# Parkinson’s Disease: An Overview

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# Epidemiology

- Worldwide prevalence
  - 1% of population greater than 65 years
  - 3% of population greater than 85 years
  - 187/100,000
- US prevalence
  - 1.6% of population over 65
  - In MA = 860,000 x 1.6% = **13,760** people
- North American prevalence
  - ~1 million people
- Annual incidence (new cases) of 20/100,000

# Epidemiology

- M:F about 2:1
- Less common in blacks and Asians
  - HOWEVER, PD is generally not well studied in diverse populations
- Average onset age = 63
- 5-10% of people have symptoms < 45

# PD Projection

- In the most populous nations will double by 2030 from 4.3 million to 9.5 million worldwide.
- Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease
- Enormous public health challenge
- We need to plan for diagnosis, treatment and research purposes

Dorsey et al, Neurology 2007;68:384-386

# Cardinal Signs

- Onset of (at least 2):
  - Tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
    - **Later** in the course
- Typical asymmetrical
- Absence of another cause

# Probable & Possible Diagnostic Criteria

- Group A Features: Characteristic of Parkinson disease
  - Resting tremor
  - Bradykinesia
  - Rigidity
  - Asymmetric onset
- Group B features: suggestive of alternative diagnoses
- Features unusual early in the clinical course
  - Prominent postural instability in the first 3 years after symptom onset
  - Freezing phenomena in the first 3 years
  - Hallucinations unrelated to medications in the first 3 years
  - Dementia preceding motor symptoms or in the first year
  - Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
  - Severe symptomatic dysautonomia unrelated to medications
  - Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Gelb, Arch Neur. 1999

# MDS 2015 Revised Criteria

REVIEW

CME

## MDS Clinical Diagnostic Criteria for Parkinson's Disease


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**ABSTRACT:** This document presents the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease (PD). The Movement Disorder Society PD Criteria are intended for use in clinical research but also may be used to guide clinical diagnosis. The benchmark for these criteria is expert clinical diagnosis; the criteria aim to systematize the diagnostic process, to make it reproducible across centers and applicable by clinicians with less expertise in PD diagnosis. Although motor abnormalities remain central, increasing recognition has been given to nonmotor manifestations; these are incorporated into both the current criteria and particularly into separate criteria for prodromal PD. Similar to previous criteria, the Movement Disorder Society PD Criteria retain motor parkinsonism as the core feature of the disease, defined as bradykinesia plus rest tremor or rigidity. Explicit instructions for defining these cardinal features are included. After documentation of parkinsonism, determination of PD as the cause of parkinsonism relies on three categories of diagnostic features: absolute exclusion criteria (which rule out PD), red flags (which must be counterbalanced by additional supportive criteria to allow diagnosis of PD), and supportive criteria (positive features that increase confidence of the PD diagnosis). Two levels of certainty are delineated: clinically established PD (maximizing specificity at the



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**Funding agencies:** This study was supported by the work of the task force – i.e. meetings and tele-conferences – were supported by the MDS.

**Relevant conflicts of interest/financial disclosures:** Nothing to report.
Full financial disclosures and author roles may be found in the online version of this article.

**Received:** 3 April 2015; **Revised:** 30 July 2015; **Accepted:** 9 August 2015

**Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26424**

# Associated Problems - Early

- Loss of smell
- Depression/anxiety
- Sleep disturbance
  - REM behavior d/o
- Small handwriting
- Constipation
- Dizziness
- Urinary urgency
- Blurred vision/dry eyes
- Pain in shoulders/hip
- Dystonia

# How to Make the Diagnosis

- Clinical
  - Based on symptoms and exam findings
- Confirmatory tests
  - May be needed to evaluate for other diseases
    - MRI of brain or cervical spine, EMG (PD is NOT a "pinched nerve")
  - DaTscan SPECT
  - Skin biopsy
    - >90% sensitivity and specificity

The diagnostic discrimination of cutaneous α-synuclein deposition in Parkinson disease

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ABSTRACT

**Objective:** To determine the diagnostic discrimination of cutaneous α-synuclein deposition in individuals with Parkinson disease (PD) with and without autonomic dysfunction on autonomic testing, in early and late stages of the disease, and of short and long duration.

**Methods:** Twenty-eight participants with PD and 23 control participants were studied by skin biopsies at multiple sites, autonomic function testing, and disease-specific scales.

