Approach to Parkinson's Disease for the Family Physician

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At the end of this presentation, the viewer will be able to:

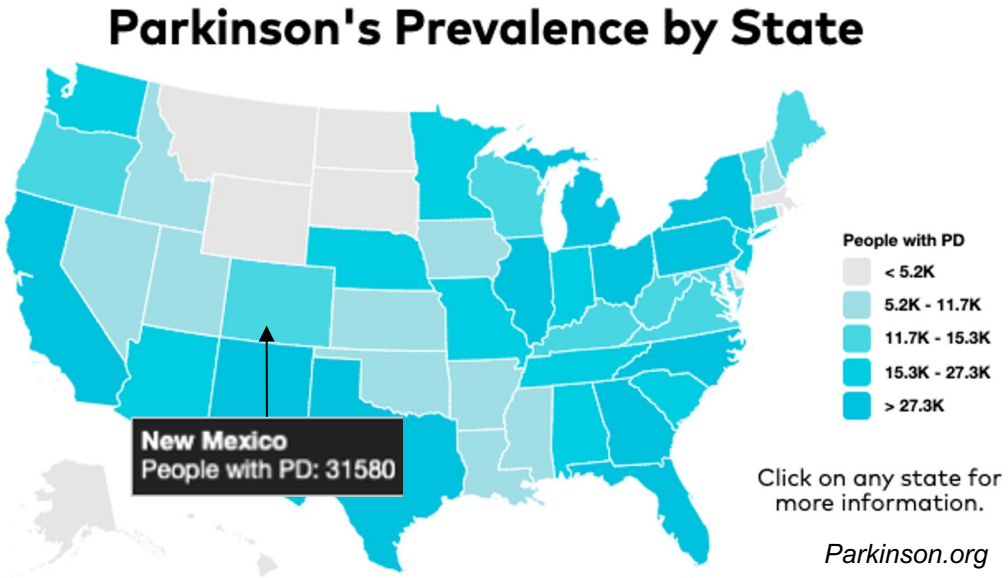
1. Recognize the typical symptoms and signs of Parkinson’s disease
2. Definitively diagnose Parkinson’s disease based on the physical exam
3. Understand the myths and methods of treatment across the course of disease

Disclosures

Abbvie Pharmaceuticals - advising; not relevant to this presentation

Prevalence is rising, we need your help!

- Incidence of Parkinson's Disease is 5 to 20 in 100,000 per year
- Prevalence is >10 million people worldwide
- Men: Women = 2:1
- Risk increases with age
- 90% have no FHx
- Incidence similar in monozygotic vs dizygotic twins (environment > genetic)

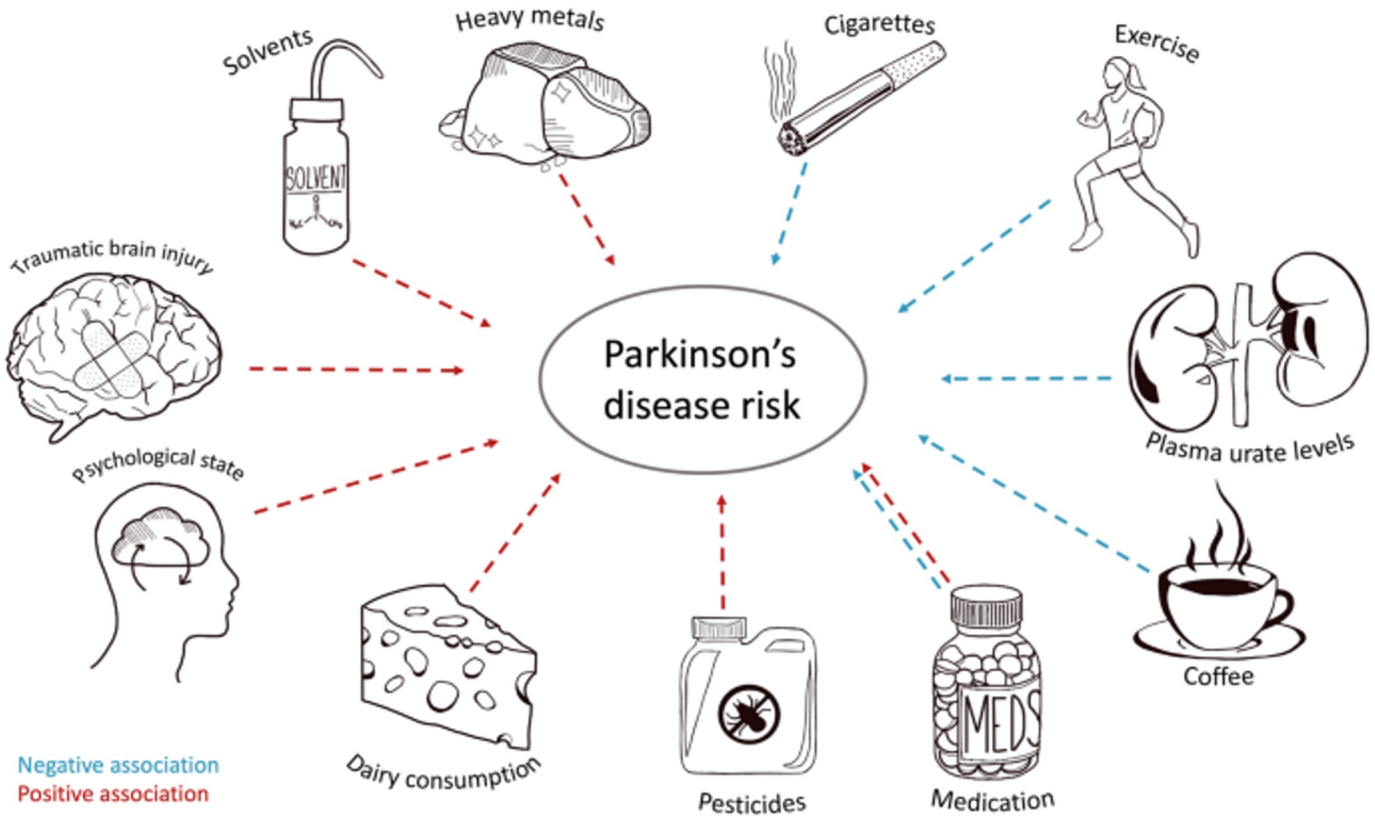


- Prevalence doubled from 1990 - 2015
- Estimated to double again by 2040
  - Longevity, decreased smoking, increased industrialization

Jankovic, Eur J Neurol 2003

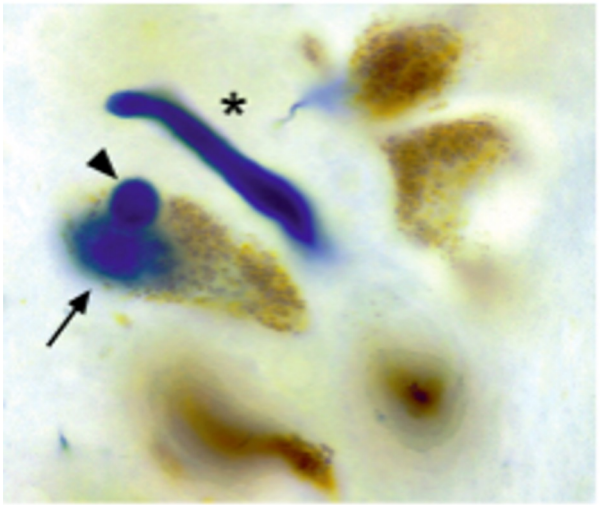
Dorsey, J Parkinsons Dis 2018

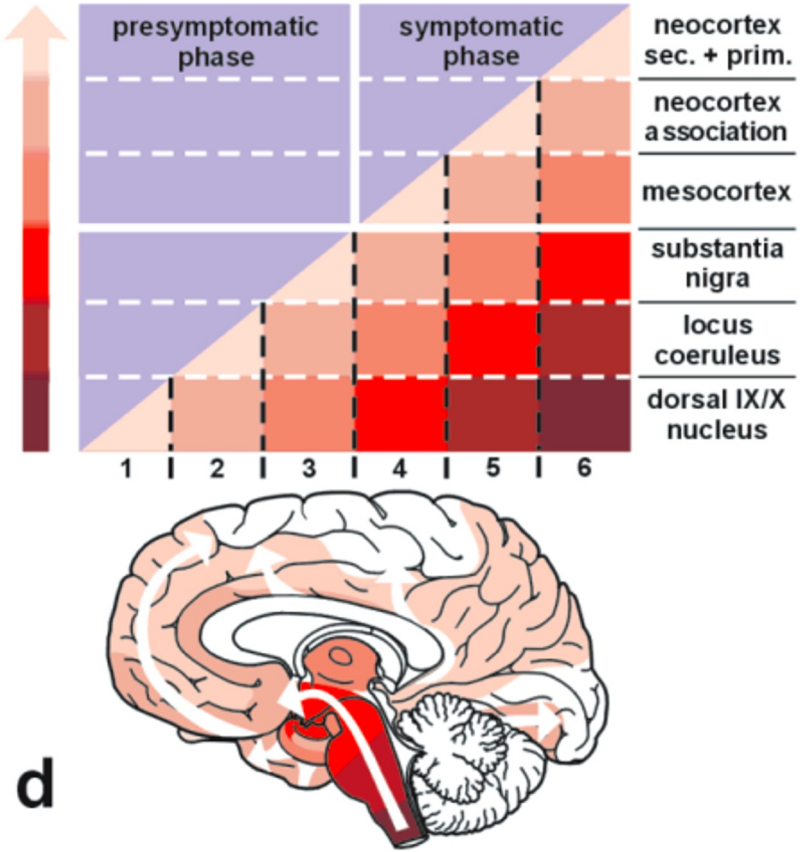
Parkinson’s disease is probably caused by the sum of multiple risk factors: environmental and genetic.



Tsalenchuk, Parkinsons Dis. 2023

The progression of Parkinson's disease symptoms corresponds to the spread of alpha synuclein pathology in the brain.





