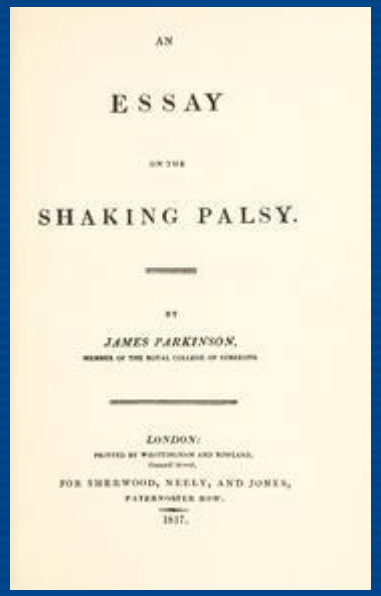
JOHNS HOPKINS
MEDICINE

Common Misconceptions About Parkinson's Disease


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

1817.

Kelly Mills, MD, MHS

Johns Hopkins Parkinson's and Movement Disorders Center

Director, Neuromodulation and Advanced Therapies Center

Objectives

- Discuss the diagnostic approaches to Parkinson's disease
- Address the influence of genetics on Parkinson's disease risk
- Discuss the concept of delaying dopamine replacement therapy to avoid motor complications of therapy
- Discuss use and timing of advanced symptomatic therapies in Parkinson's disease

Funding / Conflicts

- Funding
  - NIH / NINDS K23
  - NIH / NINDS R01 (Northwestern University)
  - Abbott / St. Jude (Site PI)
  - Parkinson Foundation

- Conflicts of Interest
  - None

Case #1

- 47 y/o mother of 2, 5 months of left hand tremor while watching TV
- More difficult shampooing hair
- Loss of smell sensation, dream enactment.

- Reason for consultation:
  - Do I have PD (**my neurologist didn't do a brain scan or labs so I don't believe her**)?
  - What can I do to stop it? **I heard there is nothing that can be done to slow down the disease.**

How do we diagnose Parkinson's?

Patient:

"I don't think my neurologist did a thorough evaluation. She did not even do an MRI of my brain. How could she know this is Parkinson's disease?"

Misconception

Parkinsonism

- Cardinal features
  - Bradykinesia (slow, small movement) — *Required*
  - Rest Tremor
  - Rigidity

Need 1

Causes of parkinsonism:

- Parkinson's disease
  - Hereditary forms
  - Sporadic
- Multiple system atrophy (MSA)
- Diffuse Lewy body disease
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration
- Frontotemporal dementia with parkinsonism
- Pallidal degenerations
- Alzheimer disease
- Spinocerebellar ataxias (types 2,3,17)
- Huntington's disease
  - Juvenile presentation
  - Later in disease course
- Wilson disease
- Acquired hepatolenticular degeneration
- Parkinsonism Dementia Complex of Guam
- Neuroferritinopathy
- Basal Ganglia calcification
- Gaucher’s disease
- GM1 gangliosidosis
- Chediak-Higashi disease
- Chorea-acanthocytosis

How do we diagnose Parkinson's?

JOHNS HOPKINS MEDICINE

Diagnosis of Clinically Established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of Clinically Probable PD requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If 1 red flag is present, there must also be at least 1 supportive criterion
   - If 2 red flags, at least 2 supportive criteria are needed
   - No more than 2 red flags are allowed for this category

Supportive criteria

(Check box if criteria met)

□ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:

- a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
- b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

□ 2. Presence of levodopa-induced dyskinesia

□ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

□ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

□ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

□ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

□ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease

□ 4. Parkinsonian features restricted to the lower limbs for more than 3 y

□ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

□ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

□ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

□ 8. Normal functional neuroimaging of the presynaptic dopaminergic system

□ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flags

□ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset

□ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment

□ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y

□ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

□ 5. Severe autonomic failure in the first 5 y of disease. This can include:

- a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
- b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

□ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset

□ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y

□ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)

□ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)

□ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Albanese et al. Movement disorders. 2015

How do we diagnose Parkinson's?

- Physical exam:
  - Bradykinesia *plus*
  - At least one of:
    - Stiffness

    or
    - Resting tremor

- Supportive criteria
  - Levodopa response
  - Levodopa-induced dyskinesia
  - Rest tremor
  - Olfactory loss or sympathetic denervation on MIBG

- "Red flags"→ signs/symptoms of other diseases

- You ***do not*** need labs or an MRI to diagnose Parkinson's, only to rule-out other things.

How do we diagnose Parkinson's?

Patient:

"I heard there is nothing that can be done to slow down the disease!"

Misconception

Treatment Overview

- Disease-modifying / Neuroprotective – slowing the disease
  - Oral medications
  - Non-pharmaceutical

- Symptomatic treatment
  - Oral medications
  - Surgical – medication infusion
  - Surgery – ablation / stimulation
  - Surgery – gene therapy

General Principals: Should you get treated?

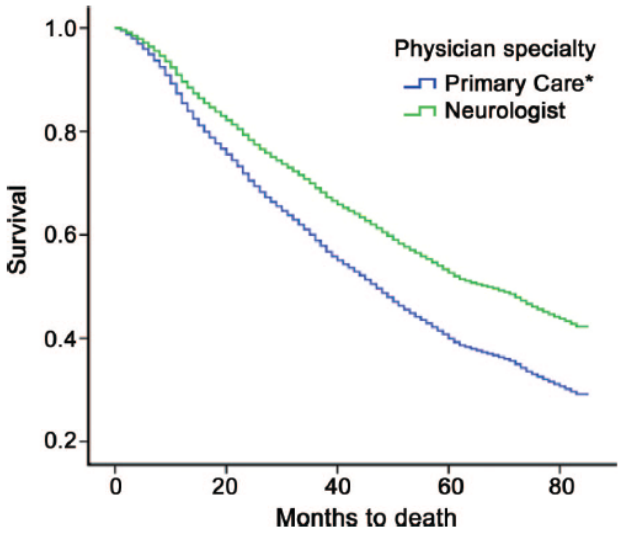
Neurologist care in Parkinson disease

A utilization, outcomes, and survival study

A.W. Willis, MD
M. Schootman, PhD
B.A. Evanoff, MD, MPH
J.S. Perlmutter, MD
B.A. Racette, MD

Address correspondence and reprint requests to Dr. Allison Wright Willis, Washington University School of Medicine, Department of Neurology, 660 South Euclid Avenue, Campus Box 8111, St. Louis, MO 63110
willisa@neuro.wustl.edu

Figure Survival of Medicare beneficiaries with incident Parkinson disease stratified by treating physician specialty, adjusted for race, age, sex, comorbidity index, and socioeconomic deprivation

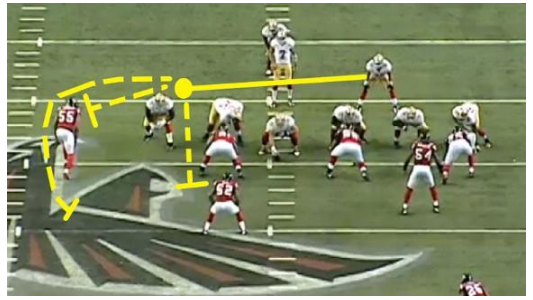


*Physicians in the following specialties: internal medicine, family practice, or geriatric medicine.

Parkinson's "neuroprotection":

- **Neuroprotection** = reversing the underlying process that kills dopaminergic cells
  - Football analogy: running back too slow → trade for a faster RB, train current running RB

- **Disease modifying** = slowing progression of the disease even if you do not directly affect this process
  - Football analogy: running back too slow → recruit better offensive line



Parkinson's "neuroprotection"

JOHNS HOPKINS MEDICINE

TABLE 3. Summary of all of the previous clinical trials evaluating putative neuroprotective therapy for PD

		Study design				
Drug	Mechanism of action	Parallel arms (PA) versus delayed start (DS) versus futility study (FS)	Placebo (P) versus active arms only (A)	Washout period	Primary outcome(s)	Result
Selegiline	MAO-B inhibition; anti-apoptotic (GAPDH inhibition); antioxidant; other	PA	P	+ (Syndepar 2 months)[21]	Need for symptomatic treatment; change in UPDRS[9]	Positive[8,9,21]
Rasagiline	Ibid	DS	P	–	Change in UPDRS	Positive[26]
THC-346	Anti-apoptotic: GAPDH inhibition; no MAO-B inhibition effects	PA	P	–	Need for symptomatic treatment	Negative[10]
Pramipexole	Dopamine agonist, antiapoptotic	DS	P	–	Change in UPDRS	Negative[28]
Pramipexole	Dopamine agonist, antiapoptotic	PA	A	–	Surrogate imaging marker	Less change in striatal β-CIT with pramipexole versus levodopa[31]
Ropinirole	Dopamine agonist, antiapoptotic	PA	A	–	Surrogate imaging marker	Less change in striatal F-dopa with ropinirole versus levodopa[30]
Levodopa	Dopamine precursor; ? trophic	PA	P	+ (2 weeks; smaller subgroup had 4 weeks)	Change in UPDRS; surrogate imaging in subgroup	Positive for UPDRS; greater change in striatal β-CIT with levodopa versus placebo[22]
Tocopherol	Antioxidant	PA	P	–	Need for symptomatic treatment	Negative[8]

Lang et al., Mov Dis, 2013

Parkinson's "neuroprotection"

JOHNS HOPKINS MEDICINE

TABLE 3. Summary of all of the previous clinical trials evaluating putative neuroprotective therapy for PD

		Study design				
Drug	Mechanism of action	Parallel arms (PA) versus delayed start (DS) versus futility study (FS)	Placebo (P) versus active arms only (A)	Washout period	Primary outcome(s)	Result
CoQ10	Bioenergetic; antioxidant	PA	P	–	Change in UPDRS	Positive[43]
		FS	P	–	Change in UPDRS	Nonfutile[34]
		PA	P	–	Change in UPDRS	Negative: early termination - futile
Mitoquinone	Bioenergetic; antioxidant	PA	P	–	Change in UPDRS	Negative[44]
Creatine	Bioenergetic	FS	P	–	Change in UPDRS	Nonfutile[36]
CEP-1347	Antiapoptotic: mixed lineage kinase inhibitor	PA	P	–	Need for symptomatic treatment	Negative: early termination - futile[32]
Immunophilin	Antiapoptotic; ? trophic	FS	P	–	Change in UPDRS	Nonfutile[34]
		PA	P	–	Change in UPDRS	Negative[46]
GDNF	Trophic	PA	P	–	Change in UPDRS	Negative[47]
Pallroden	Trophic	PA	P	–	Surrogate imaging marker	Negative[48]
GM1 ganglioside	Stimulates recovery of damaged DA neurons	PA short term (16 weeks); open-label 5 y	NA	–	Change in UPDRS	Practically defined OFF scores at 5 y same or better than at baseline[49]
Riluzole	Glutamate antagonist	PA	P	–	Need for symptomatic treatment	Negative[45]
Minocycline	Anti-inflammatory	FS	P	–	Change in UPDRS	Nonfutile[35]

