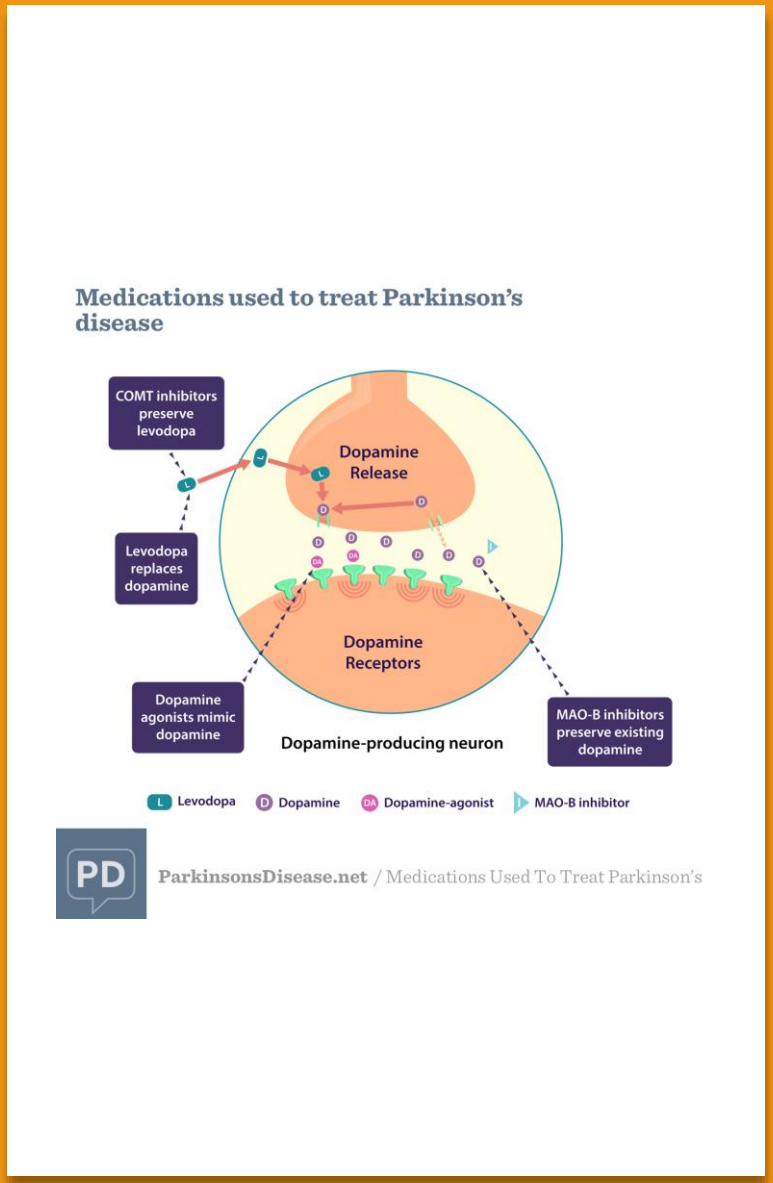
- **MAO- B Inhibitors**
  - Rasagiline
  - Selegiline
  - Safinamide
- Block enzyme that breaks down dopamine in the brain
- Mild symptomatic benefit
- Contraindications: Meperidine, tramadol, Dextromethorphan (DM), St. John's wort, cyclobenzaprine



Dopamine agonists

- Pramipexole
- Ropinirole
- Rotigotine (transdermal)

- Compared to Levodopa
  - Longer half life
  - Reduced risk of dyskinesia
  - Lower maximum effectiveness
  - Higher risk of other side effects



Others

- COMT Inhibitors (Entacapone)
  - Used with each dose of levodopa
  - Block peripheral breakdown of levodopa
- Amantadine
  - Low efficacy, several mechanisms of action
  - Useful in treating dyskinesias
- Anticholinergics
  - Used mainly in younger patients
  - Most effective for tremor
  - High risk of side effects

Inhaled Levodopa

- FDA Approved in December 2018
- Pulmonary administration of Levodopa
- Onset of action much faster
- Bypasses slowed gastric emptying
- No food interaction