**Results:** Skin biopsies provide >90% sensitivity and >90% specificity to distinguish PD from control participants across all biopsies sites with quantification of either pilomotor or sudomotor α-synuclein deposition. All individuals with PD have significantly higher cutaneous α-synuclein deposition than control participants, even those individuals with PD and no evidence of autonomic dysfunction. Deposition of α-synuclein is most prominent in sympathetic adrenergic nerve fibers innervating the arrector pili muscles, but is also present in sudomotor (sympathetic cholinergic) nerve fibers. α-Synuclein is present even in the early stages of disease and disease of short duration. α-Synuclein ratios were higher in individuals with autonomic failure, with more advanced stages of disease and disease of longer duration.

**Conclusions:** The α-synuclein ratio provides a sensitive and specific diagnostic biomarker of PD even in patients without autonomic failure.

**Classification of evidence:** This study provides Class III evidence that cutaneous α-synuclein deposition accurately identifies patients with PD. *Neurology*® 2016;87:505–512

GLOSSARY

**H&Y** = Hoehn & Yahr; **IENFD** = intraepidermal nerve fiber density; **MDS-UPDRS** = Movement Disorders Society Unified Parkinson's Disease Rating Scale; **PD** = Parkinson disease; **PD-AF** = Parkinson disease with autonomic failure; **PD-NAF** = Parkinson disease with no autonomic failure; **PGP 9.5** = protein gene product 9.5; **PMNFD** = pilomotor nerve fiber density; **ROC** = receiver operating characteristic; **SGNFD** = sweat gland nerve fiber density.

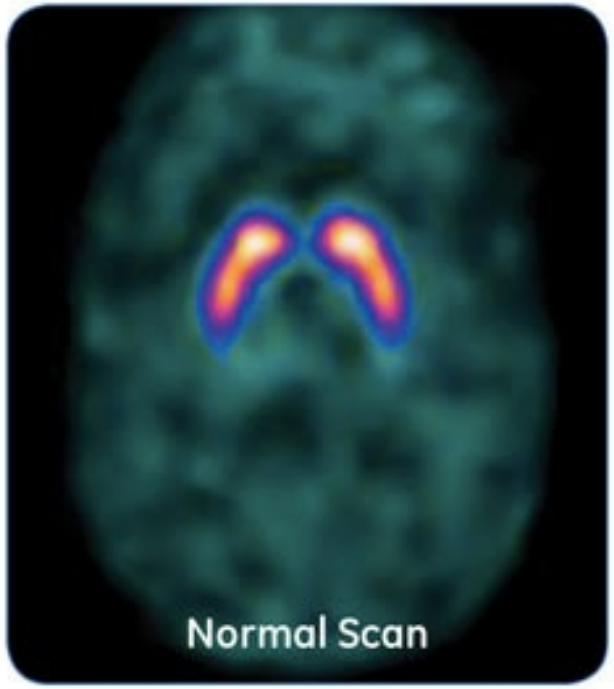
Parkinson disease (PD) is characterized clinically by motor manifestations that include tremor, rigidity, and bradykinesia and pathologically by the deposition of α-synuclein within Lewy bodies and Lewy neurites.[1]

We, and others, have recently reported that deposition of α-synuclein can be detected within cutaneous autonomic nerve fibers using the punch biopsy technique.[2–5] In a prior study, using an antibody that measured total (both phosphorylated and native) α-synuclein, we observed high amounts of α-synuclein deposition in all individuals with PD and low amounts of α-synuclein deposition in healthy control participants. The α-synuclein deposition correlates with measures of sympathetic adrenergic and cardiac parasympathetic function.[2,3] But it is still not known whether the utility of cutaneous α-synuclein deposition as a biomarker in PD is restricted to those patients with PD who have autonomic dysfunction. Further, because clinically significant autonomic dysfunction usually (although not always) occurs late in the course of PD,[6,7] we also sought to define the relationship between cutaneous α-synuclein deposition disease severity and disease duration. We therefore studied a new cohort of participants with PD with a broad range of disease duration, severity, and autonomic dysfunction with the following prospective aims: to determine the diagnostic discrimination of cutaneous α-synuclein deposition in individuals with