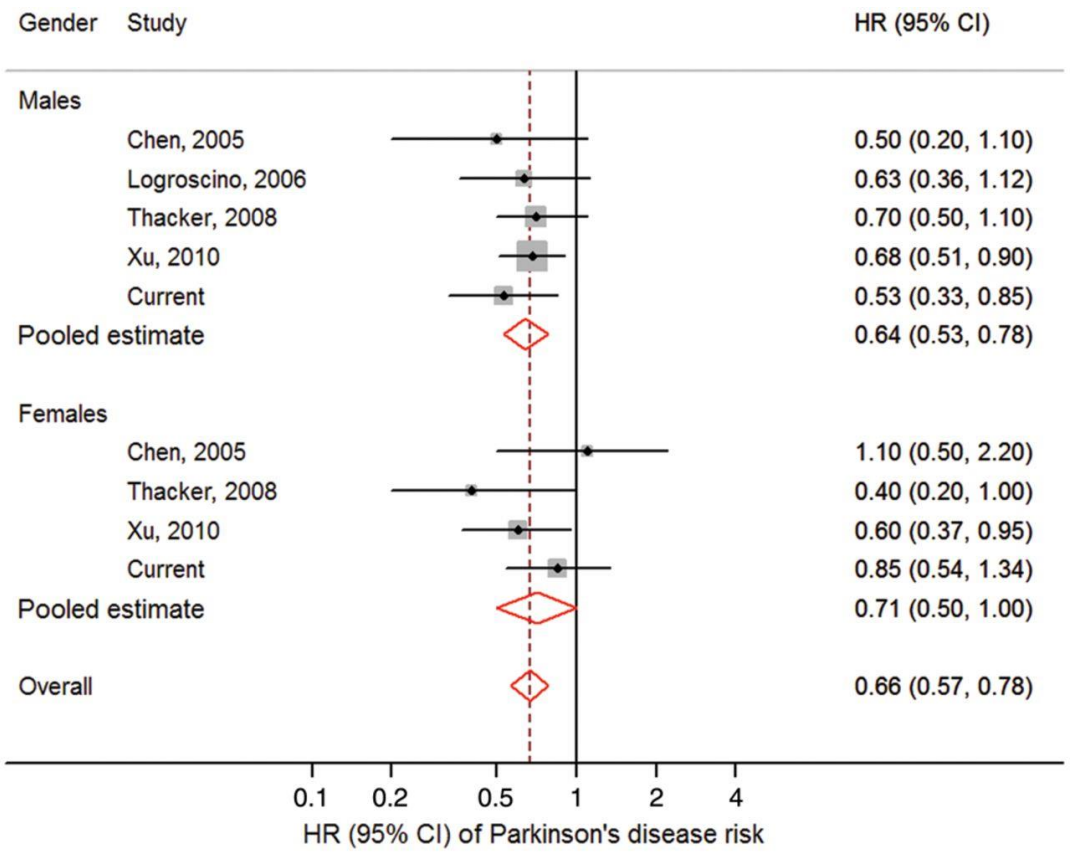
Lang et al., Mov Dis, 2013

Parkinson's "neuroprotection": Current Trials

- **Isradapine** –phase III trial just closed, awaiting results
- **Antibodies** against **α-synuclein** – phase IIb
- **Nilotinib** – phase IIb/III enrolling
- **GLP-1 agonists**
  - **Exenatide** – phase III start-up
  - **NYL-01** – phase I

Parkinson's disease-modifying: Exercise

- Neuroprotective vs. disease-modifying ?
  - Animals
    - Exercise stimulates GDNF release (Cohen et al. J Neurochem 2003;**85**:299-305.)
    - Forced exercise attenuates parkinsonism from MPTP (Tillerson et al. J Neurosci 2001;**21**:4427-35.)
  - Humans
    - Increases urate, assoc. with slower progression
    - Total physical activity associated with PD risk



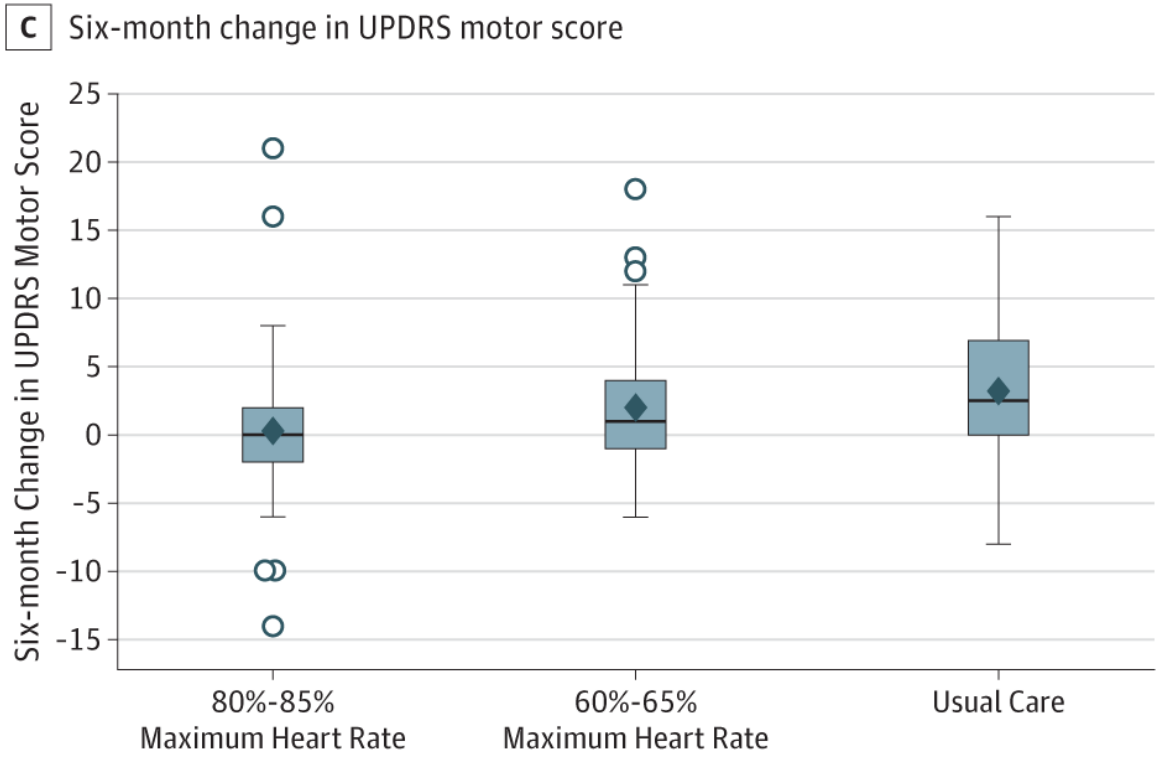
Yang et al. Brain. 2015 Feb;138(Pt 2):269-75.

Parkinson's disease-modifying: Exercise

- But what kind of exercise? (Shulman et al., JAMA Neurol, 2013)
  - low-intensity → most increase in walking distance and pace
  - high-intensity → most increase in cardiovascular performance
  - Stretching / resistance → most increase in muscle strength

Parkinson's disease-modifying: Exercise

- How intense should exercise be? (Shenkman, JAMA Neurol, 2017)
  - 3-point difference in UPDRS after 6 months
    - (average disease progression = ~3 points per year)
  - AE's
    - 9 in **high intensity** exercise group (N=45)
    - 0 in **usual care** (N=40)



Parkinson's "neuroprotection": Research

- Ask a Parkinson's researcher

- Web resources:
  - http://clinicaltrials.gov/
  - https://foxtrialfinder.michaeljfox.org/

Case #2

- 67 y/o M with 14 years of PD, now with complications of medical therapy and early cognitive impairment
- Family history: maternal uncle with PD
- Reason for consultation:
  - No one in my family has PD so it has to be due to something in my environment, right?

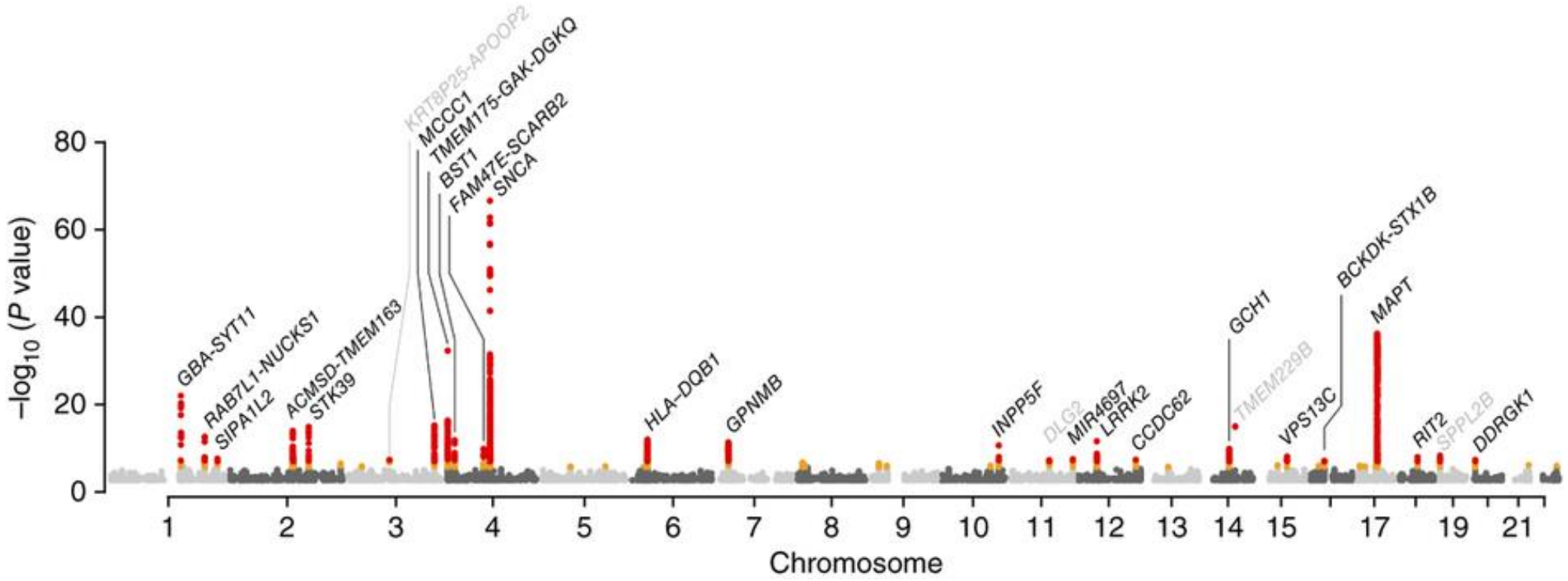
Misconception

“Cause” of Parkinson’s disease

- **Genetics** – complex genetic disorder

- **Environment**
  - Pesticides like paraquat, rotenone, 2,4-D (Pouchieu et al. Int J Epidem 2017)
    - Gloves reduce risk of PD in farmers
    - Higher prevalence in rural areas
    - Milk consumption associated with risk
  - Saturated fats (Kamel et al. Park Rel Dis. 2014)
  - Ozone and fine particulate matter (FM2.5)
  - Traumatic brain injury in late life (Goldman et al. Eur J Neurol. 2015)