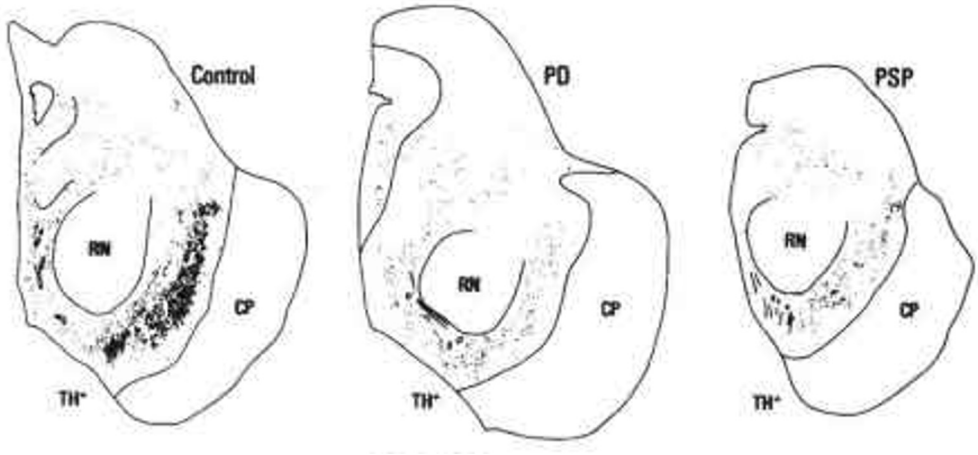
Braak, J Neurol 2002

Symptoms occur once 60-80% of nigral dopamine neurons have been lost.

Mean age of onset is 60s

Pathology in substantia nigra begins 4-7 years before patient presents to the clinic.

- Dopamine levels have decreased to at least 50% below normal when patients become symptomatic.
- Rate of change of the pathology declines exponentially over time.

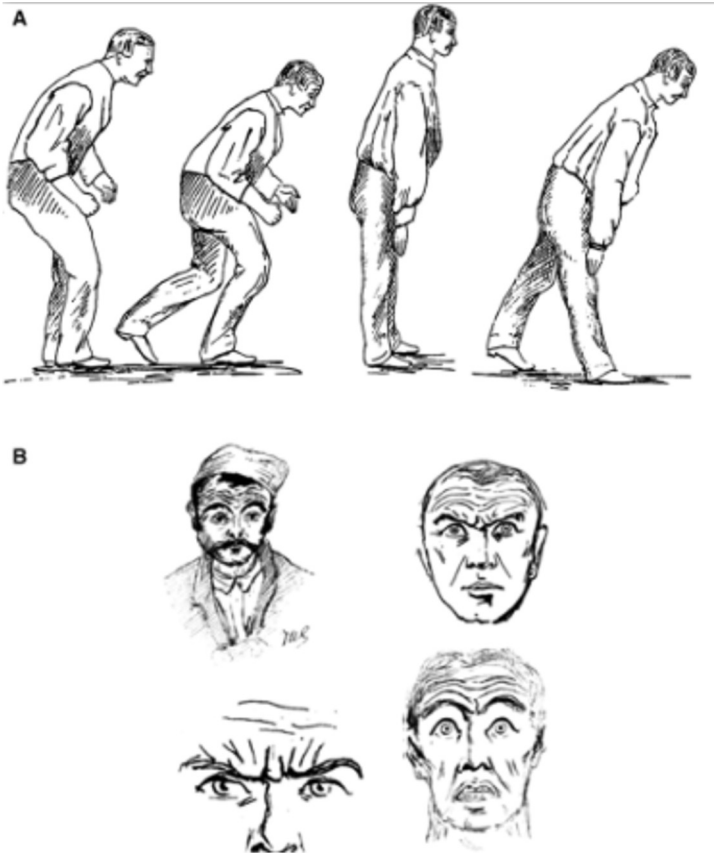


Aquino C, Mov Disord, 2015
Hirsch E, Nature 1988
Zesiewicz, Continuum, 2019

Prognosis

- Life expectancy, with improvement in access to care, is comparable to overall population
  - except in young-onset PD 14.6 (+/- 7.7 years)

- Shortened survival:
  - Males
  - Lack of tremor
  - Predominant postural instability, gait disorder
  - Symmetric motor signs, poor dopaminergic therapy response
  - Cognitive impairment, hallucinations



Zesiewicz, Continuum, 2019
Jankovic Eur J Neurol 2003

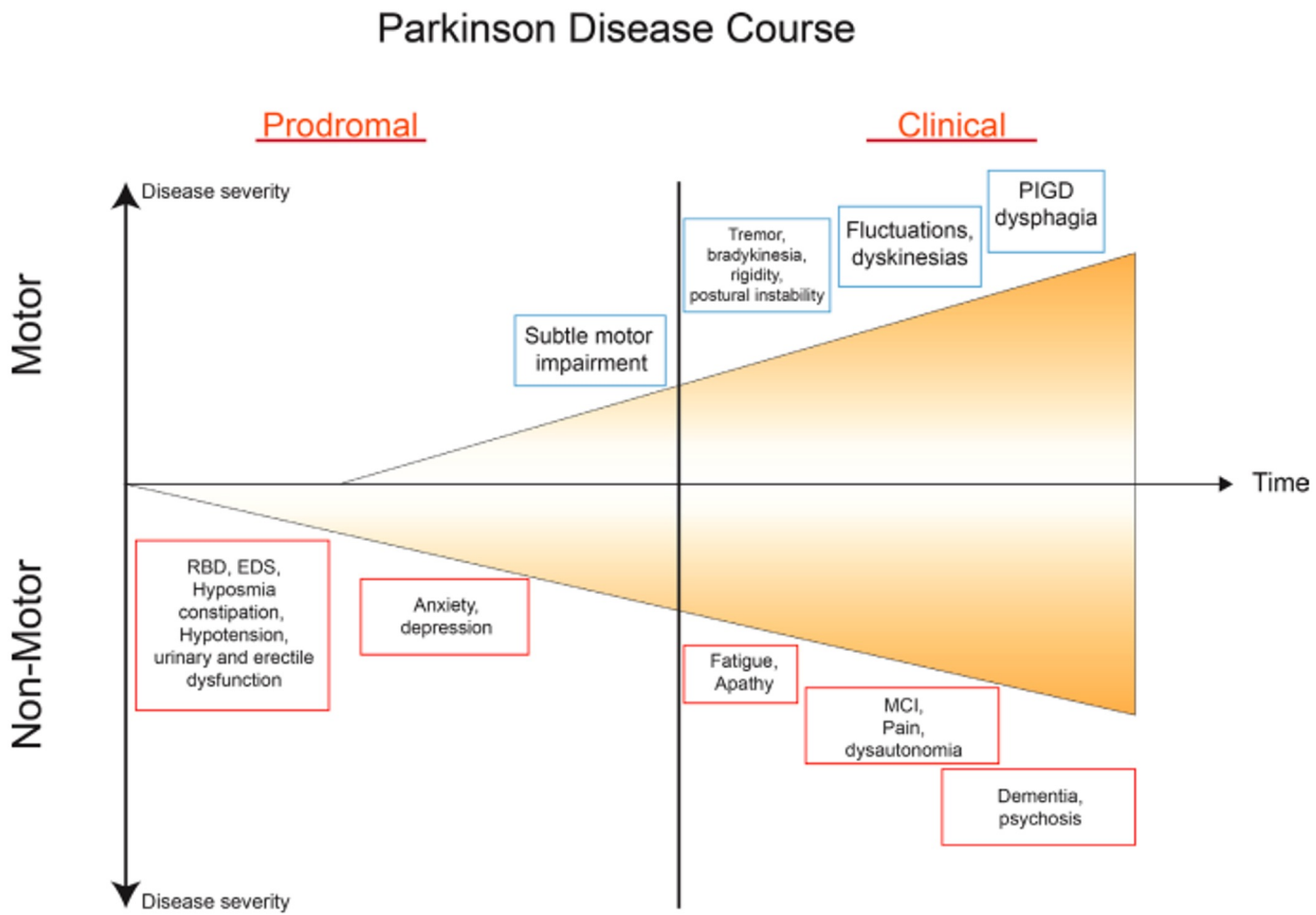


Figure 1 Course of PD from prodromal phase to clinical phase, including levodopa-related complications. PD, Parkinson's disease; PIGD, postural-instability-gait-disorder; RBD, rapid eye movement sleep behaviour disorder.

UK Brain Bank Clinical Diagnostic Criteria

1. **Bradykinesia**

   and at least one of the following:

1. Rigidity
2. Rest Tremor
3. Postural instability

Supporting features:

- Unilateral onset
- Levodopa Responsive

Clarke et al, NIHR Journals Library, 2016




Frucht 2020. Movement Disorders Phenomenology. Springer, Cham

Red flag symptoms indicate atypical parkinsonism

Progressive Supranuclear Palsy (PSP): Early falls, prominent bulbar symptoms, symmetric onset, rapid progression, prominent gait impairment with early freezing

Multiple System Atrophy (MSA): Severe and early urinary complaints, early orthostatic complaints, ataxia

Dementia with Lewy Bodies (DLB): Early cognitive impairment, delirium with mild insult

Corticobasal Syndrome (CBS): Severe asymmetry, cognitive impairment/dementia, cortical signs like apraxia