Istradefylline (Nourianz)

- Once daily pill
- Novel mechanism of action
- **Blocking adenosine receptors in the brain**
- Significant for improving good ON time – adjunctive medication for patients taking Levodopa

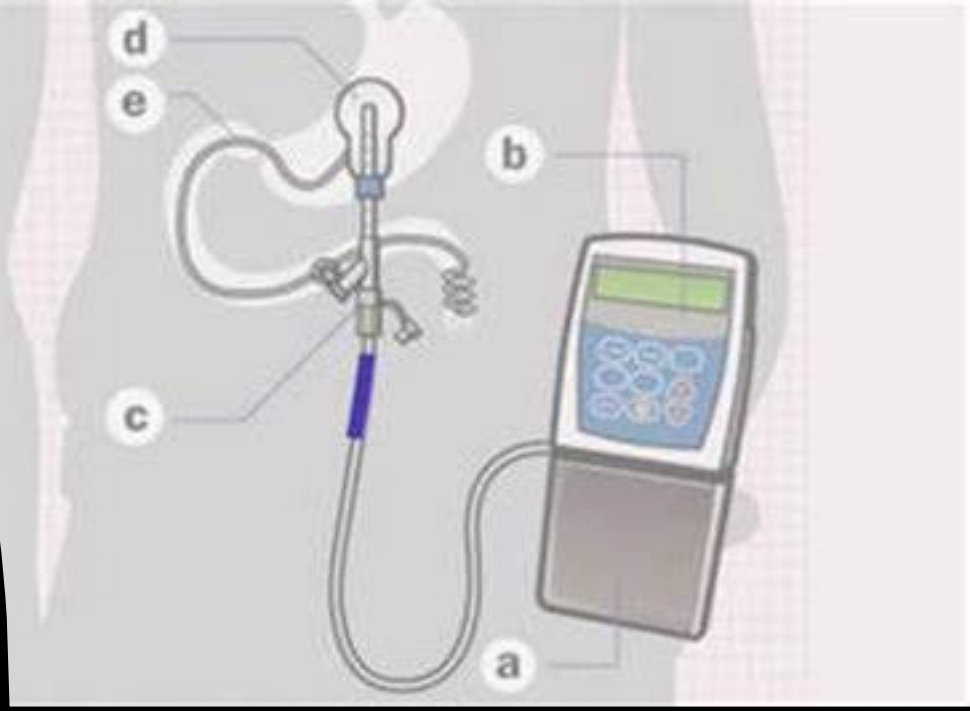
Drug class	Dopaminergic activity	A_{2A} receptor activity
A_{2A} receptor antagonist		✓
Levodopa/carbidopa	✓	
COMT inhibitor	✓	
Dopamine agonist	✓	
MAO-B inhibitor	✓	
Other	✓[a]	

Motor complications with PD progression

- Infusion therapies
- DBS

Duopa

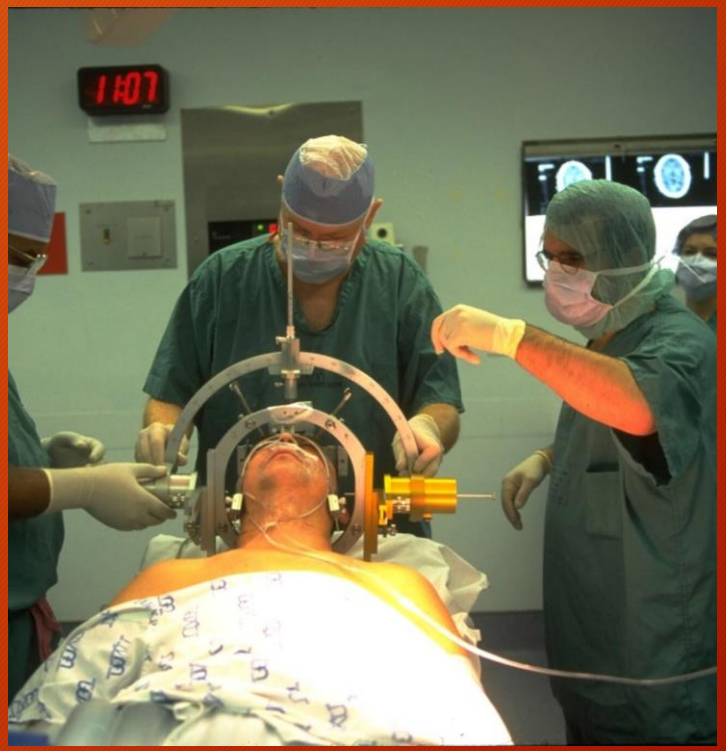
- Carbidopa-Levodopa intestinal gel
- Infused via an intra-jejunal tube in the abdomen with external pump
- Very good for patients with a lot of fluctuations in their symptoms and dyskinesia
- Offers more consistent symptom benefit