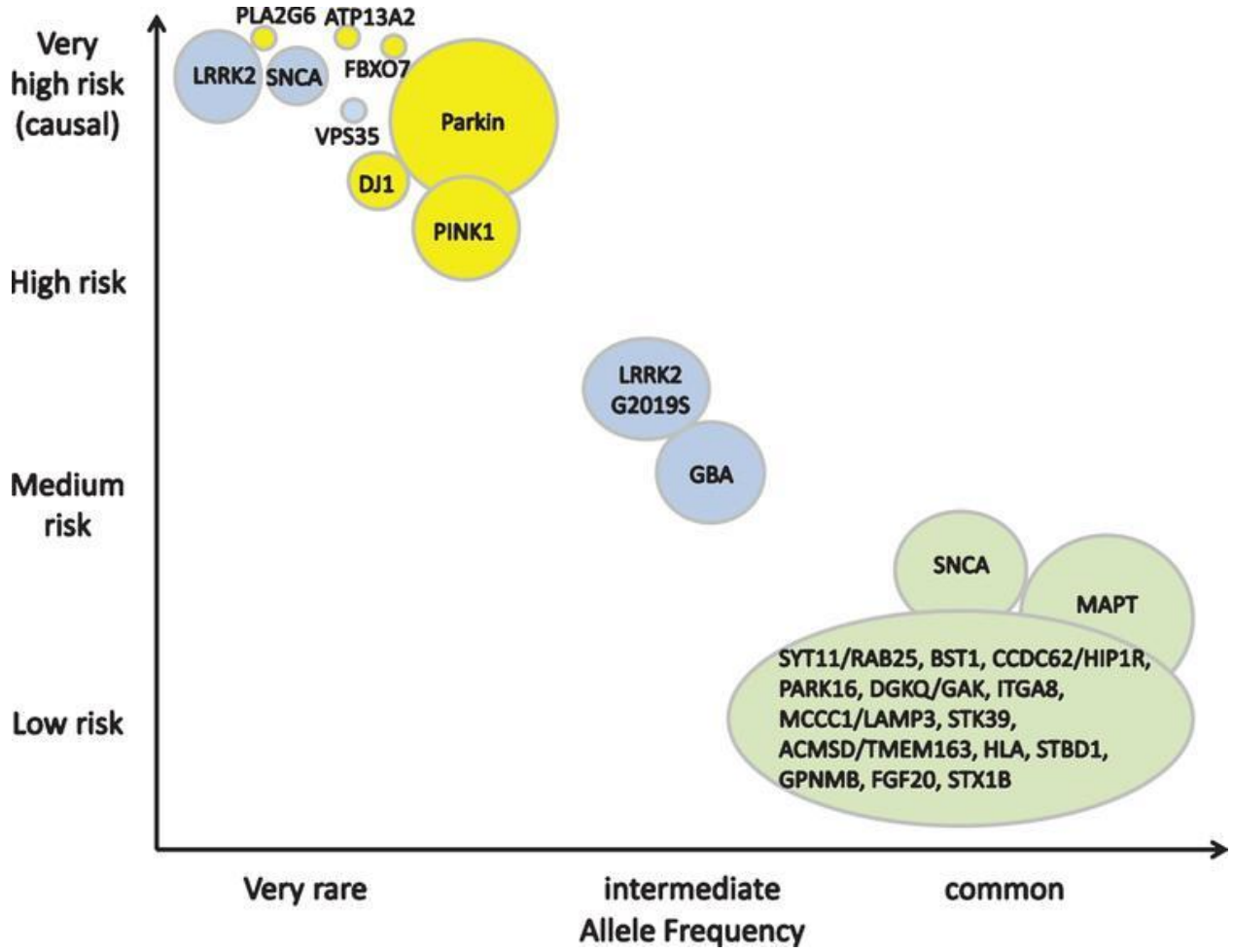
Genetics of Parkinson's disease



- Genomes of 13,700 PD patients and 95,282 controls compared
- 44 genes found to influence PD risk
- Risk is cumulative with the more genes you have

Nalls et al. Nat Genet. 2014 Sep;46(9):989-93

Genetics of Parkinson's disease



Gasser at al. Journal of Parkinson's Disease, vol. 5, no. 2, pp. 209-215, 2015

Genetics of Parkinson's disease

- What I tell patients:
  - Yes in 10% of cases
  - 90% of cases – some increased risk if in your family, but ***not*** high risk

Case #3

- 62 y/o F with PD for 5.5 years. Becoming disabled from hobbies and work by tremor
- Breakthrough tremor despite pramipexole 1.5 mg TID + amantadine 100 mg TID

- Reason for consultation:
  - My neurologist recommended carbidopa/levodopa, are there any alternatives?
  - Me: Why?

JOHNS HOPKINS MEDICINE

Misconception

I heard that you should hold off on starting levodopa until you're very disabled because you can only use it for about 5 years before you develop dyskinesias or other problems

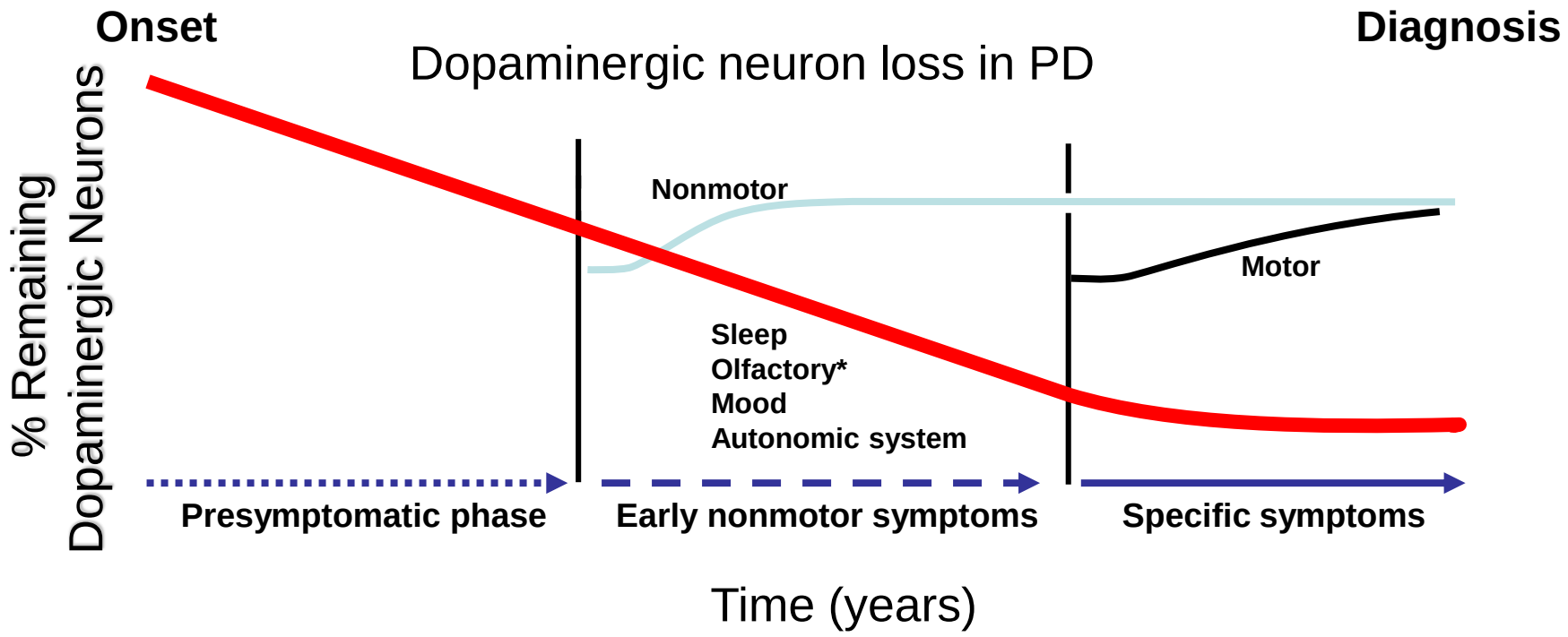
Treatment Overview

- Disease-modifying – slowing the disease
  - Oral medications
  - Non-pharmaceutical
- Experimental / future therapies
- Symptomatic treatment
  - Oral medications
  - Surgical – medication infusion
  - Surgery – ablation / stimulation
  - Surgery – gene therapy

Goal of Dopamine Replacement Therapy

- Reduce motor (movement) symptoms
  - Slow movement (bradykinesia)
  - Stiffness (rigidity)
  - Tremor
  - *Some types* of gait impairment
- Does not alter underlying disease course
- Exception → less early disability reduces later disability

Why dopamine replacement is needed



***Olfactory dysfunction may predate clinical PD by at least 4 years.**

Halperin et al. *Neurotherapeutics*. 2009;6:128-140.

Symptomatic Treatment: Motor

Two main types

Dopamine replacement

- Carbidopa/**levodopa**
  - **Sinemet**
  - **Parcopa**
  - **Duopa**
  - **Rytary**
  - **Inbrija**
- Dopamine agonists
  - **Pramipexole** (Mirapex)
  - **Ropinirole** (Requip)
  - **Apomorphine** (Apokyn)
  - **Rotigotine** (Neupro)
  - Pergolide
  - Bromocriptine

Other

- Amantadine / Gocovri
- Trihexyphenidyl (Artane)
- Dopamine extenders
  - Entacapone
  - Opicapone
  - Tolcapone
  - Selegiline
  - Rasagaline

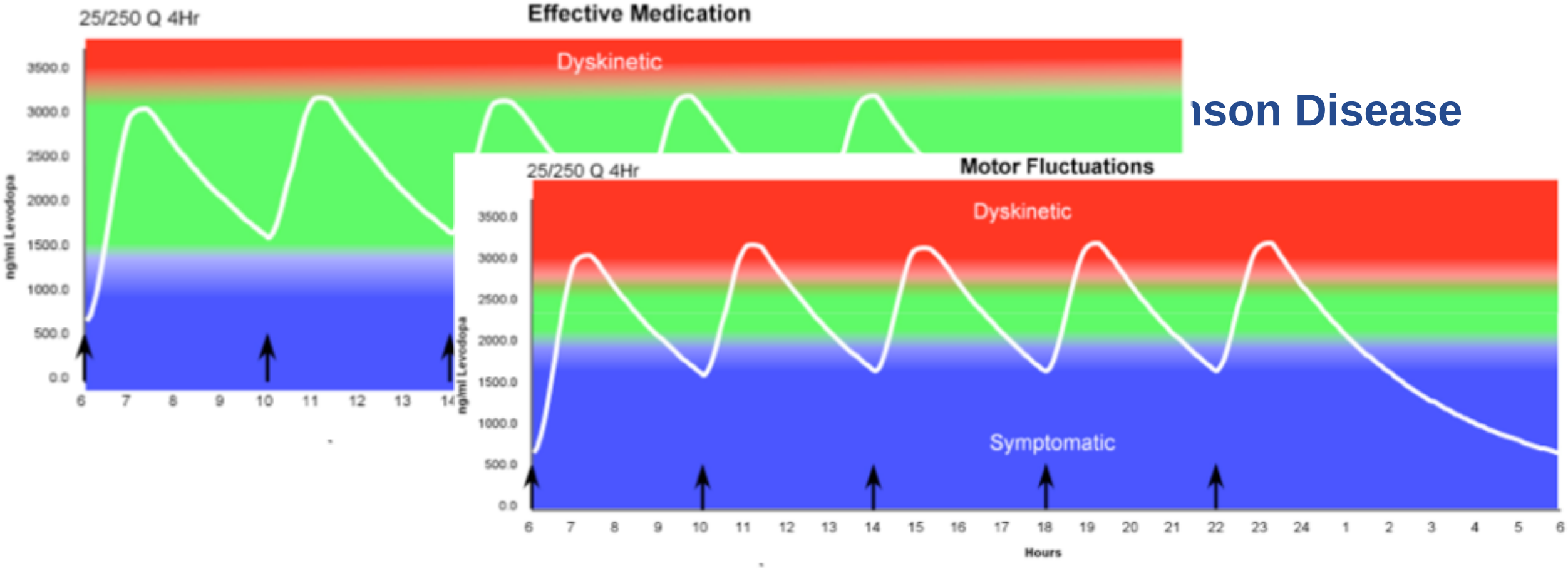
Symptomatic Treatment: Motor

Dopamine replacement

- Levodopa
  - Carbidopa reduces nausea: **Sin + emet IR**
  - Half-life ~ 1.5 hours
  - More effective in reducing motor symptoms
    - Ropinirole (class I)
    - Pramipexole (class I)
    - Pergolide (class I)