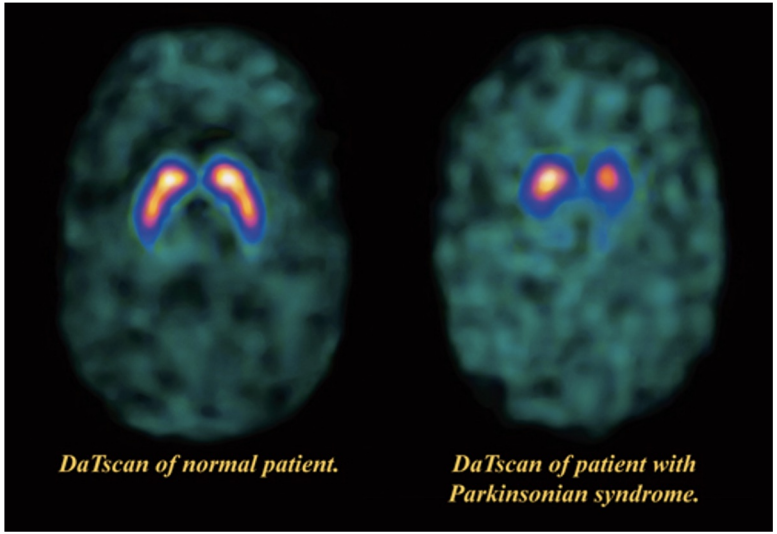
DaTscan: Dopamine transporter SPECT

Useful in differentiating PD from ET

NOT a perfect confirmatory test for PD

Does NOT differentiate PD from atypical parkinsonism

Radiation exposure



Treatment

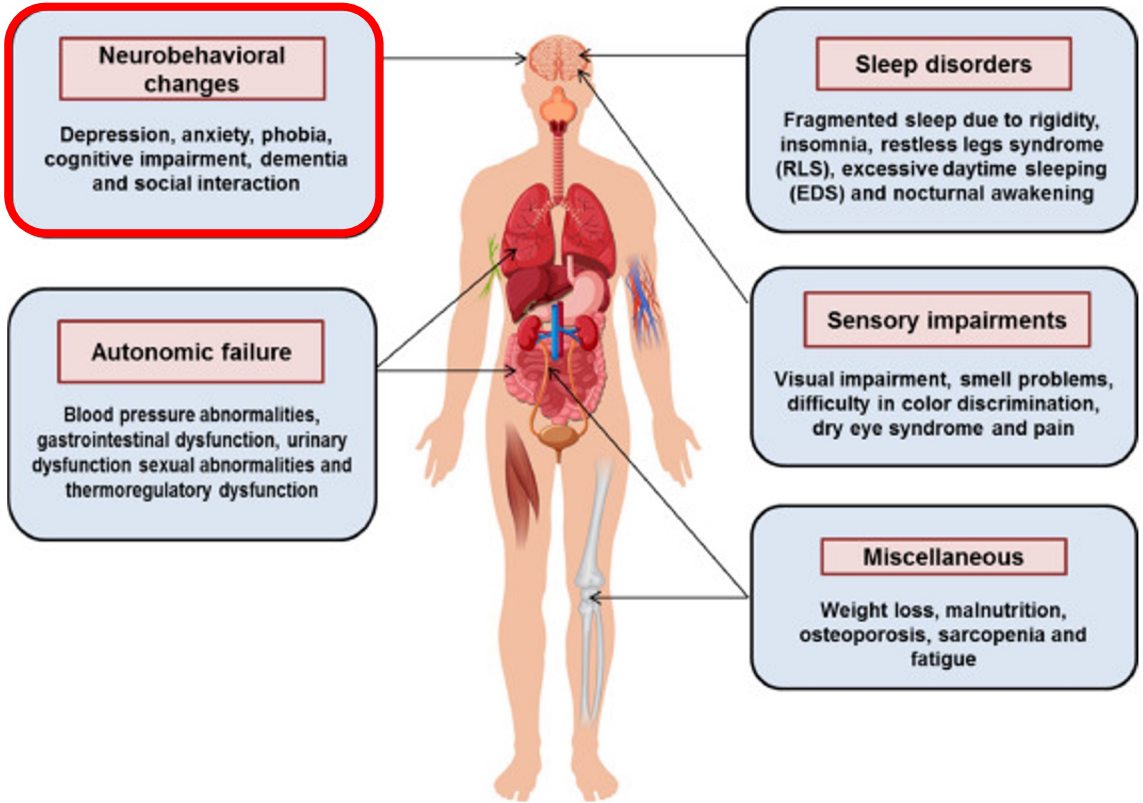
Non-motor symptoms

Motor symptoms:

- Disease modifying: exercise, diet

- Symptomatic: medications, surgeries

Non-motor symptoms in Parkinson's disease



Gupta, Curr. Res. Behav. Sci. 2021

Neuropsychiatric symptoms:

Dementia

- Workup for treatable causes
- Management:
  - Caregiver education
  - delirium prevention
  - daytime engagement/sleep optimization
  - Cholinesterase inhibitor
- Mitigate:
  - Elopement, phishing/catfishing

Psychosis

- Workup for treatable causes
- Management
  - Cholinesterase inhibitors
  - Antipsychotic: quetiapine, clozapine, pimavanserin

Depression and anxiety

- psychotherapy, mindfulness
- Sertraline, escitalopram; mirtazapine; duloxetine/venlafaxine
- buspirone, hydroxyzine
- ECT
- Benzodiazepines

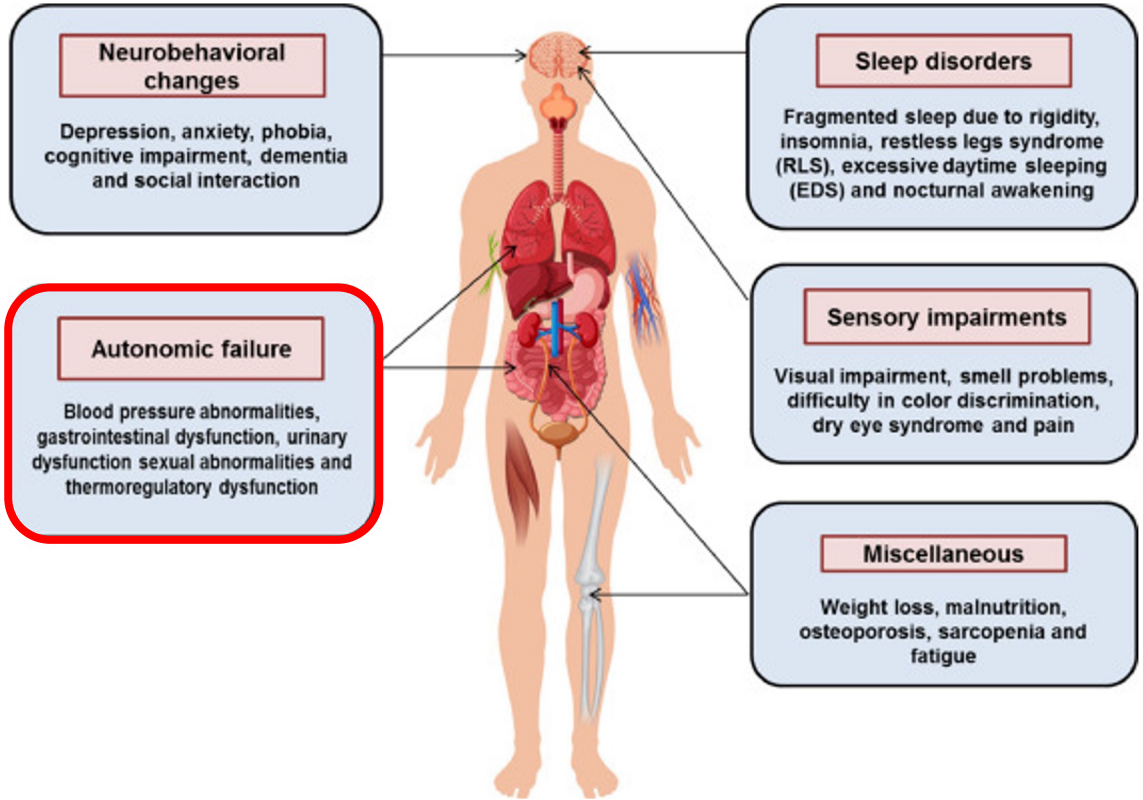
Apathy

- Optimize sleep/wake, bright light therapy, structured time
- stimulants don’t seem to help

Impulsivity

- SSRIs
- reduce dopaminergics

Katz, Neurotherapeutics, 2020



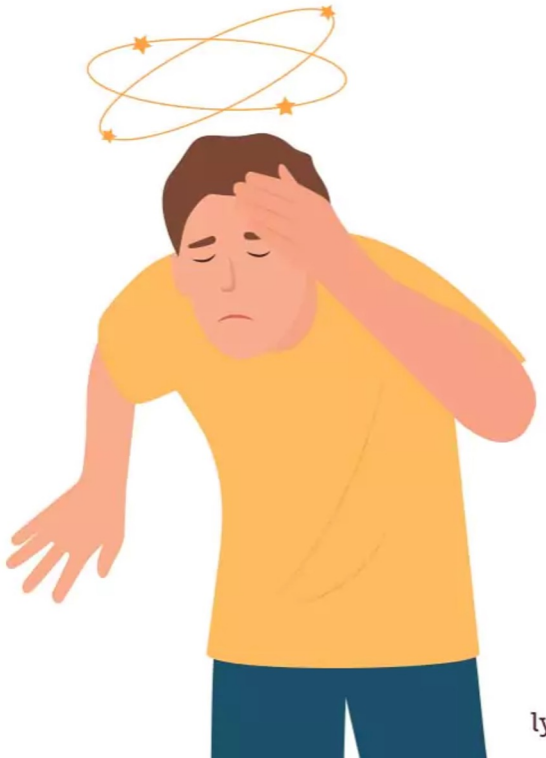
Gupta, Curr. Res. Behav. Sci. 2021

Optimize lifestyle modifications for orthostatic hypotension before reaching for medications.