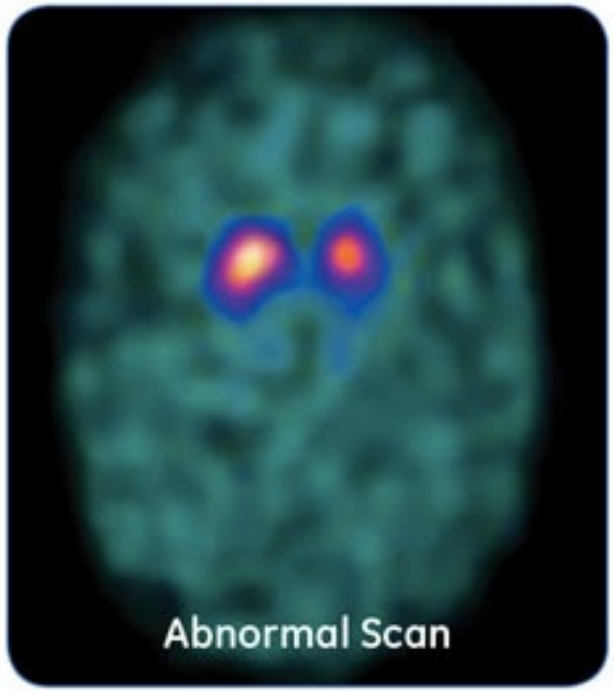
Supplemental data at Neurology.org

From the Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

# DaTscan




"Comma"-shaped
Possible essential tremor




"Period"-shaped
Possible parkinsonian syndrome

# What Causes Parkinson's Disease?

- Unknown
- Probable combination of factors:
  - Genetic (<10% of cases)
  - Toxic
  - Infectious
  - Other/unknown
- First degree relatives have increased risk of developing PD in their lifetime.

# Various Inheritance Patterns

| | |
|---|---|
| Autosomal recessive (11 genes) | • *ATP13A2*, *DNAJC6*, *FBXO7*, *PRKN/PARK2*, *PARK7*, *PINK1*, *PLA2G6*, *SLC6A3*, *SPR*, *SYNJ1*, *VPS13C* |
| Autosomal dominant (4 genes) | • *CHCHD2*, *LRRK2*, *SNCA*, and *VPS35* |
| X-linked recessive (2 genes) | • *RAB39B* and *TAF1* |
| AD or AR | • Pathogenic variants in *GCH1* |
| Susceptibility genes | • *GBA and MAPT*, *EIF4G1*, *GIGYF2*, *HTRA2*, *UCHL1* |

Source: Prevention Genetics

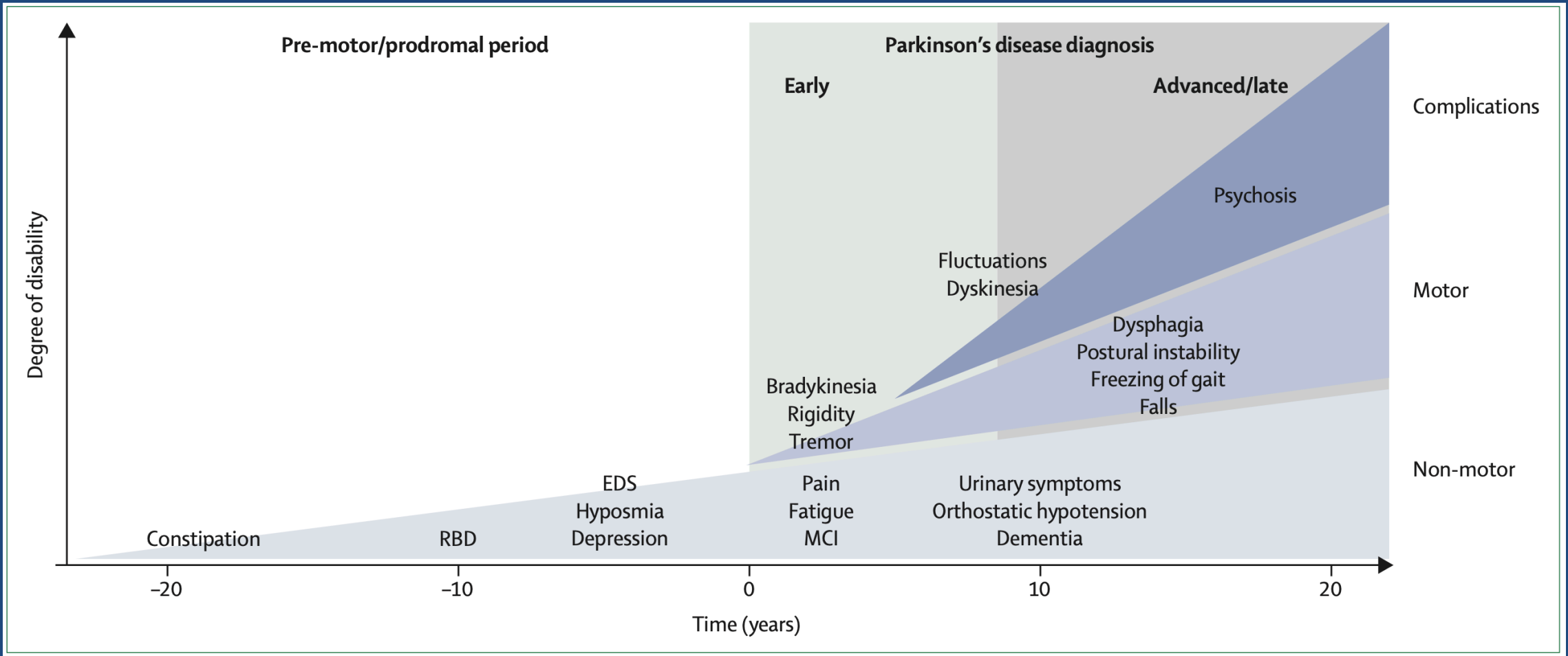
# Some Causes of "Parkinsonism"