Motor fluctuations

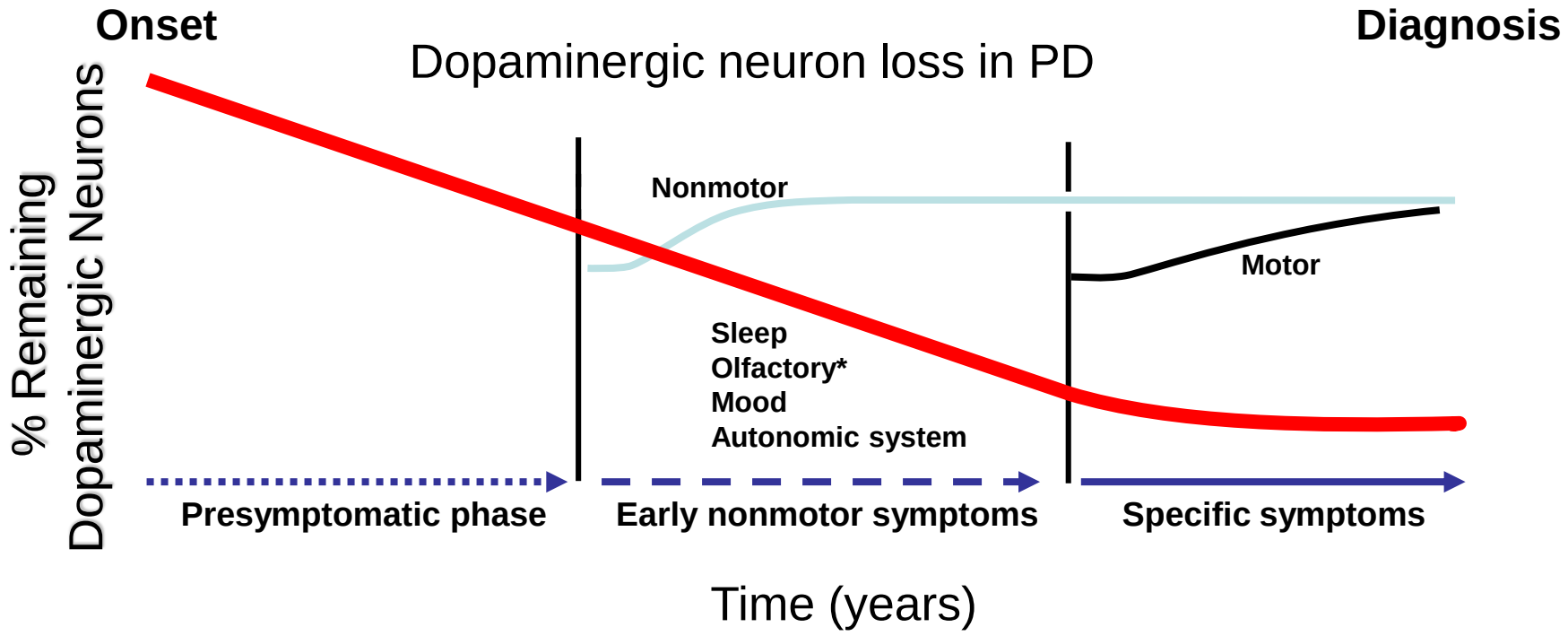
Early Parkinson Disease



http://people.virginia.edu/~rf3y/Elias/Motor_Fluctuations.html

Symptomatic Treatment: **Motor**

Dopamine replacement

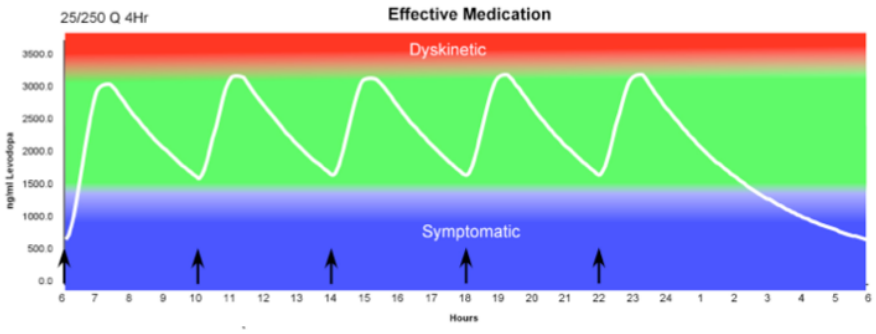


***Olfactory dysfunction may predate clinical PD by at least 4 years.**

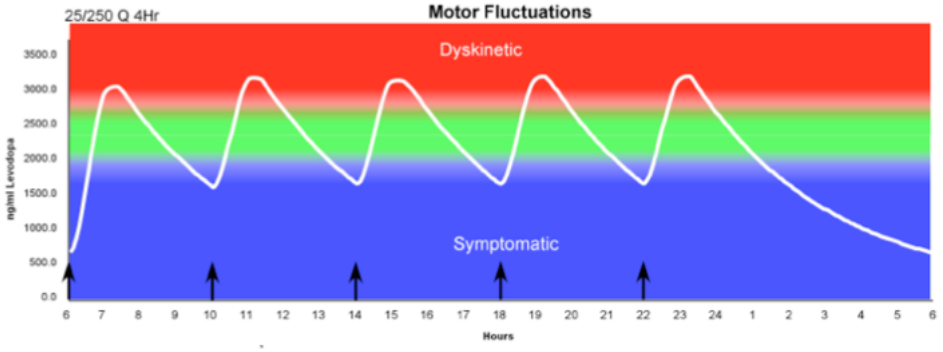
Halperin et al. *Neurotherapeutics*. 2009;6:128-140.

Motor fluctuations

Early Parkinson Disease



Later Parkinson Disease

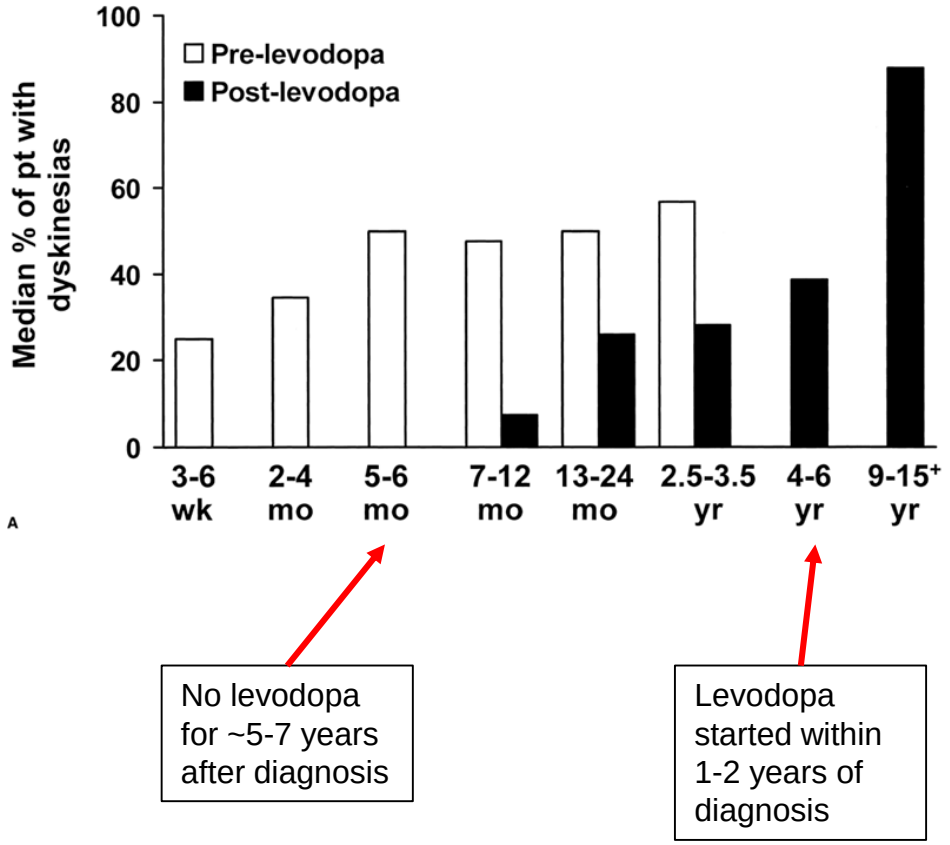


Does using levodopa earlier in the course of disease cause you to get levodopa-induced dyskinesia earlier?

Does using levodopa earlier in the course of disease cause you to have “wearing-off” earlier than if you delay treatment?

http://people.virginia.edu/~rf3y/Elias/Motor_Fluctuations.html

When do levodopa-induced dyskinesias occur?

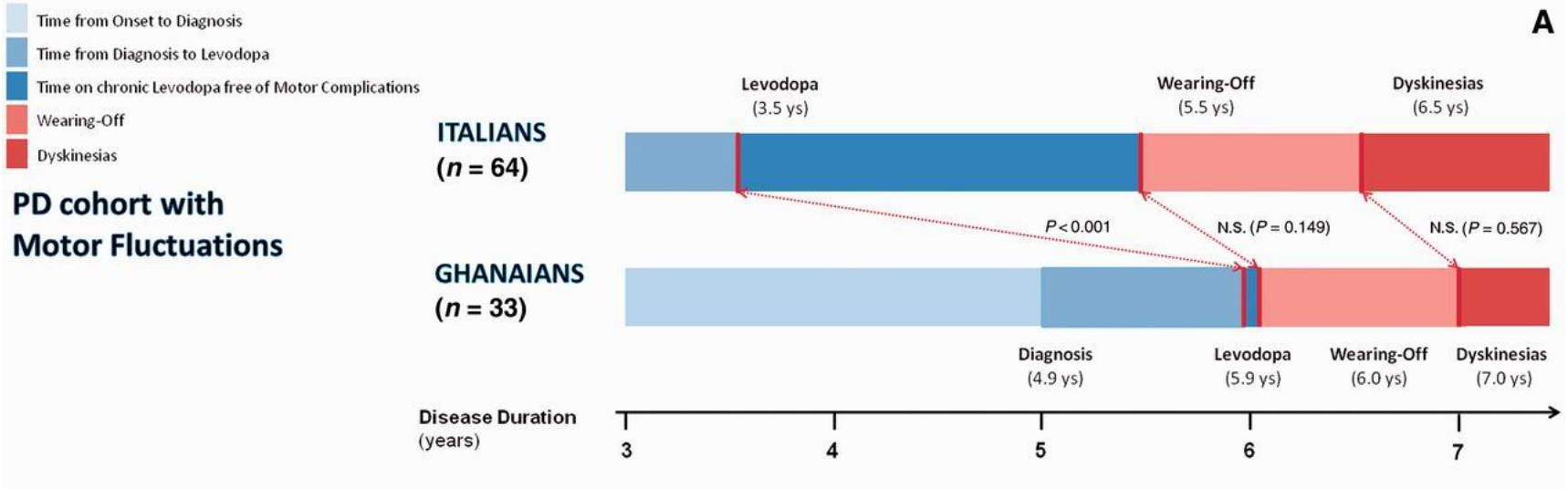


Some of the risk depends on **how long you have had PD not how long you take levodopa**

Alshkog et al. Movement Disorders. 2001. 16(3):448-458

Symptomatic Treatment: Motor

Levodopa-induced **dyskinesias**



Much of the dyskinesia risk depends on how long you have had PD

Cilia et al. Brain. 2014 Oct;137(Pt 10):2731-42.

Symptomatic Treatment: Motor

Levodopa-induced **dyskinesias**

"The present study provides evidence that motor fluctuations and dyskinesias are not associated with the duration of exposure to levodopa therapy, but rather to disease progression itself….

Therefore, there **is no reason to delay the initiation of adequate levodopa therapy** in patients with Parkinson's disease. In contrast with past drug trials, **recent experimental studies** suggest that the best therapeutic option to delay the molecular changes in gene expression, synaptic morphology and abnormal corticostriatal connectivity associated with dyskinesias may be early initiation of levodopa treatment (Marin et al., 2009)"

Cilia et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain 2014. e-pub

Case #3

- 57 y/o F with PD for 7 years
- Levodopa wears-off after 2.5 hours
- Has bothersome dyskinesia when levodopa is working
- Treatments
  - Entacapone worsened dyskinesa
  - Pramipexole and ropinirole caused sedation at work
  - Trihexyphenidyl caused cognitive impairment

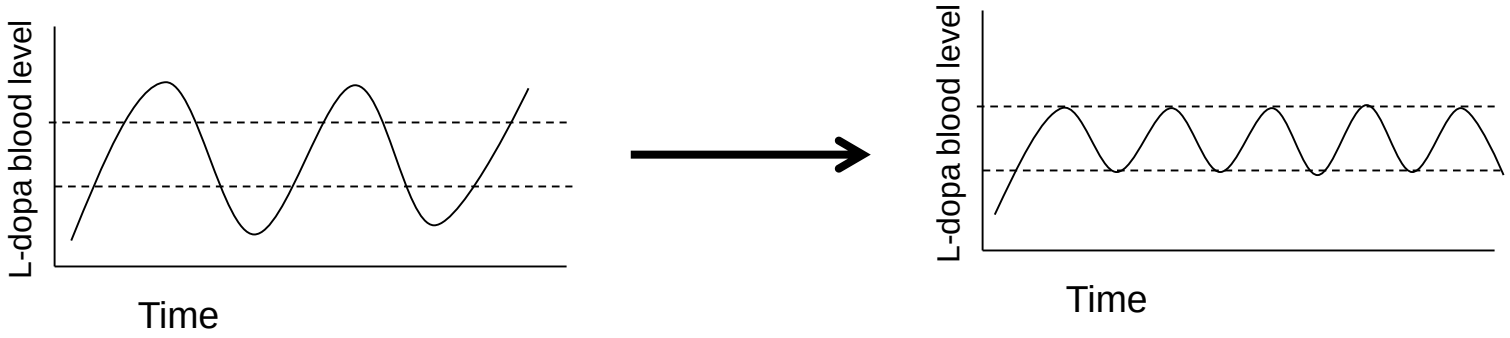
- Reason for consultation:
  - **My neurologist recommended that I consider Deep Brain Stimulation (DBS) or levodopa infusion therapy (Duopa). I've heard Deep Brain Stimulation (DBS) is for when you are only "really advanced" and I don't feel that bad. Should I consider it?**