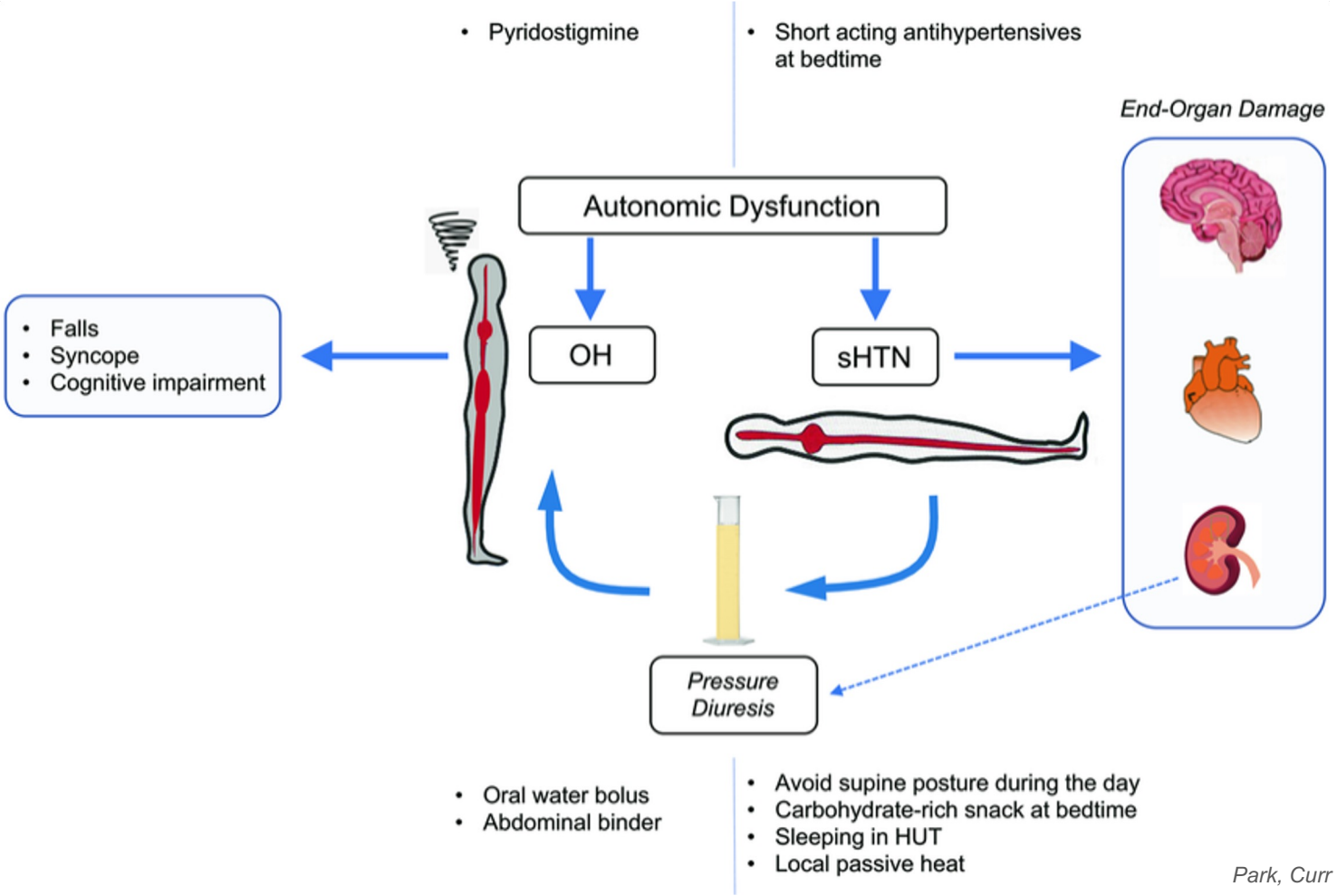
- Elevate head of bed
- Abdominal binder, compression stockings
- Liberalize salt and water in diet
- Small, low carb meals, avoid alcohol
- Avoid heat, hot showers

- **Reduce antihypertensives**
- Reduce dopaminergics

- Caffeine
- Midodrine, Droxidopa, Fludrocort, Pyridostigmine

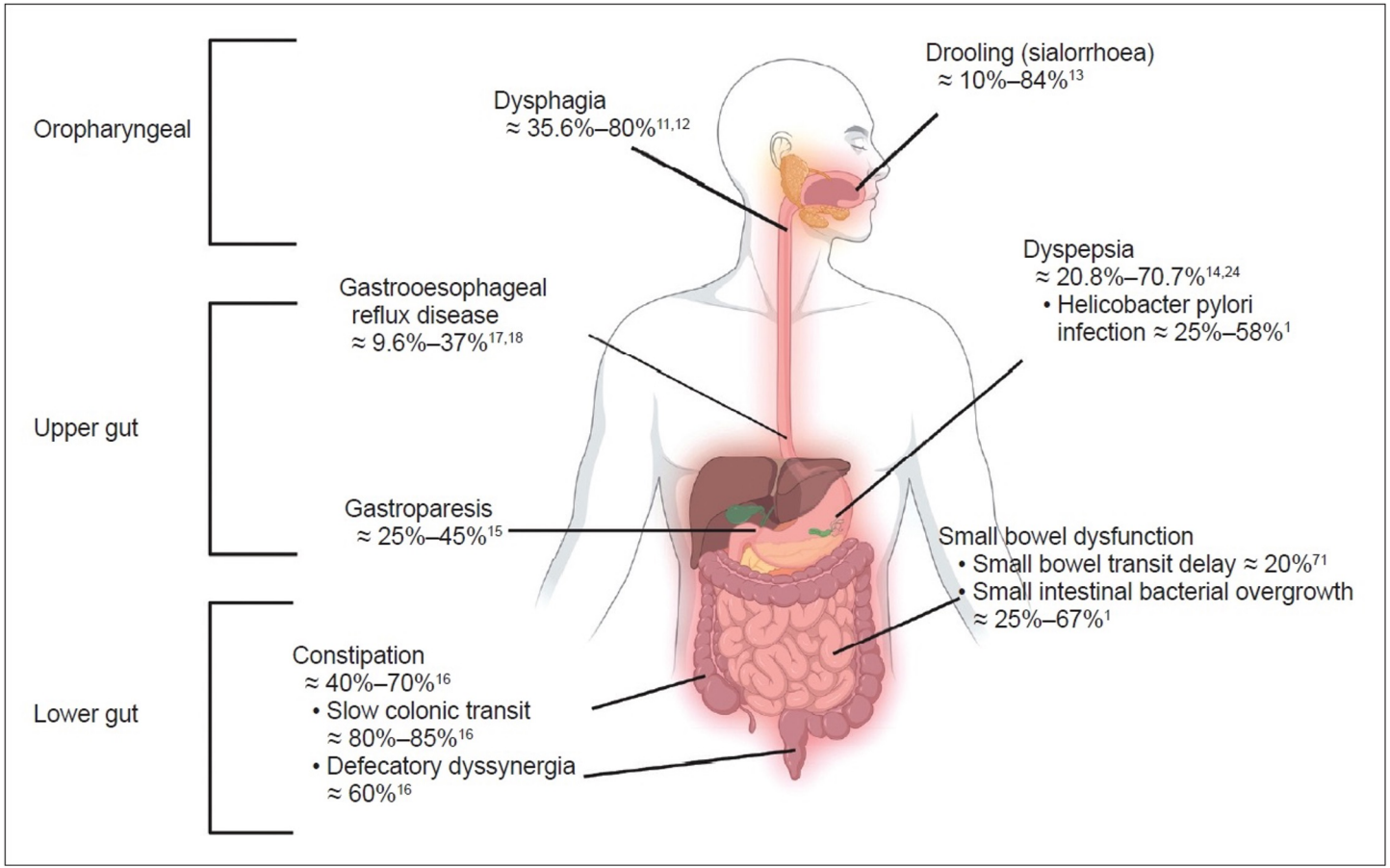


Nocturia and orthostatic hypotension: a vicious cycle.

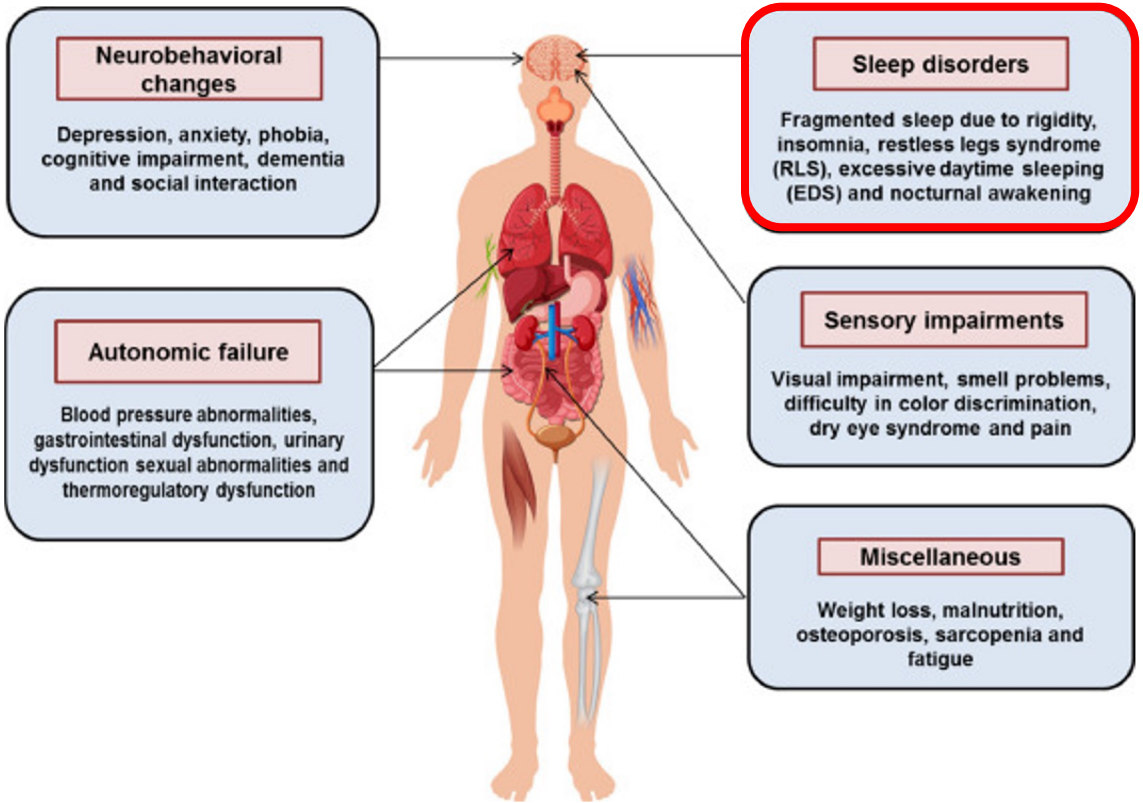


Park, Curr Hypertens Rep 2022

The whole GI tract is impacted in parkinsonism.