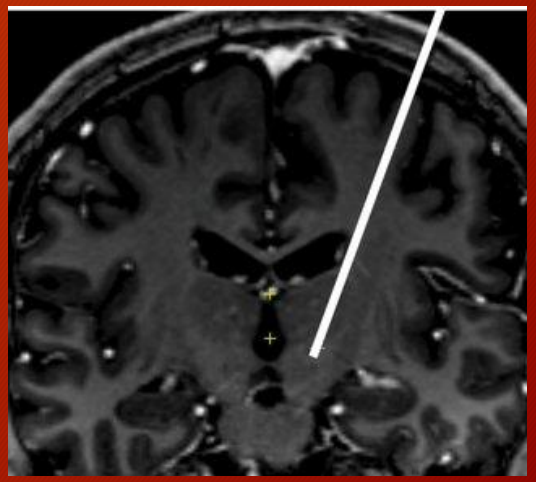


Deep Brain stimulation

- High frequency electrical stimulation of target structures through implanted electrodes
- Electrodes connect to Implantable pulse generator (IPG) by a wire
- IPG can be programmed

- FDA approved for tremor in PD in 1996
- Approved for other Parkinson's symptoms in 2002
  - Improves cardinal symptoms of PD (rigidity, bradykinesia)
  - Treats medication resistant tremor
  - Improves fluctuations and dyskinesias





Who's a candidate for DBS?

- Onset of motor fluctuations
- Medication resistant tremor
- Short period of "ON" time between doses
- Requiring doses frequently
- Side effects from medications

Who's not a candidate?

- Poor responders to Levodopa
- Frequent falls/severe balance problem
- Dementia
- Poor surgical candidates

High intensity focused Ultrasound (HIFU)- Approval in 2018

- “Incisionless” brain surgery (Exablate)
- **Unilateral only**
- “Minimally invasive”
  - high energy ultrasound beams to generate brain lesions
- Should be considered invasive procedure since brain tissue is destroyed
- Vast majority have sustanined benefit at 3 year follow up

Slow down progression?