Misconception

Oral Management of motor complications

"Wearing-off" and dyskinesia

- Smaller doses of dopamine replacement, more frequently



- Extenders
  - COMT inhibitors: entacapone (Stelevo), opicapone, tolcapone
  - MAO-B Inhibitors: rasagaline, selegiline

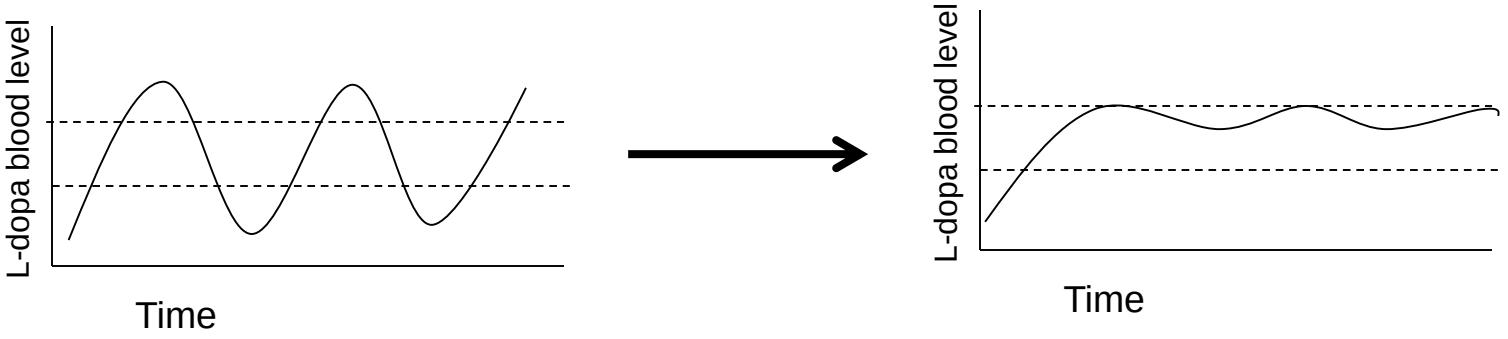
- Adjunctive therapy:
  - dopamine agonist: pramipexole, ropinirole, rotigotine
  - Rescue therapy: Apokyn injection, Apokyn ODT, Inbrija
  - Amantadine, anticholinergics (trihexyphenidyl)

Advanced treatment of “motor complications”

- Deep brain stimulation
- More continuous levodopa
  - Duopa

Deep Brain Stimulation

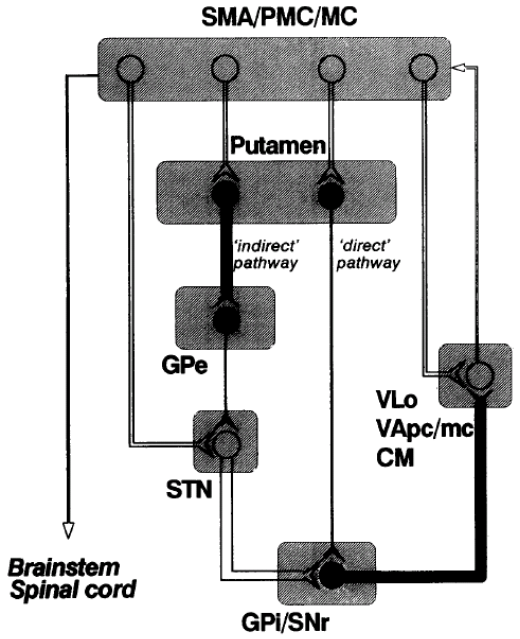
- Goals:
  - Reduce motor fluctuations

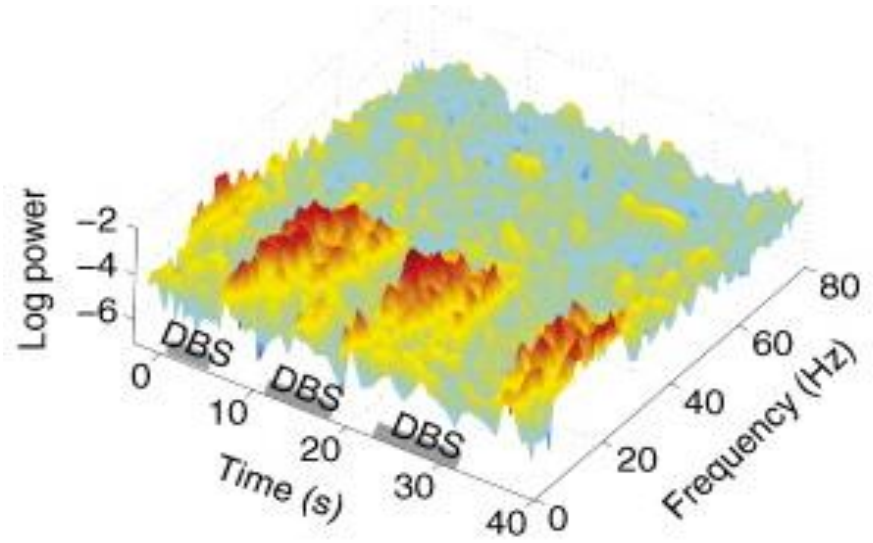


  - Medication-refractory tremor

DBS: Mechanism

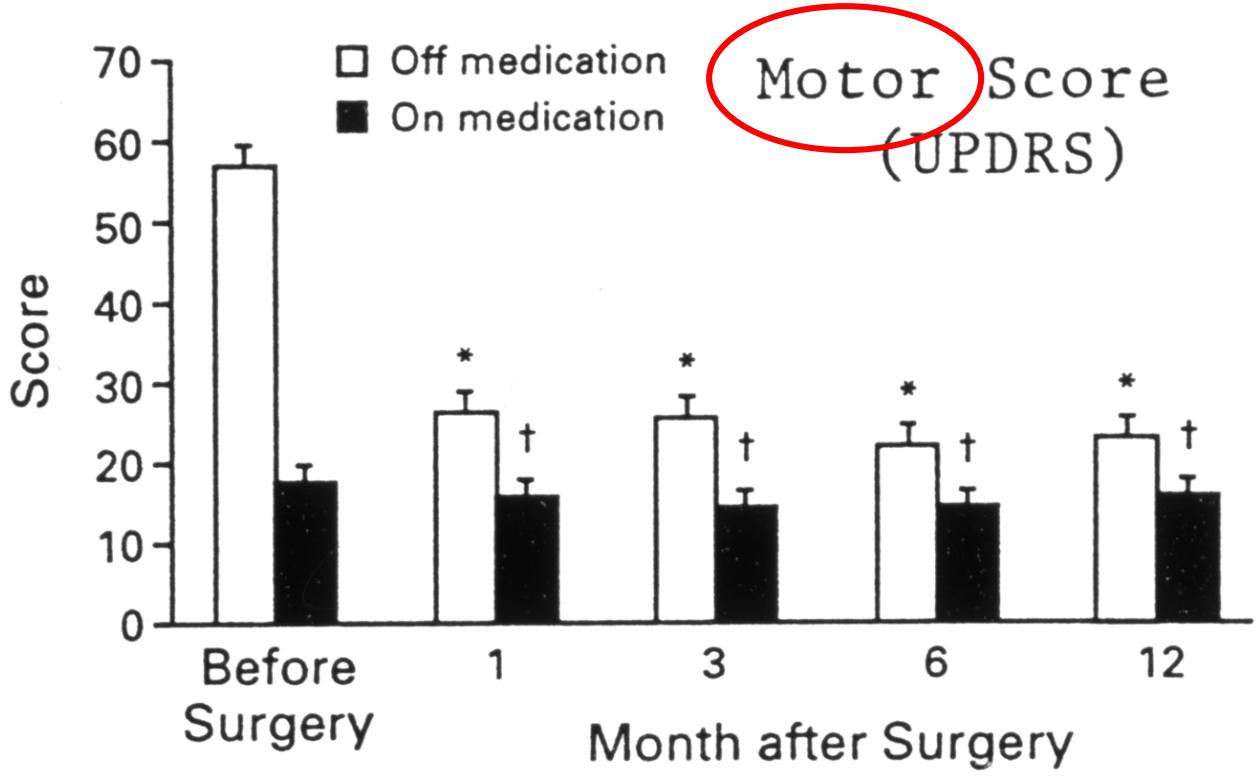
- How does it work?
  - Problematic brain arrhythmia
  - Stimulation “disrupts” arrhythmia





DBS: Efficacy

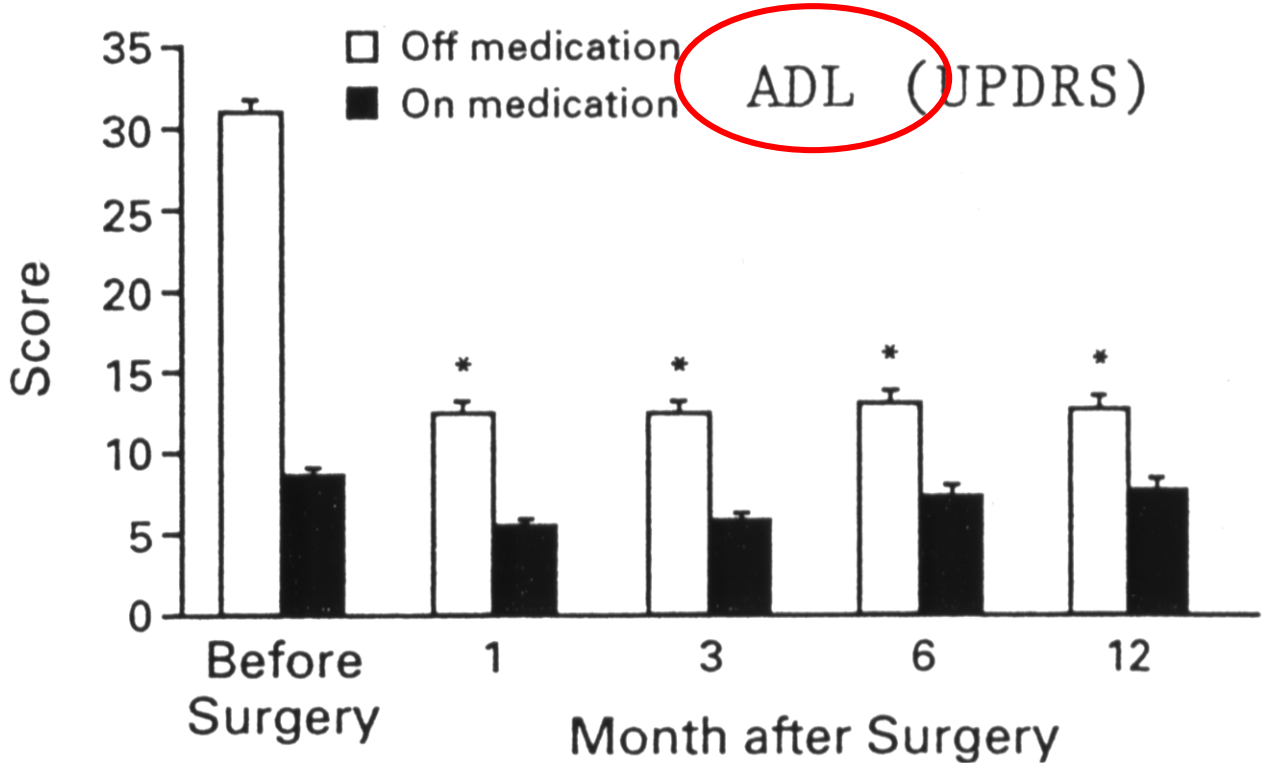
- Does it help?