Tan, J Mov Disord. 2023



Gupta, Curr. Res. Behav. Sci. 2021

Sleep dysfunction affects the whole family.

RBD:

- padding on corners, floor, bedrail.
- Move levodopa earlier
- start melatonin, clonazepam, quetiapine

Insomnia:

- Sleep hygiene, CBT, Bright light therapy.
- CD/LD overnight
- melatonin, mirtazapine, trazodone, quetiapine

EDS:

- Caffeine, strategic napping
- modafinil, methylphenidate

H. Royden Jones, *Netter's Neurology, 2nd Edition*

Exercise and diet are disease modifying

- **American Academy of Neurology Quality Indicators:** Neurologists should recommend 150 min/week of at least moderate intensity aerobic exercise.

Factor et al. *Neurology.* 2016;86(24):2278-2283.

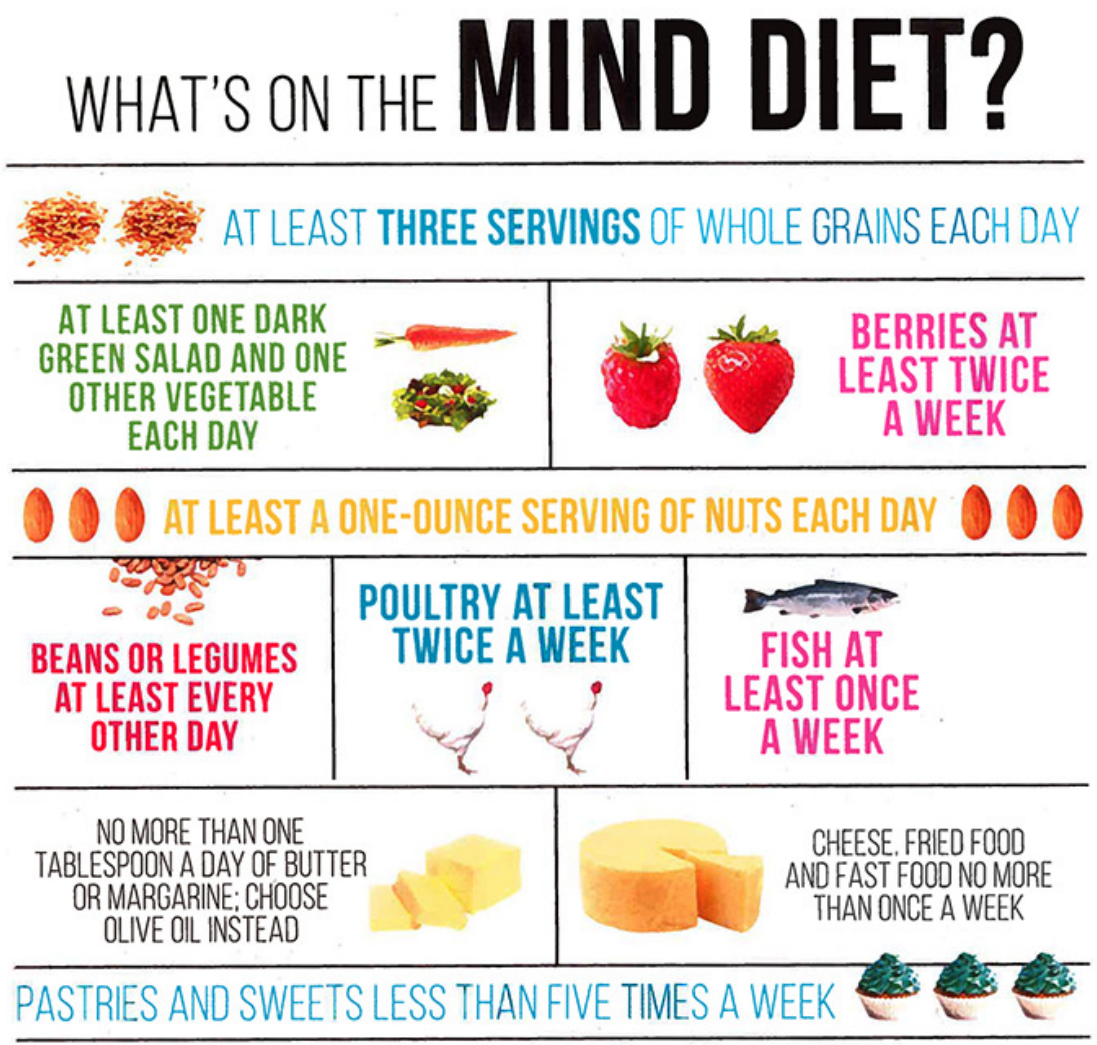
"Regular exercise at baseline were associated with better QOL, mobility, and physical function, less progression of disease, less caregiver burden and less cognitive decline one year later, after controlling for demographic and disease severity variables." - Oguh O et al. Parkinsonism Relat Disord. 2014

Factor SA, Neurology, 2016
Oguh O, Parkinsonism Relat Disord, 2014

- Olive oil
- Red wine

Moderation of:

- Red meats
- Butter and stick margarine
- Cheese
- Pastries and sweets
- Fried or fast food



pacificneuroscienceinstitute.org

- MIND diet adherence a/w reduced incidence and slower progression compared to MeDi. *Agarwal et al, J Nutr Health Aging 2018*

- MIND diet adherence a/w higher age of PD onset. *Fox et al, Nutrients, 2022*

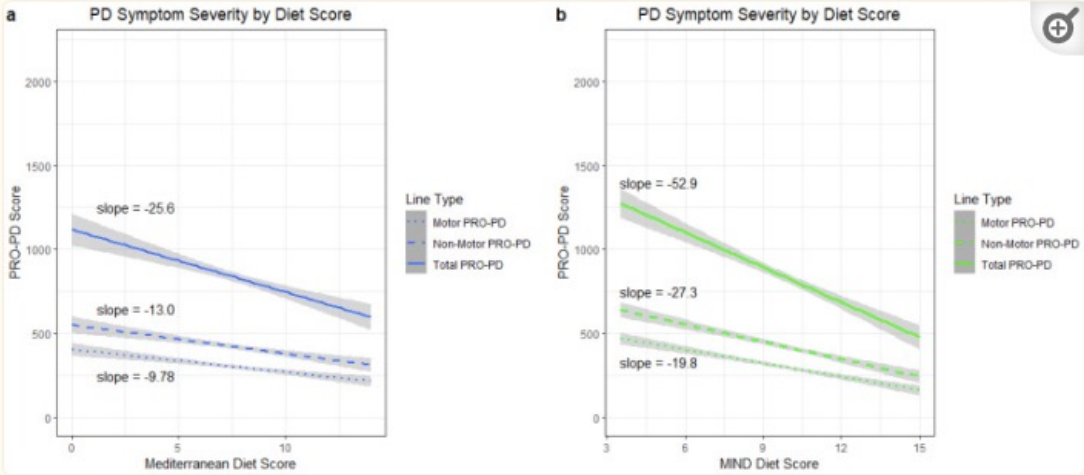


Figure 1

(**a**) Linear regression of PRO-PD score by Mediterranean Diet Score adjusted for age, gender, income, and years since diagnosis with non-motor and motor PRO-PD sub-scores. (**b**) Linear regression of PRO-PD score by MIND Score adjusted for age, gender, income, and years since diagnosis with non-motor and motor PRO-PD sub-scores.

Fox DJ, Nutrients, 2022

Symptomatic treatment - a review of medications

Levodopa: synthetic dopamine

Carbidopa: AADC inhibitor, reduces levodopa peripheral breakdown

Entacapone: COMT inhibitor, reduces peripheral levodopa breakdown

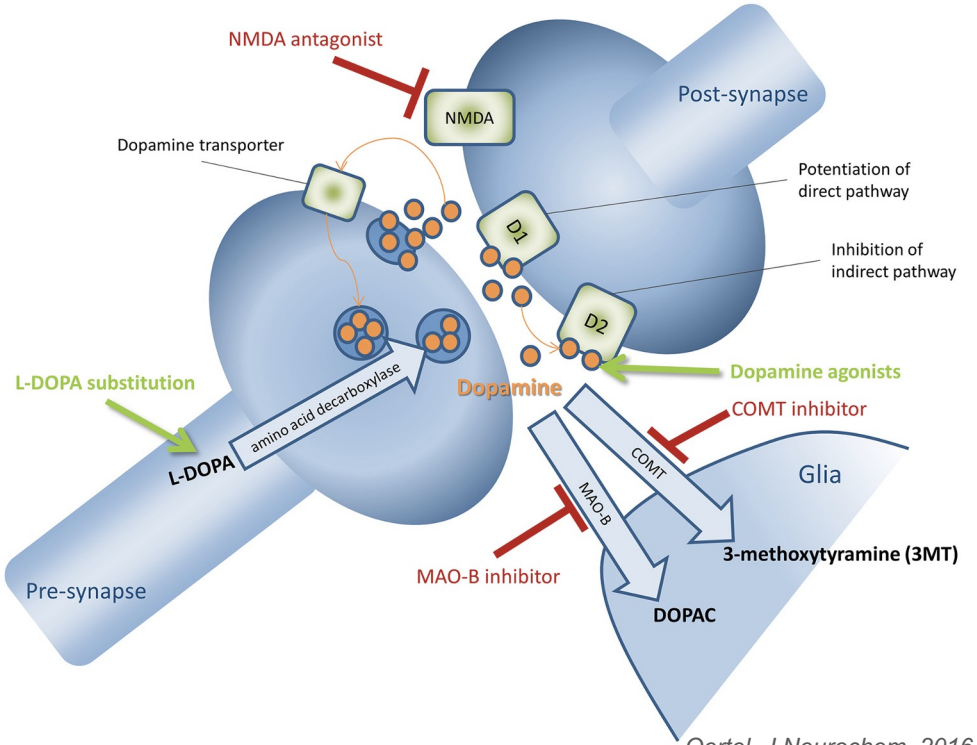
Rasagiline, Safinimide, Selegiline: MAO-B inhibitors, reduces dopamine breakdown