- Neuroprotection
- Medication
- Diet
- Exercise

Previous/ongoing clinical trials for neuroprotection in PD

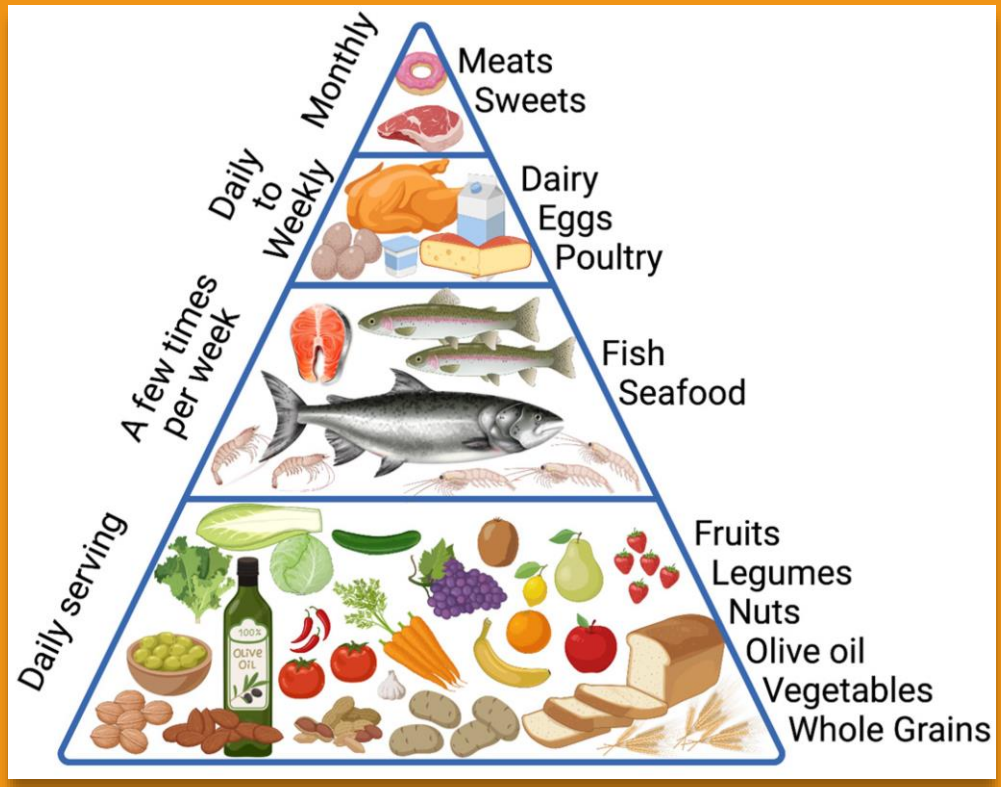
- Selegiline
- Rasagiline
- Tocopherol (Vitamin E)
- Inosine (anti-oxidant)
- Zonisamide
- Glutathione
- N-acetylcysteine (anti-oxidant)
- Green tea
- Co-Q10
- Mitoquinone
- Creatine
- GDNF
- Minocycline
- Pioglitazone
- Exenatide
- Nicotine patch
- Erythropoietin

Alpha- synuclein as therapeutic target?

- Alpha synuclein is intimately associated with Parkinson's disease and Lewy Body dementia
- Missense mutations in the alpha- synuclein gene (SNCA) and gene multiplications cause AD disease
- Genome wide associated studies (GWAS) identify the SNCA locus as one of the stronger genetic risk factors for sporadic PD

Mediterranean Diet and Parkinsons

- Cardiovascular benefits
- Neuroinflammation and oxidative stress are recognized as factors in PD
- Reduces the incidence of inflammatory states (anti-oxidant and anti-inflammatory states



Typology of the Study	Country	Period of Follow Up	Individuals Involved	Dietary Pattern	Results	Ref
Longitudinal	USA	16 years	49,692 + 81,676 (2 cohorts)	MeDiet-related	**MeDiet-related diet protects against PD onset**	[34]
Longitudinal	Sweden	20 years	47,128	MeDiet	**MeDiet reduces PD risk**	[35]
Longitudinal	USA	4.6 years	706	MIND; DASH; MeDiet	MIND **reduces PD risk** MIND and MeDiet slow PD progression	[37]
Case-control	USA		257 PD + 198 controls	MeDiet	MeDiet reduces PD risk	[38]
Cross-sectional	Canada		167 PD + 119 controls	MIND MeDiet	MIND and MeDiet protect against PD onset	[27]
Cross-sectional	USA		1053 PD	MeDiet-related	MeDiet-related foods slow PD progression	[39]
Randomized clinical trial	Iran	10 weeks	80 PD	MeDiet	MeDiet improves both cognitive functions and locomotor performance in PD patients	[40]
Cross-sectional	Greece		1731	MeDiet	MeDiet protects against prodromal PD symptoms	[42]
Longitudinal	USA	16 years	47,679	MeDiet-related	MeDiet-related protects against prodromal PD symptoms	[43]
Randomized clinical trial	USA	8 weeks	52 PD	MeDiet	MeDiet improves constipation symptoms in PD patients	[22]
Single-arm clinical trial	USA	5 weeks	8 PD + 8 controls	MeDiet	MeDiet improves constipation symptoms in PD patients	[44]