Limousin et al., NEJM, 1998

DBS: Efficacy

- Does it help?



Limousin et al., NEJM, 1998

Surgical symptomatic treatment: Motor

Deep Brain Stimulation

Current Medications:

	0430	0700	0900	1100	1200	1300	1400	1500	1600	1700	1800	19:15	21:30	2300	0230
c/l IR 25/100	1.5	1.0	1.5	1.5	1.0	1.0	1.0	1.0	1.0*	1.0	1/2	1.0*	0.5	1/2	1.0
c/l CR 25/100	1													1	
Pramipexole 1 mg	1		1					1		1		1			
rasagaline 1 mg	1														

* booster dose of 1/2 Sinemet IR 25/100

15 doses / day

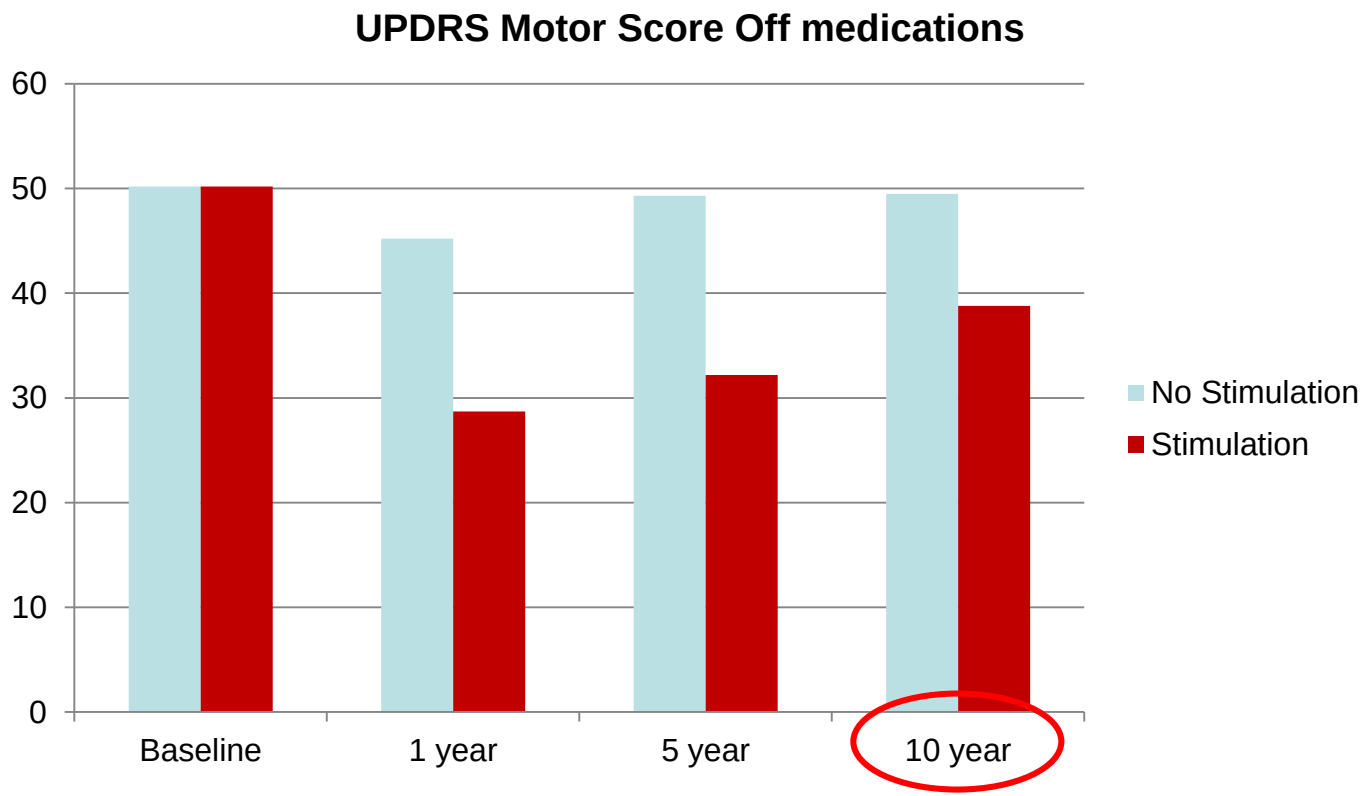
Patient's Medication List:

Medicine/Time 8-11-15	5:00 am	7:00 am	9:00 am	11:00am	12 pm	1:00 pm	2:00 pm	3:00 pm	4:00 pm	5:00 pm	6:00 pm	7:30 pm	9:00 pm-	11 pm-	11:30 am AN	2:30 am -
Rytary (48.75/195 MG)	3.0-		-	3.0					3:00			-	3:00	-	-	-
	-				-	-						-	-	-		
Azilect (1MG)	1.0															
Mirapex (1 MG)	1.0		1.0			-	1.0	-	-	-	1.0	-	-	-		
Sinamet (25/100 MG)	-	-	1.0-	1.0	-	-	1.0	-	1.0		1.0	-	0.5	0.5-	-	1.0
	-	-			-	-		-		-		-			-	

7 doses / day

DBS: Effect Duration

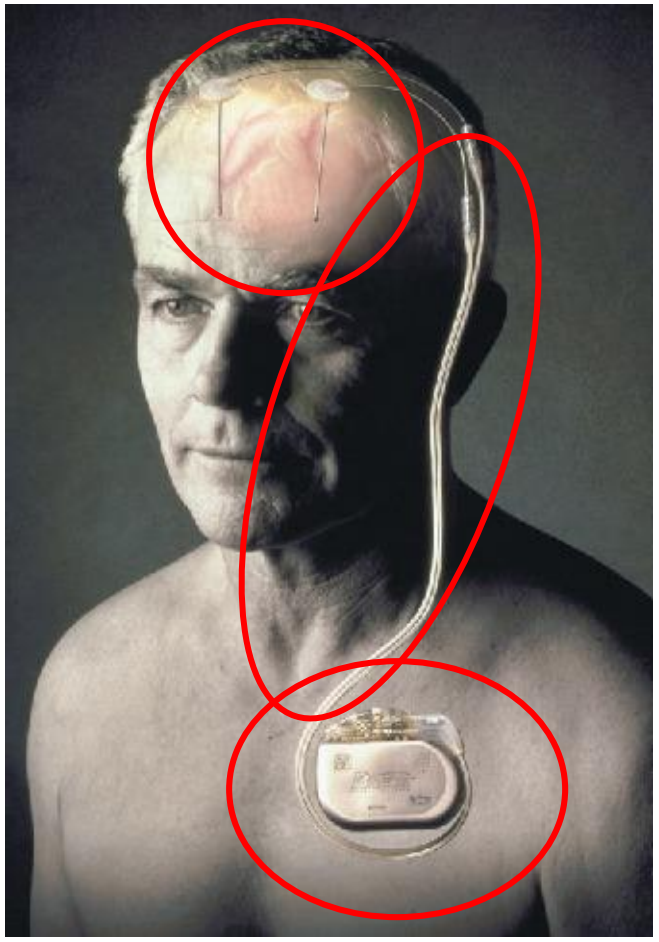
- How long does it work?



Adapted from Castrioto etal., Mov Dis, 2012

DBS: Device

- What is it?
  - Implantable Pulse Generator (**IPG**) → battery and computer
  - **Lead extenders** → under skin from IPG to brain leads
  - **Brain leads** → go from under skin through skull into deep brain target

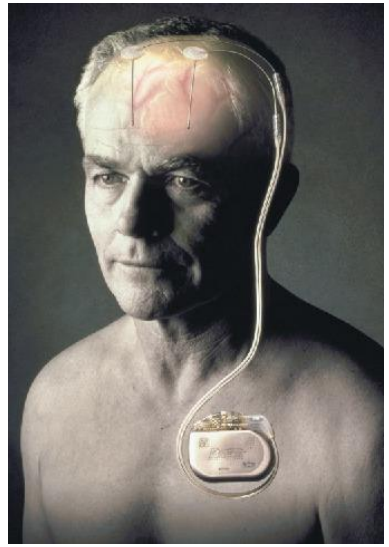


DBS: Programming

DBS: Candidate selection

- Who is a good candidate?
  - Idiopathic Parkinson disease
  - Symptoms that respond to levodopa but:
    - **Fluctuations** (wearing-off)

      And/or
    - **Dyskinesias**
  - Little or no cognitive impairment (dementia)
  - Healthy surgical candidate



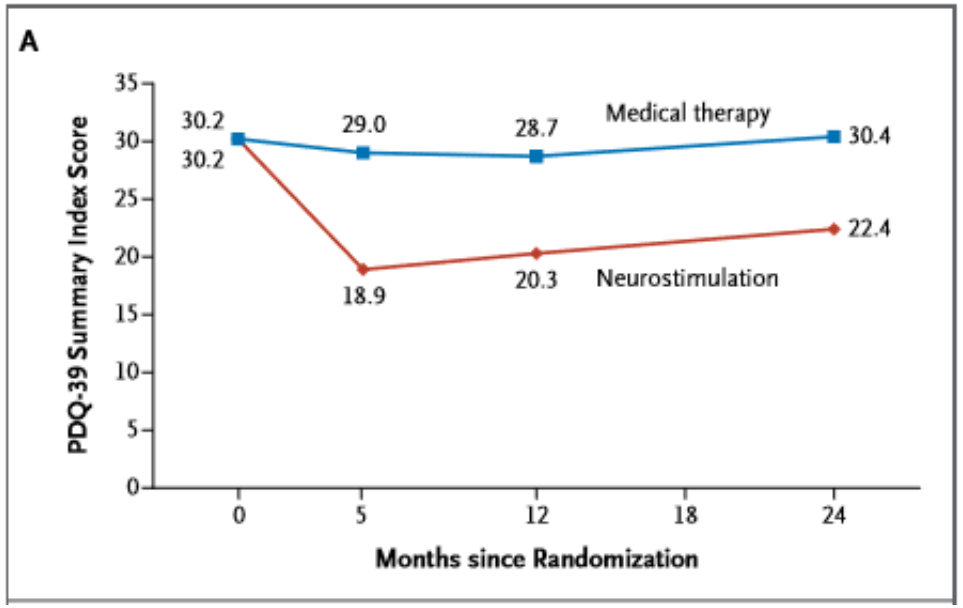
DBS: Candidate selection

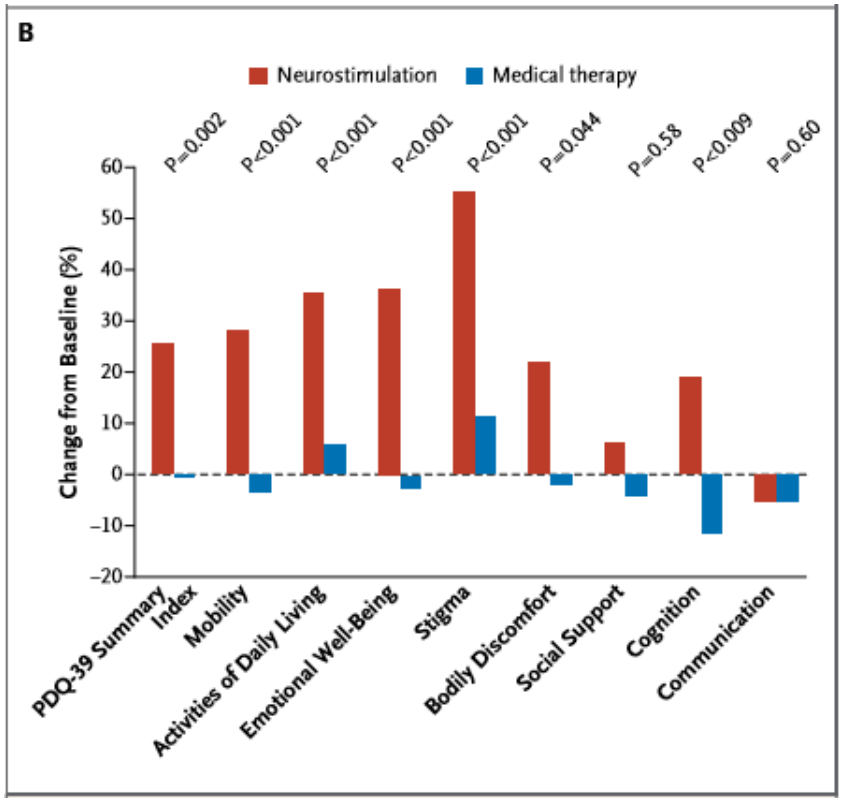
- Who is NOT a good candidate?
  - Dementia or severe cognitive impairment
  - Major psychiatric issues
  - Substantial medical problems