Ropinirole, Pramipexole, Rotigotine: Dopamine agonists:

Trihexyphenidyl: anticholinergic

Amantadine: NMDA antagonist; increases DA release, blocks reuptake

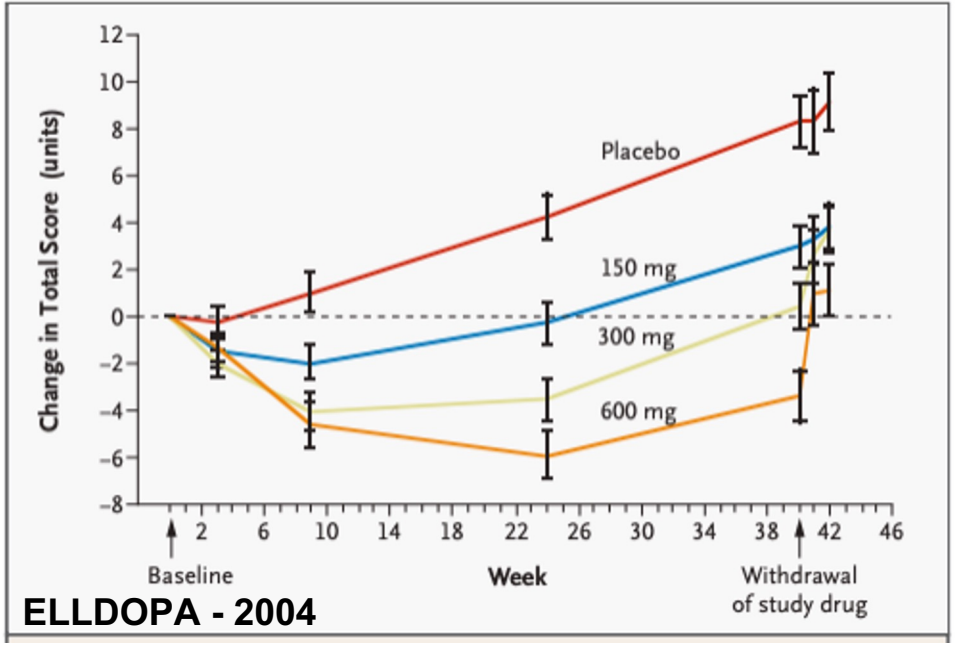
Istradefylline (Nourianz): Adenosine antagonist



Espay, Neurol Clin Pract, 2017.

Oertel, J Neurochem. 2016

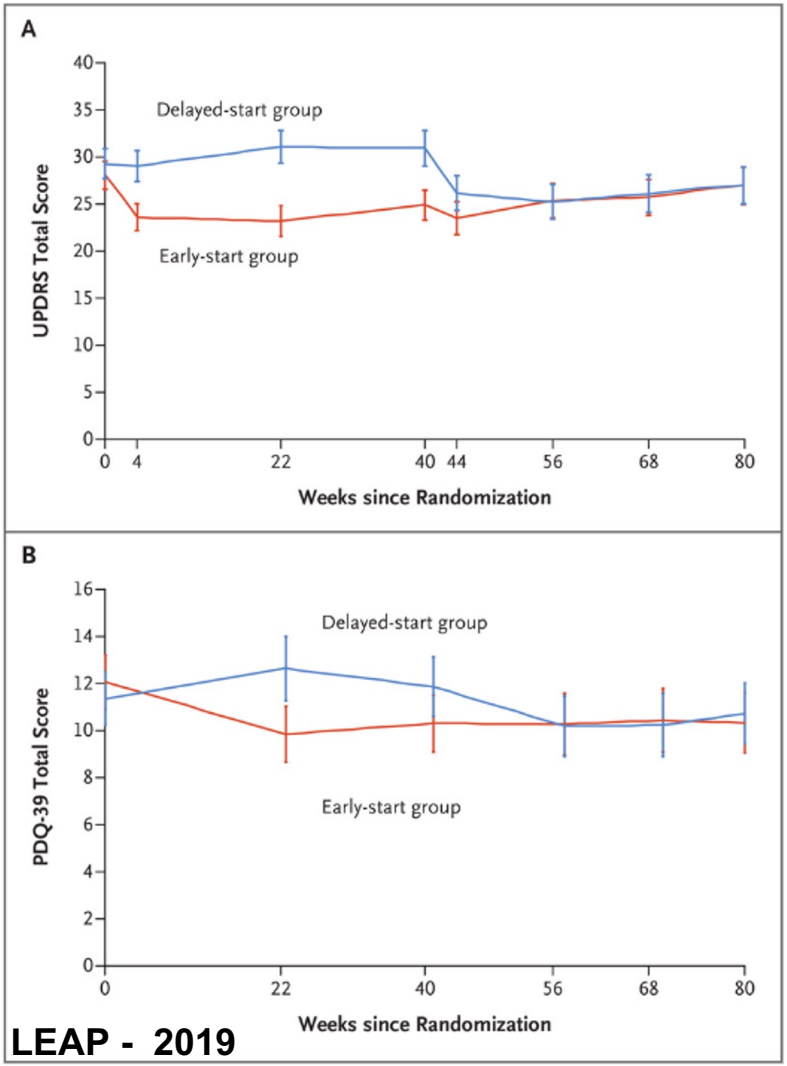
Myth 1: Levodopa is neurotoxic



ELLDOPA - 2004

"No evidence that cumulative lifetime dose of LD affects progression or burden of LB pathology in PD" (adjusted for gender, age at onset, duration of PD, duration of DA therapy)

Queen Square Neuropathology - 2014



LEAP - 2019

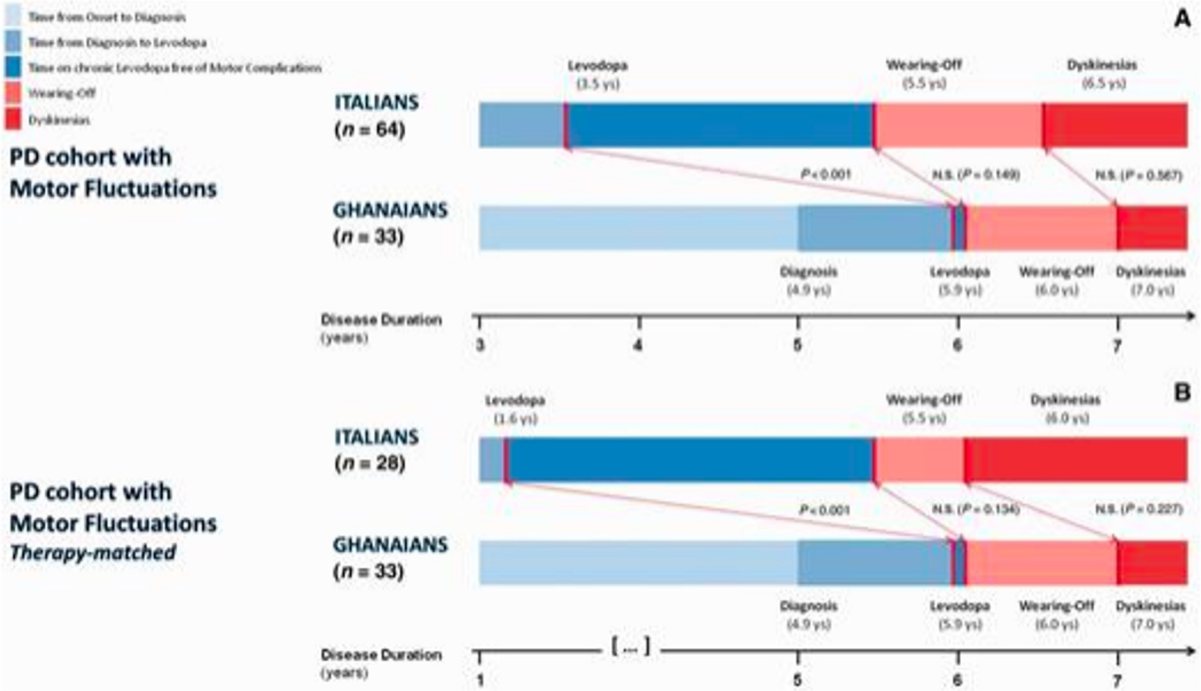
Myth 2: Levodopa-sparing delays dyskinesia

dyskinesias are from the pulse of levodopa, reduced with tonic release

dyskinesia onset depends on *time with disease*, not upon cumulative levodopa exposure