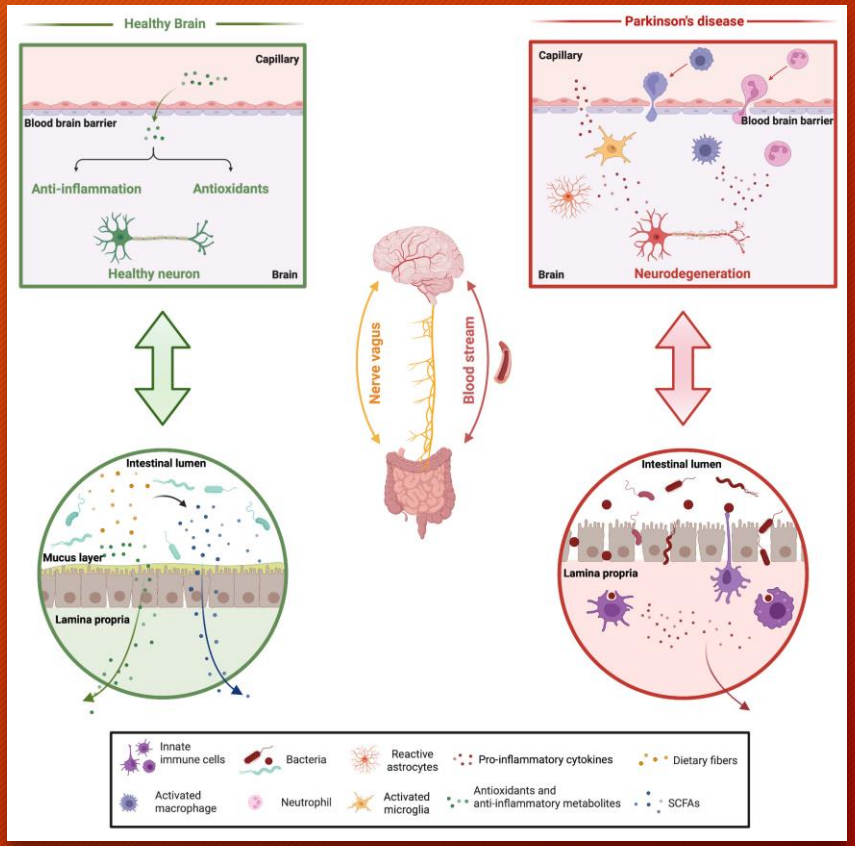
Mediterranean diet

- Overall emerging trend- diet somehow protective against PD onset and progression
  - Anti-oxidant and anti-inflammatory properties
    - Vitamins
    - Omega 3 polyunsaturated fatty acids
    - Polyphenols ie) resveratrol and olive tree derivatives
  - Influences the gut microbiota composition

Bisaglia M. Mediterranean Diet and Parkinson's Disease. *International Journal of Molecular Sciences*. 2023; 24(1):42. https://doi.org/10.3390/ijms24010042

Mediterranean diet

- **Western diet (high in animal protein)**
  - promotes growth of **bacteria** that likely leads to **systemic inflammation** and damage to blood brain barrier
- **Med diet (high in fiber)**
  - promotes short chain fatty acids which exert a crucial function on maintaing integrity of intestinal barrier



Exercise

ROLE OF EXERCISE IN MODIFYING THE RISK FOR DEVELOPING PD

ROLE OF EXERCISE IN MODIFYING PARKINSON'S DISEASE PROGRESSION

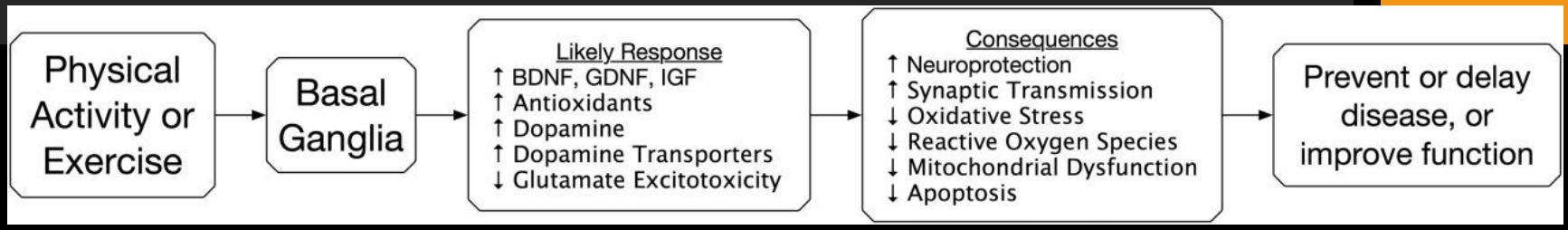
Activity in early adulthood associated with reduced risk of PD