- Factors making it less likely to succeed
  - Mainly gait symptoms, no levodopa response
  - Little or no levodopa response
  - Poor social support or ability to return for programming

DBS: Timing

- EARLYSTIM trial → 4 years or more of PD, early motor complications
  - Quality of life better with DBS than medical therapy
  - Largest improvements in ADL function, emotional well-being, and stigma





Schupach et al. NEJM 2013;368:610-22

DBS: Timing

- EARLYSTIM trial
  - Adverse events

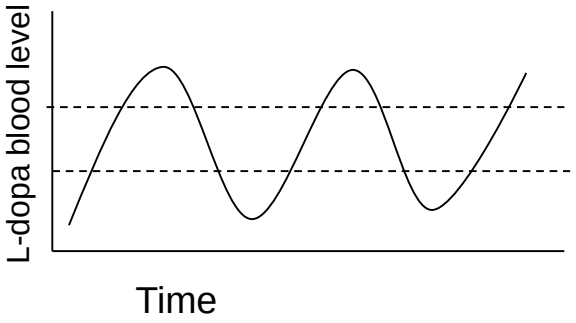
Balance benefit against risks

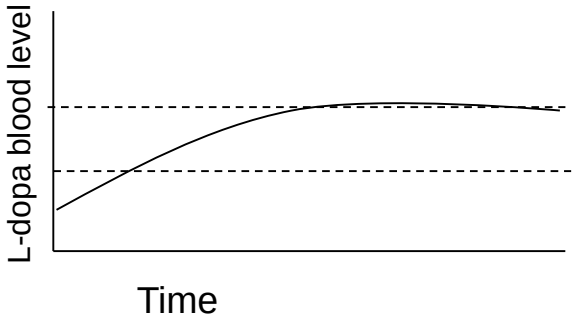
Table 3. Adverse Events.*

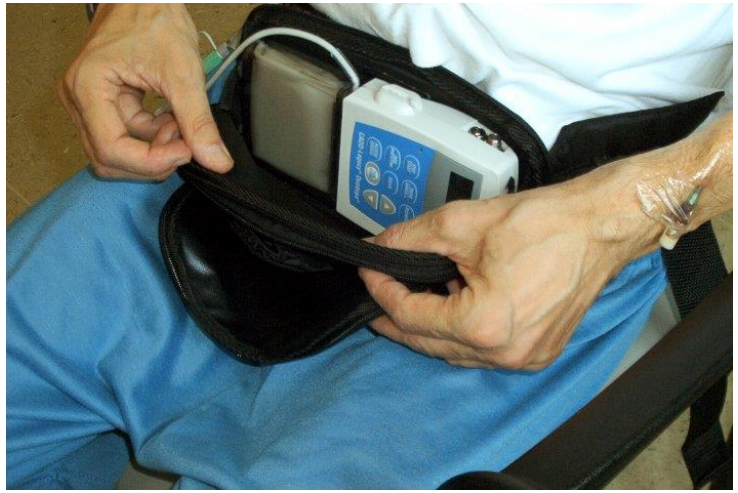
Event	Neurostimulation (N=124)		Medical Therapy (N=127)	
	no. of events	*no. of patients with event (%)*	*no. of events*	*no. of patients with event (%)*
Serious adverse events	123	68 (54.8)	128	56 (44.1)
Death, all by suicide	2	2 (1.6)	1	1 (0.8)
Life-threatening event	14	12 (9.7)	17	9 (7.1)
Event related to medication or stimulation	24	24 (19.4)	52	38 (29.9)
Worsening of mobility†	5	5 (4.0)	13	11 (8.7)
Motor fluctuations	0	0	7	7 (5.5)
Dyskinesia	1	1 (0.8)	2	2 (1.6)
Psychosis or hallucinations	0	0	8	6 (4.7)
Anxiety	0	0	3	2 (1.6)
Impulse control disorder	1	1 (0.8)	5	5 (3.9)
Depression	6	6 (4.8)	3	1 (0.8)
Suicidal ideation	1	1 (0.8)	0	0
Suicide attempt	2	2 (1.6)	2	2 (1.6)
Cardiac disorder	0	0	2	2 (1.6)
Injury	3	3 (2.4)	0	0
Respiratory or thoracic disorder	1	1 (0.8)	0	0
Other	4	4 (3.2)	7	5 (3.9)
Event related to surgery or device	26	22 (17.7)	—	—
Impaired wound healing	4	4 (3.2)	—	—
Intracerebral abscess or edema	2	2 (1.6)	—	—
Dislocation of device‡	5	4 (3.2)	—	—
Reoperation necessary§	4	2 (1.6)	—	—
Other	11	10 (8.1)	—	—
Event related to Parkinson's disease	57	39 (31.5)	58	31 (24.4)

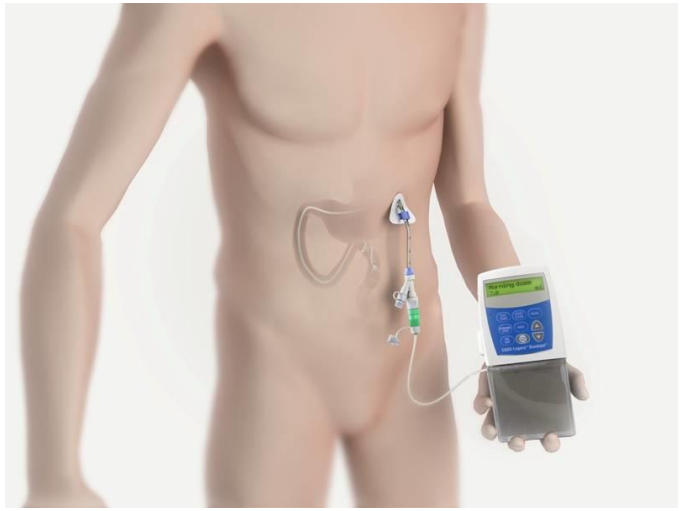
Schupach et al. NEJM 2013;368:610-22

Carbidopa/levodopa enteral suspension (Duopa)



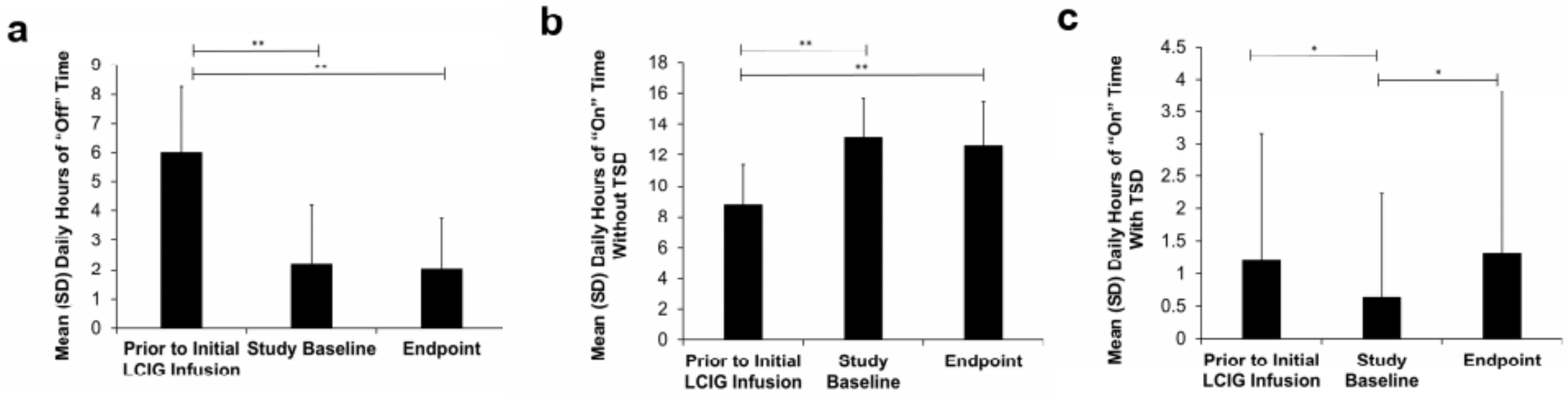






Carbidopa/levodopa enteral suspension (Duopa)

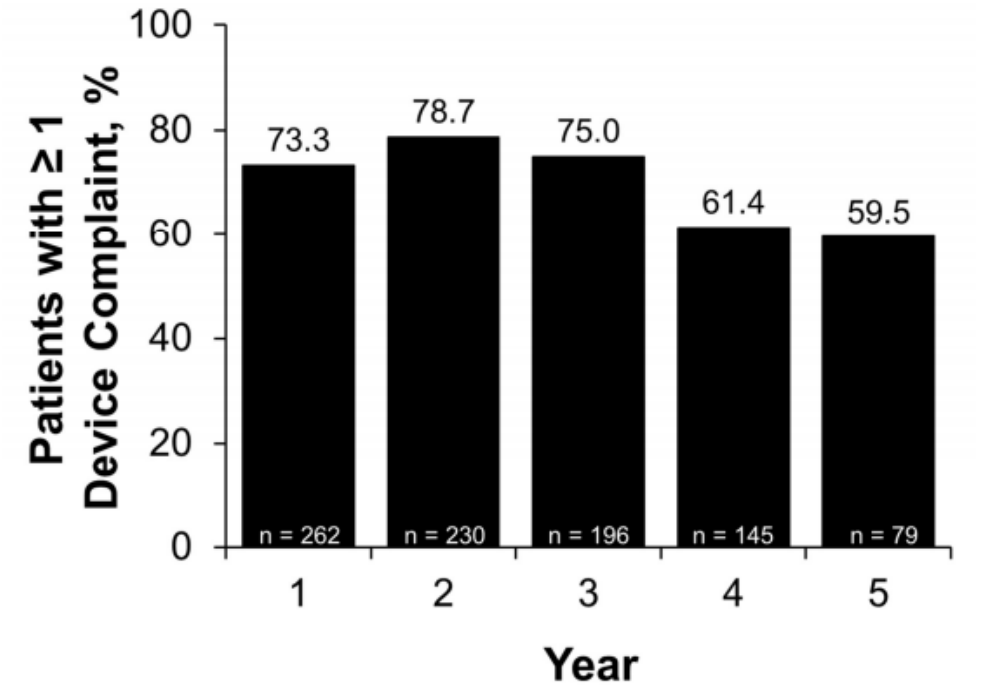
- Long-term outcomes at 52 weeks: Benefits

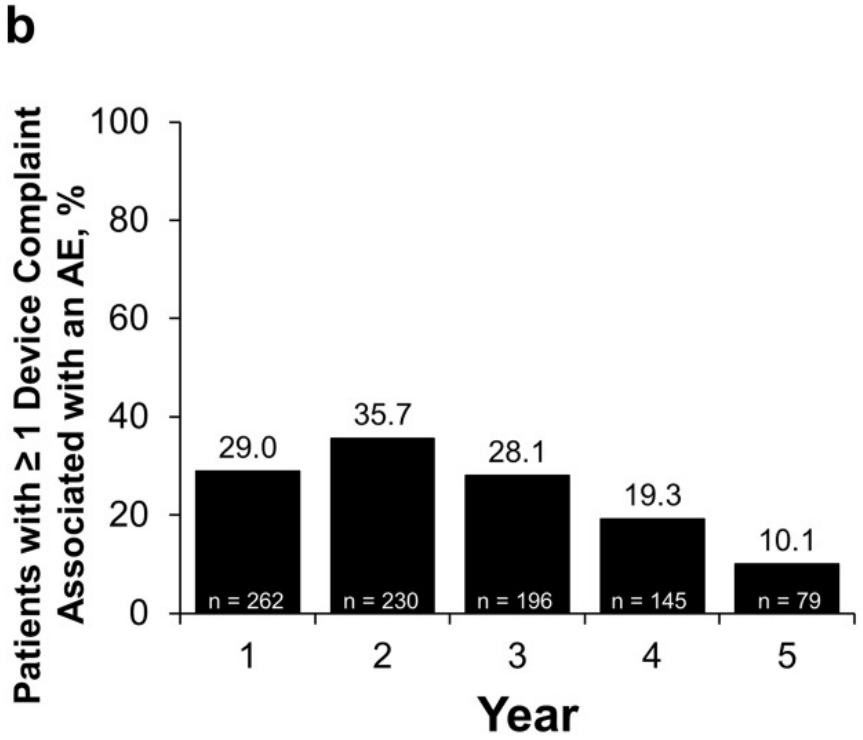


Fernandez et al. Movement Disorders. 2018; 33(6):928-936

Carbidopa/levodopa enteral suspension (Duopa)

- Long-term outcomes at 52 weeks: Adverse Events





Fernandez et al. Movement Disorders. 2018; 33(6):928-936

Questions?