The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa

Figure 2

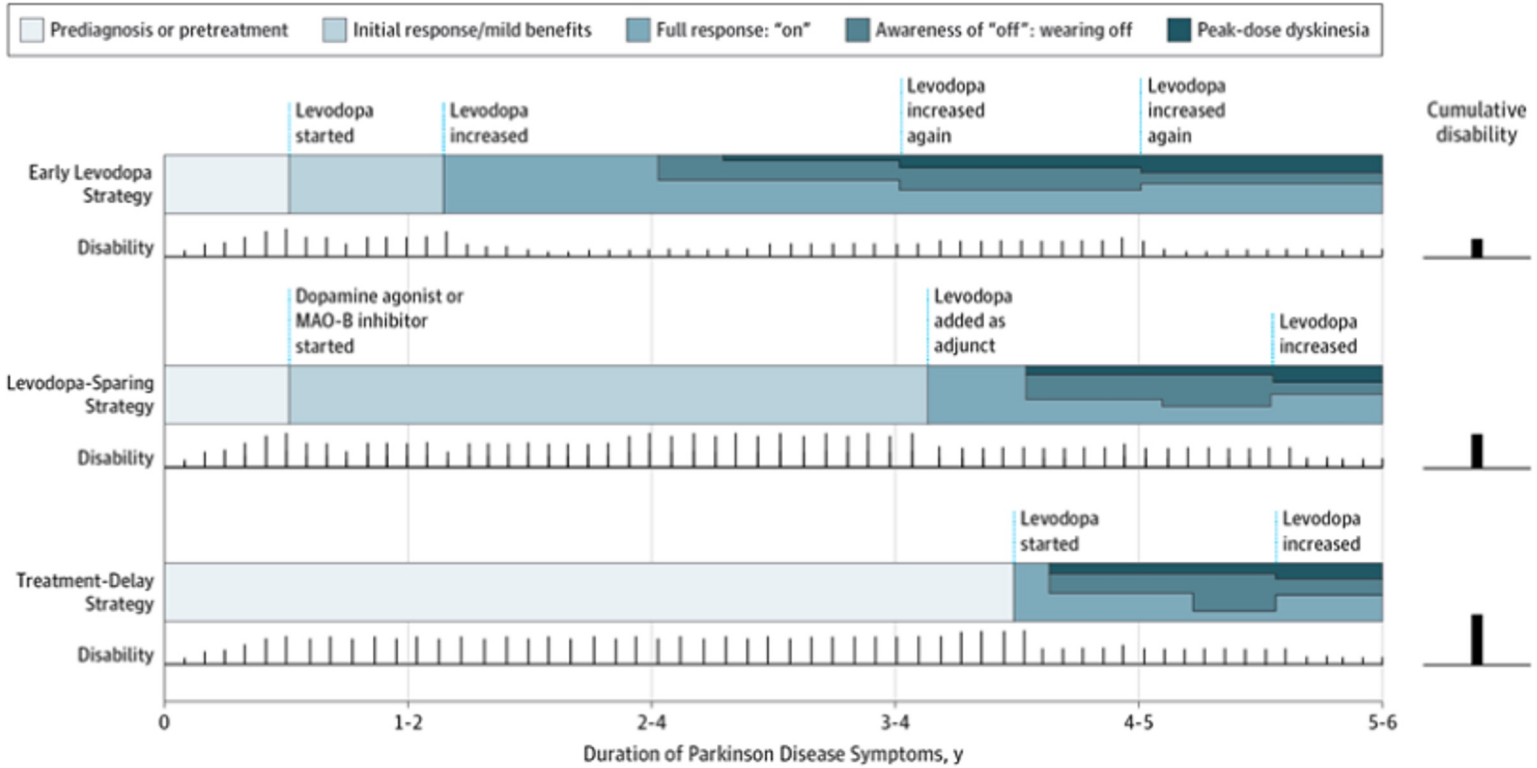


Cilia et al, Brain. 2014

Common Myths in the Use of Levodopa in Parkinson Disease

When Clinical Trials Misinform Clinical Practice

Figure. Theoretical Models of Levodopa Use and Associated Disability



Espay & Lang, JAMA Neurol, 2017

Early Parkinson's Disease: 1-3+ years into disease

- There is no benefit to withholding or delaying treatment
- To start or not to start medication?
  - Be sure of your diagnosis
  - Do symptoms warrant treatment
- Use Levodopa
  - Young patients - address disability (workforce, childcare, etc)
- Timing of levodopa doses
- Dopamine agonists ok in patients younger than 65-70yo
- MAO-B inhibitors in early/mild patients
- EXERCISE for disease modification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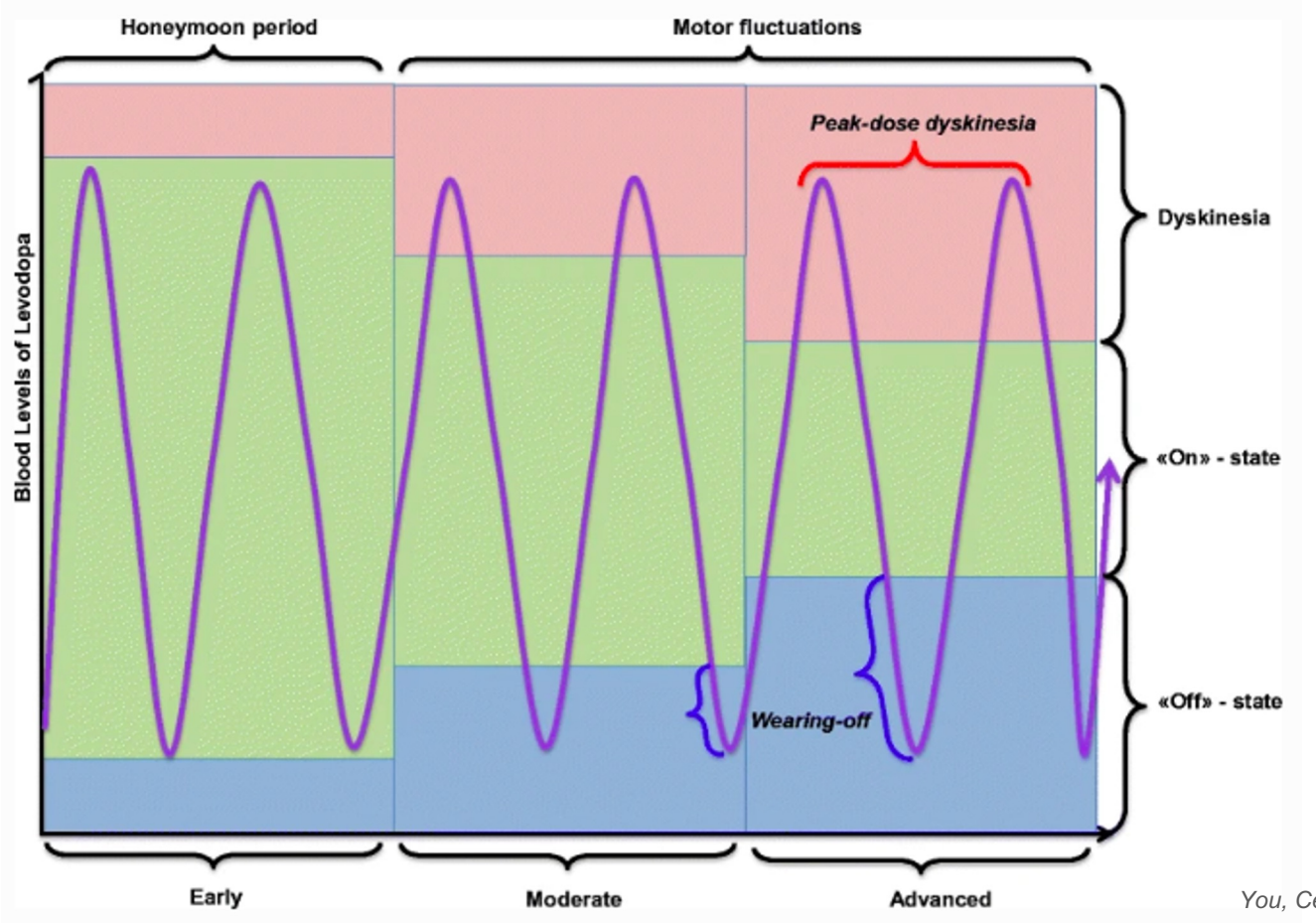
Treating motor complications

Moderate Parkinson's Disease: 3-5 years into disease



You, Cell TIssue Res, 2018.

@spazzyjules

Advanced Parkinson's Disease: 10 years

MORE motor fluctuations

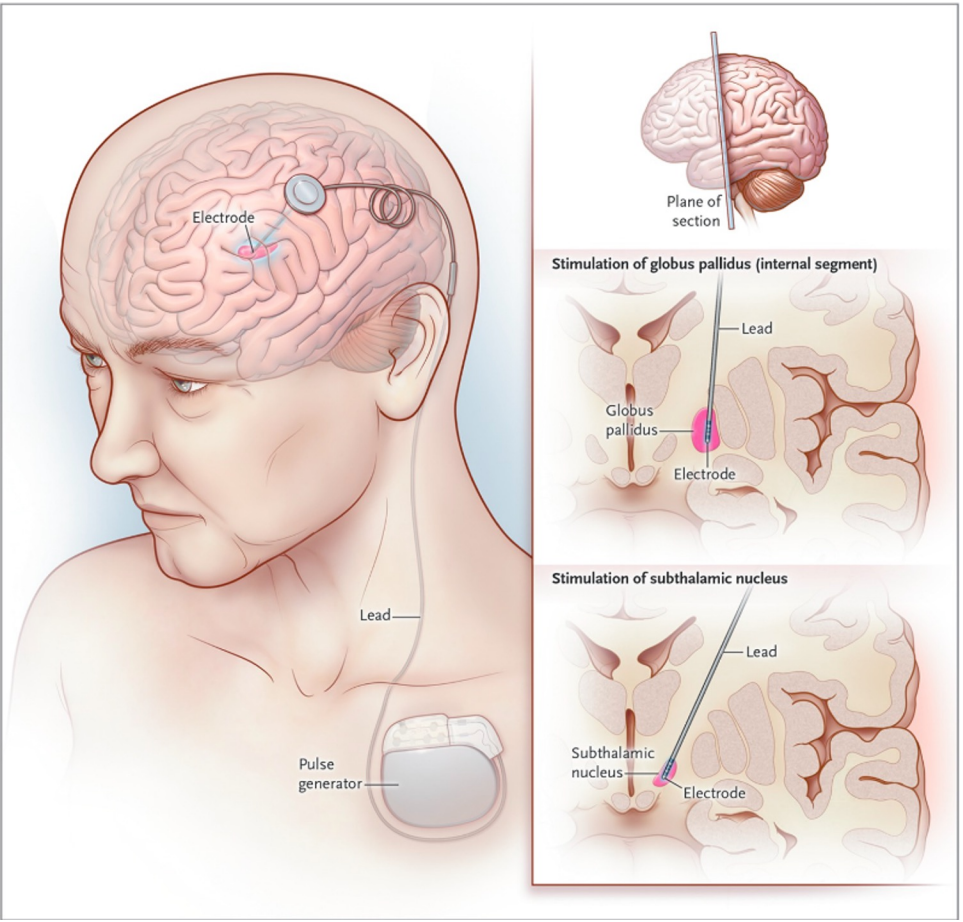
Resistant axial symptoms (FOG and balance)

Treatment:

- Minimize OFF time
- Minimize ON time with troublesome dyskinesia
- Optimize levodopa doses, timing, absorption
- Extend LD effect with COMT inhibitors, Rytary, CD-LD CR
- OFF rescue treatments (Inbrija, Apokyn)
- Dyskinesia treatment with amantadine

Consider surgical interventions

Surgical treatments - DBS



Okun N Engl J Med 2012

Symptoms that respond to DBS	Symptoms that do not respond to DBS
Tremor	Falls
Bradykinesia	Freezing
Rigidity	Speech problems
Dyskinesias	Most nonmotor symptoms
Motor fluctuations	

An established diagnosis of PD using UK Brain Bank criteria.