The role of physical exercise in the occurrence of Parkinson's disease

A J Sasco [1], R S Paffenbarger Jr, I Gendre, A L Wing

Affiliations

Arch Neurol. 1992;49(4):360-365



- LaHue SC, Comella CL, Tanner CM. The best medicine? The influence of physical activity and inactivity on Parkinson's disease. Mov Disord. 2016 Oct;31(10):1444-1454. doi: 10.1002/mds.26728. PMID: 27477046.

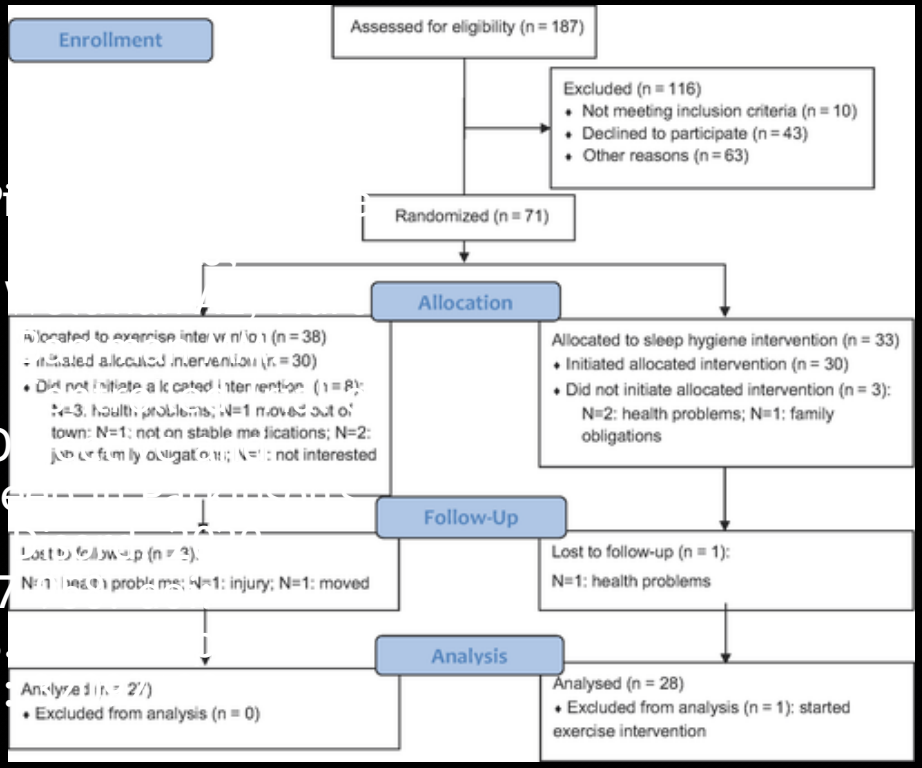
Type of exercise

Probably doesn't matter

Bottom line:

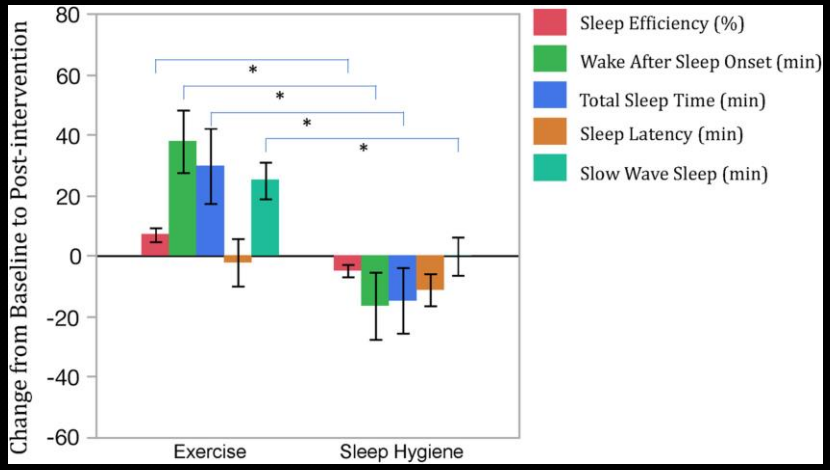
- Start early- aerobic (vigorous)- possible disease modifying effects
- 3X/week- 30-40 minutes 70-85 % HR max

Randomized, Controlled trial of Exercise on Objective and subjective sleep in Parkinson's disease



- Amara AW, Memon RA, P SC, Reams J, Edwards DA, CP, Cutter G, Randomized, Exercise on O Subjective Sl Disease. Mov Jun;35(6):947 10.1002/mds. Feb 24. PMID:

- High intensity exercise training improved:
  - Sleep efficiency
  - Total sleep time
  - Time in slow wave sleep
  - Wake after sleep onset



Exercise induced sleep changes

- Exercise improves mood
- Increase in BDNF (brain derived neurotrophic factor)
- Reduction in inflammation
- Increase in growth hormone
- Changes in autonomic function
- Neurotransmitter alterations

Cannabinoids in Parkinson's disease?

- Several cannabinoids based medicines are currently approved for other indications
- Endocannabinoid system is highly expressed in the basal ganglia
- Pre-clinical research suggests possible motor benefit

Study design	Number of patients	Cannabinoids	Results	Authors
Patient survey	84	Smoked cannabis	**Forty-six percent of patients described some benefit; 31% reported improvement of rest tremor, 45% of bradykinesia and 14% of LID**	Venderová et al.[88]
Patient survey	9	Cannabis	**Seven patients (78%) reported improvement of mood and sleep**, two patients reported improved motor symptoms, not specifically dyskinesias	Finseth et al.[89]
Case series	5	Smoked cannabis, 1 g cannabis (2-9% THC)	**No benefit for tremor** following single administration	Frankel et al.[90]
Open-label	22	Smoked cannabis, 0.5 g cannabis	Thirty minutes after smoking cannabis, **patients reported** improvement in tremor, rigidity, bradykinesia, pain, and sleep	Lotan et al.[91]
Four-week open-label	6	CBD up to 400 mg/day	Improvements on the Brief Psychiatric Rating Scale and Parkinson Psychosis Questionnaire	Zuardi et al.[92]
Case series	4	CBD 75 or 300 mg/day	Benefits for rapid eye movement sleep behavior disorder	Chagas et al.[93]
Randomized, double-blind, placebo-controlled crossover	5	Nabilone	Significant reduction of the Rush Dyskinesia Disability Scale and total LID time; two patients reported improvement in painful off-dystonia	Sieradzan et al.[94]
Four-week randomized, double-blind, placebo-controlled crossover	17	Cannador (1.25 mg CBD and 2.5 mg THC)	**No improvement of LIDs** on multiple outcomes.	Carroll et al.[95]
			No significant changes for motor symptoms (UPDRS-III), quality of life (PDQ-39) or sleep	
Randomized, double-blind, placebo-controlled	8	Rimonabant	No effect on motor symptoms or LID (UPDRS and standardized videotape)	Mesnage et al.[96]
Randomized, double-blind, placebo-controlled	21	CBD 75 or 300 mg/day	**No changes for total UPDRS** or any subscales.	Chagas et al.[97]
			Improvement for total PDQ-39 score and activities of daily living subscores for the CBD 300 mg/day group	

Summary

- Many genes- accumulation of many low risk variants combined with life style and environmental risk factors
- Exercise and diet are protective for delaying onset and slowing progression
- Treatment is symptomatic
- Many advancements in medication and surgical options for living well with PD

Parkinson's Association of West Michigan

MICHIGAN PARKINSON FOUNDATION™