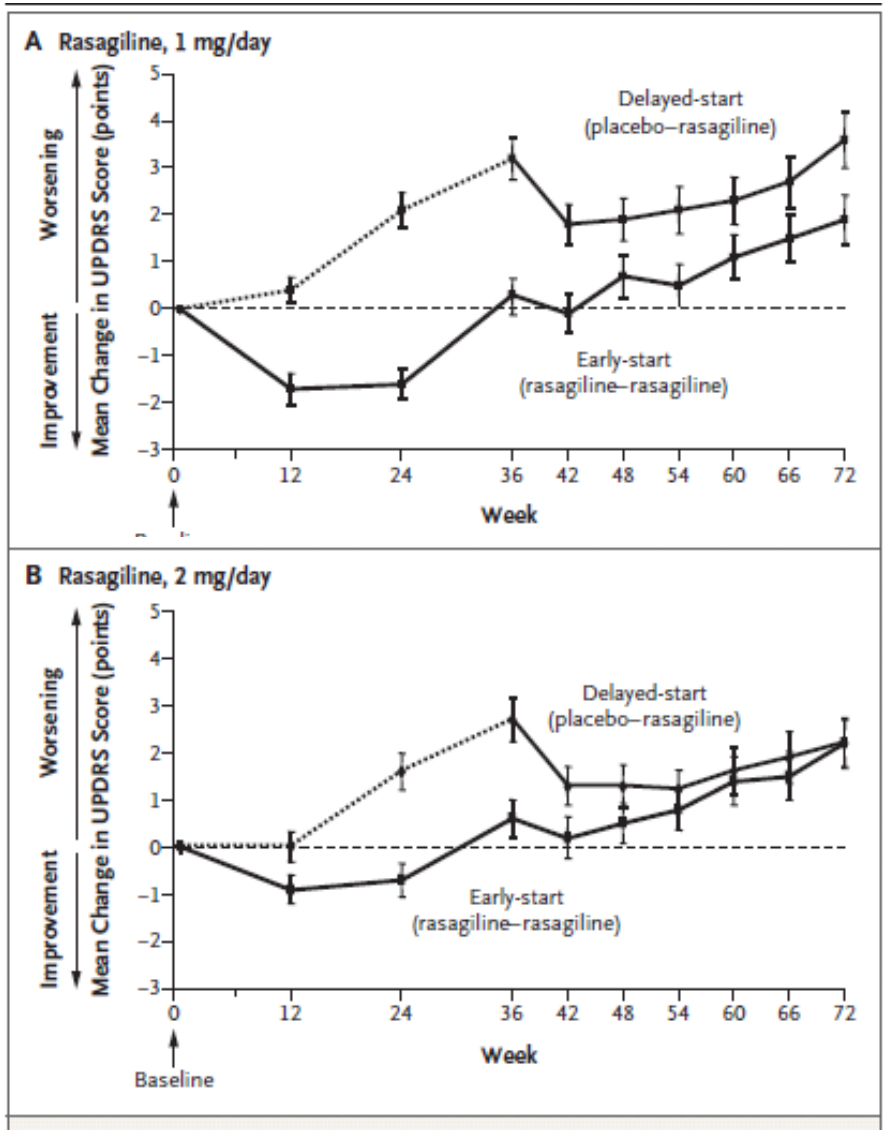
- Need advice?
- Parkinson Foundation of the NCA (parkinsonfoundation.org)
- National Parkinson Foundation (NPF.org)
- Michael J. Fox Foundation (MJFF.org)
- Call 410-502-0133 ask for Chelsea
  - Advice on referrals
  - Direct you to a local support group
  - Other questions

Thanks

Extra Slides

JOHNS HOPKINS
MEDICINE

Parkinson's "neuroprotection": Rasagaline (Azilect)

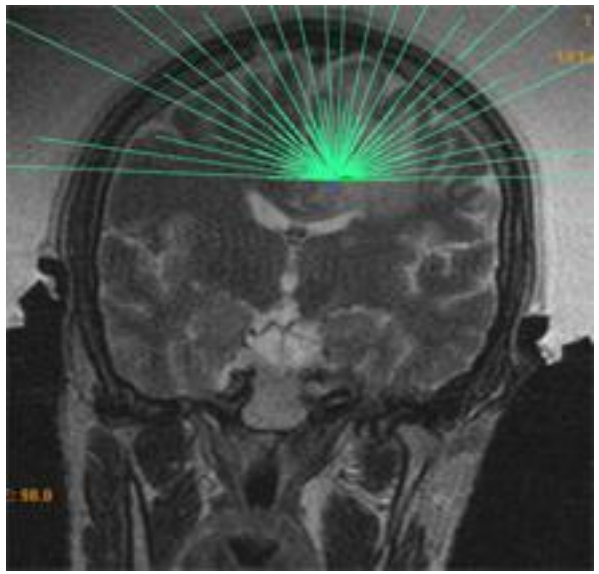


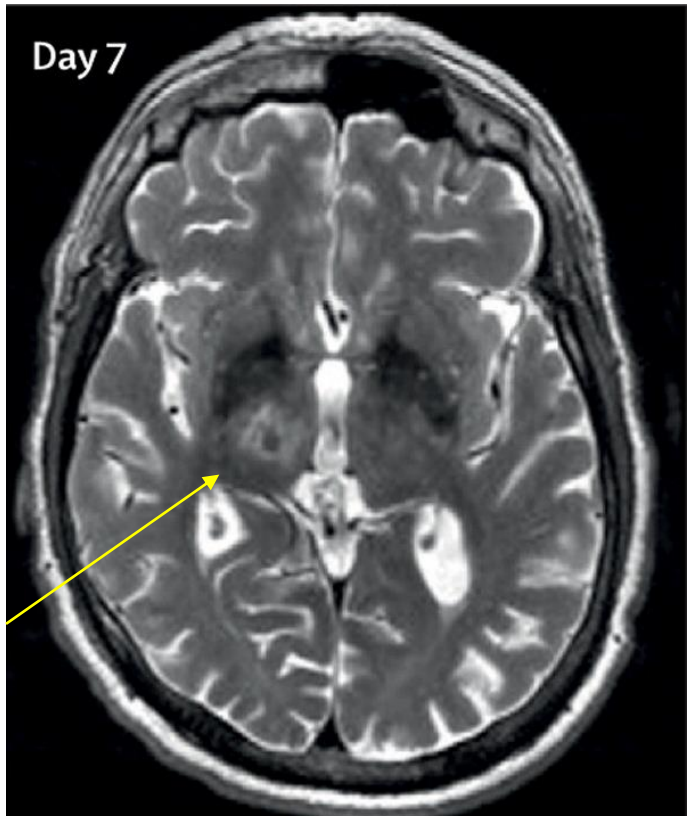
- **1 mg** a day: patients who had taken it retained a lower movement score after the placebo group had started
- **2 mg a day**: both groups ended up having *the same* movement score
- Consider
  - FDA did not approve for "neuroprotection"
  - Is improvement of 2 UPDRS points important to patients
  - $$ Cost $$

Olanow et al., NEJM, 2009

MRI-guided Focused Ultrasound

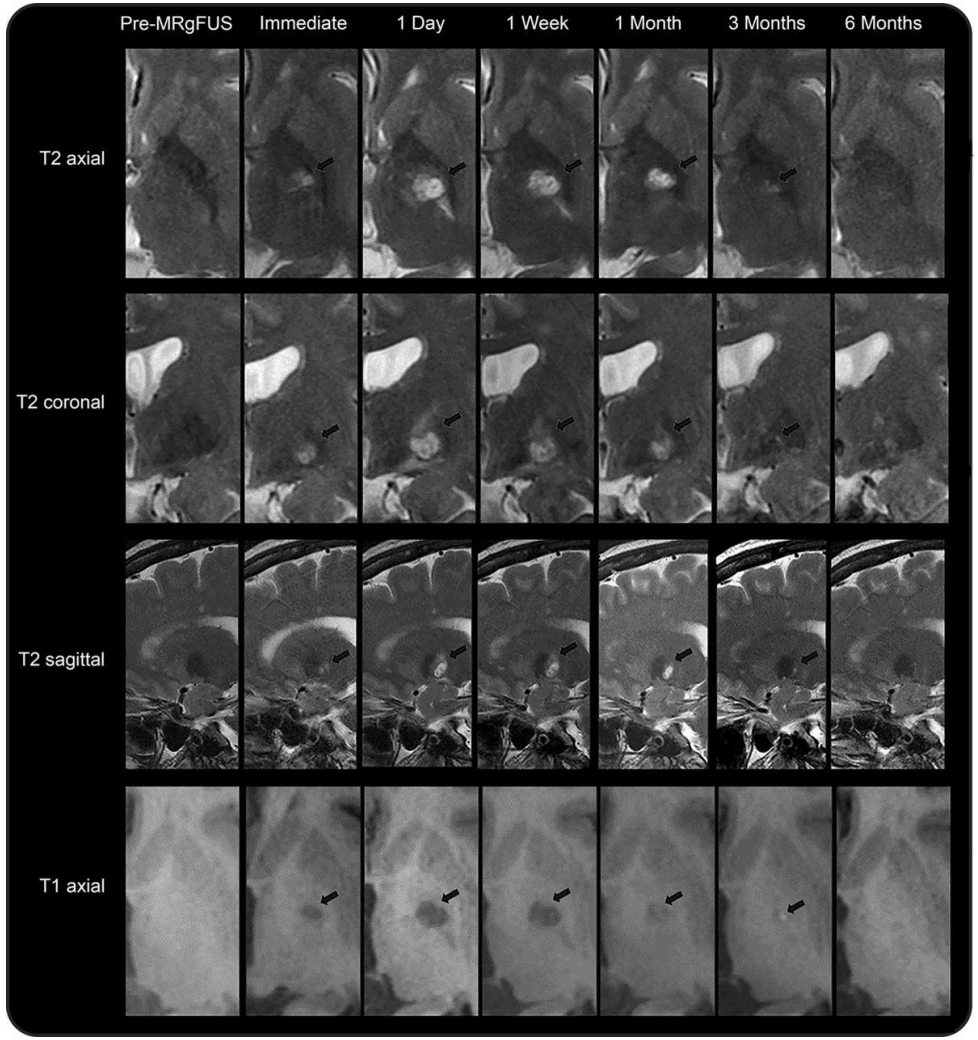
- Just FDA-approved for essential tremor
- NOT approved for PD





MRgFUS Pallidotomy in PD

- 1 patient
- 320 mm^3 ablated
- Bilateral PD
- UPDRS part III “off”
  - Baseline 31
  - 1 week -> 12
  - 1 month -> 12
  - 3 months -> 13
  - 6 months -> 14



Young Cheol Na et al. Neurology 2015;85:549-551