No contraindications to surgery under general anaesthesia.

A life expectancy of 5+ years, considered by a multidisciplinary team assessment.

Motor complications severe enough to compromise function and quality of life significantly.

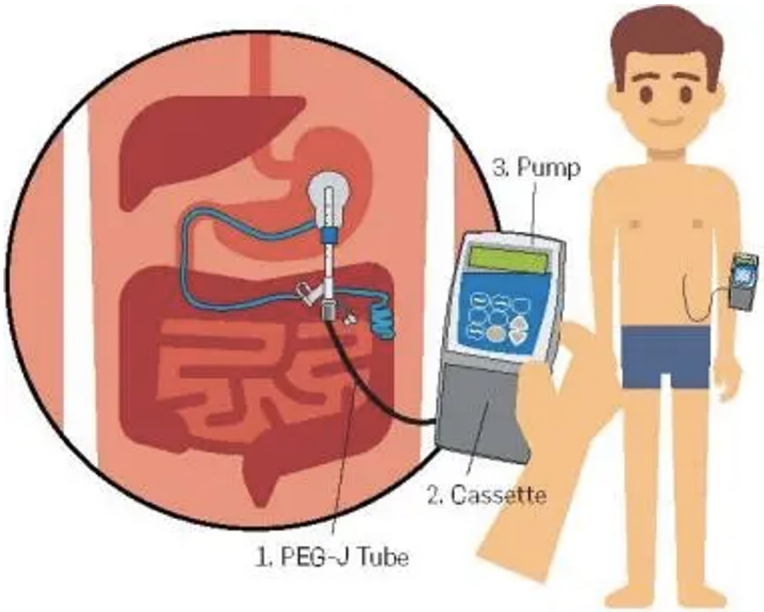
Physician assessment shows the patient spends >30% of the day in a disabling “off” state or with disabling dyskinesia.

The patient remains levodopa responsive, with >40% improvement in unified Parkinson’s disease rating scale (UPDRS) Part 3 scores following the usual levodopa morning dose.

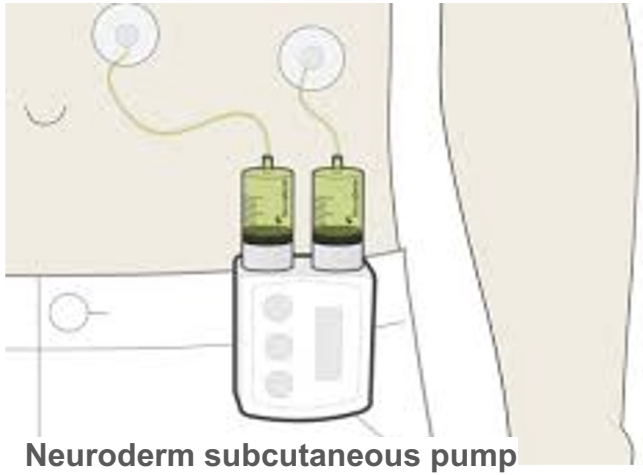
The patient has no clinically significant cognitive impairment on the Dementia Rating Scale (score <6).

Malek, Neurol India 2019

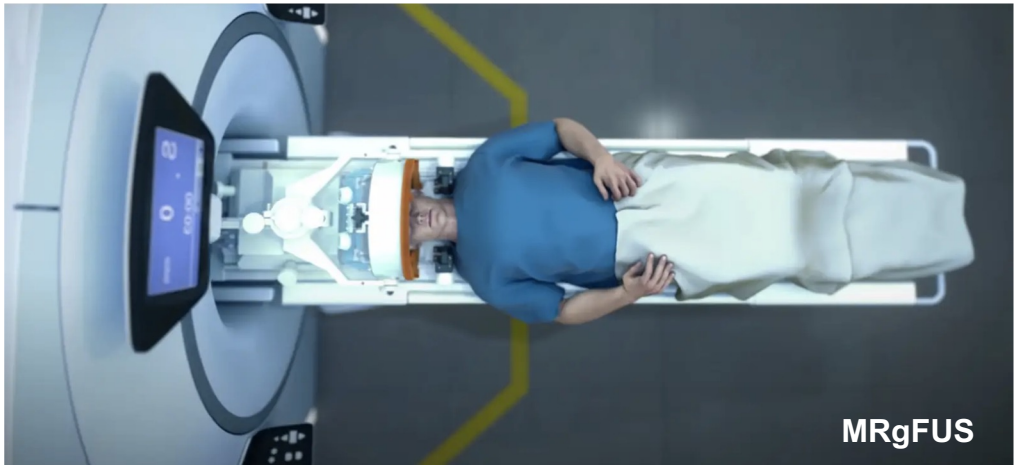
Invasive interventions



Duopa - jejunal pump



Neuroderm subcutaneous pump



What might the end of life look like?

Causes of death:

- 70% die from related complications of PD

Indicators for hospice:

- Recurrent infections, falls, hospitalizations; frequent aspiration/dysphagia
- Mortality in PD within 6-12mo: accelerated weight loss, reduce dopaminergic meds due to neuropsych side effects, BMI <18.5.

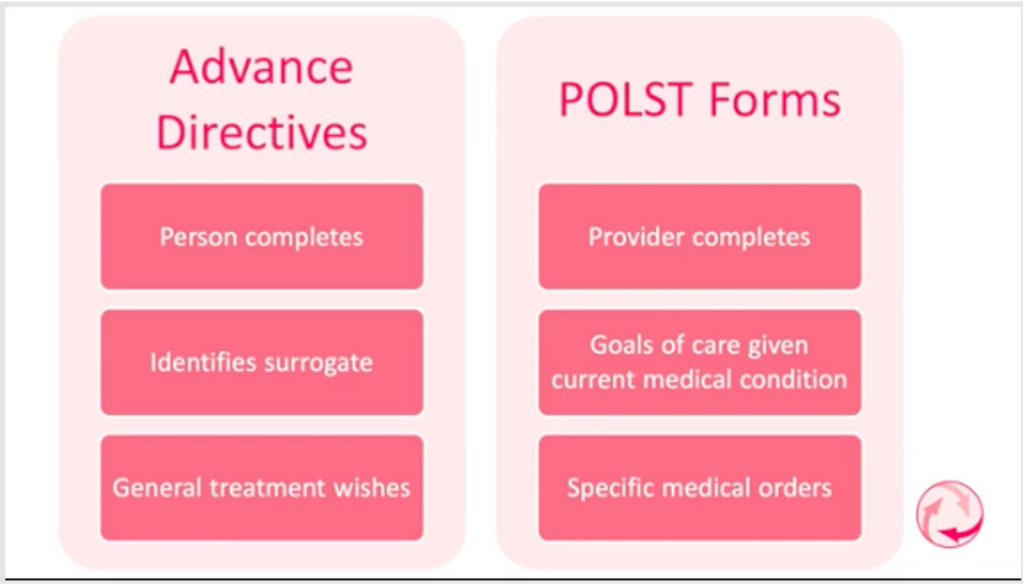
End of life experience:

- Increasing cognitive fluctuations, bed-ridden, intermittent awareness/alertness.
- Cachexia, physical pain, dyspnea, paranoid delusions/hallucinations, difficulty communicating
- Medically futile treatments: high-cal supps, feeding tubes, thickened liquids, artificial hydration
- ***Medications to avoid:*** antiemetics, neuroleptics, anticholinergics

Miyasaki, Parkinsonism Relat Disord, 2012

Katz, J Palliat Med, 2018

Advanced care planning is associated with reduced inpatient death and increased in-home death in PD patients.



polst.org

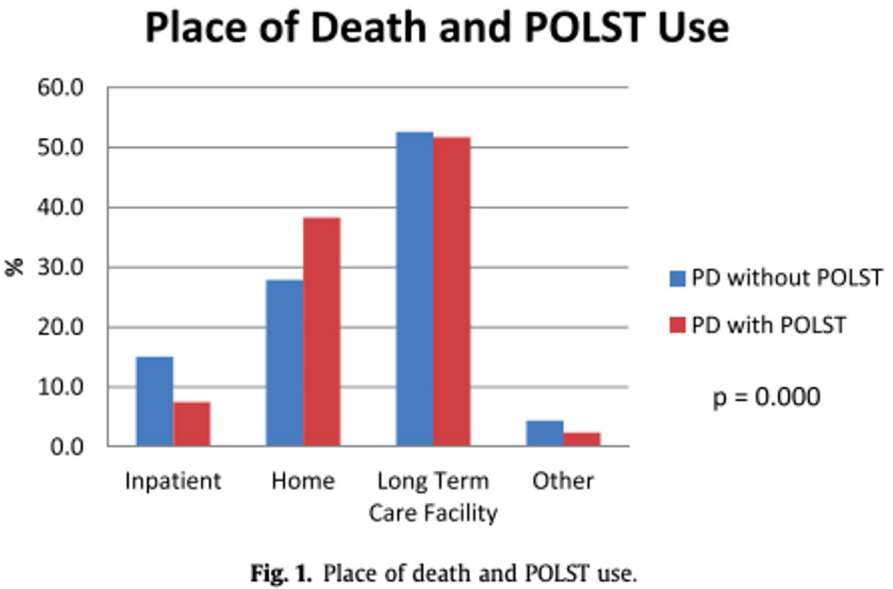


Fig. 1. Place of death and POLST use.

the **conversation** project

Tuck, Parkinsonism and Related Disord, 2015

@markxhogben

Questions?

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