- Drugs
  - Anti-psychotics
  - Anti-nausea
  - Illicit drugs
- Multi-Systems Atrophy
  - Shy-Drager
  - Striato-nigral degen.
  - OPCA
- Progressive Supranuclear Palsy
- CBGD
- Vascular disease
- Dementia with Lewy Bodies
- Normal Pressure Hydrocephalus
- Wilson's disease
- Huntington's disease
- Alzheimer's Disease
- Dystonia
- Structural lesion

# PD vs. ET

- James Parkinson:
  - “In the real Shaking Palsy, the agitation continues full force whilst the limb is at rest and unemployed; and even if sometimes diminished by calling the muscles into employment.”
- He noted tremors liable to be confused include those due to alcohol abuse, tea and coffee abuse, and old age.

# Time Course of PD Progression




Kalia & Lang Lancet 2015

# Non-motor Symptoms of PD

**Psychiatric**

- Mood disturbance
  - Depression
  - Agitation
  - Anxiety and panic attacks
- Dementia
- Hallucinations
- Delirium

**Autonomic**

- Orthostatic hypotension
- Constipation
- Urinary problems
- Sexual problems
- Sweating and thermoregulation

**Sleep disorders**

- Parasomnias
  - REM Sleep behavior disorder
- Insomnia – maintenance or early awakening
- Sleep fragmentation
- Restless legs syndrome
- PLMS
- Excessive daytime sleepiness
- Sudden onset of sleep

**Sensory**

- Hyposmia
- Pain
- Paresthesias
- Altered sensation
- Restless legs

# FDA-Approved Medications for PD

- Carbidopa/levodopa
  - Sinemet®
    - (10/100), 25/100, 25/250
  - Sinemet CR®
    - 25/100, 50/200
  - Rytary®
  - Stalevo® (carbidopa/levodopa/entacapone)
  - Duopa®
  - Parcopa® (dissolvable carbidopa/levodopa)
  - Inbrejia®
- COMT Inhibitors
  - Entacapone
  - Tolcapone
  - Opicapone
- Dopamine agonists
  - Ropinirole (and XL)
  - Pramipexole (and ER)
  - Rotigotine (topical patch)
  - Apomorphine (injectable and SL)
- MAOB Inhibitors
  - Selegiline
  - Zydis® selegiline
  - Rasagiline
  - Safinamide
- Anti-cholinergic
  - Trihexyphenidyl
  - Benztropine
- Amantadine
  - Immediate release
  - GoCovri®
  - Osmolex ER®
- Adenosine A2A Receptor Antagonist
  - Istradefylline
- Other
  - Rivastigmine
  - Pimavanserine
  - Droxidopa

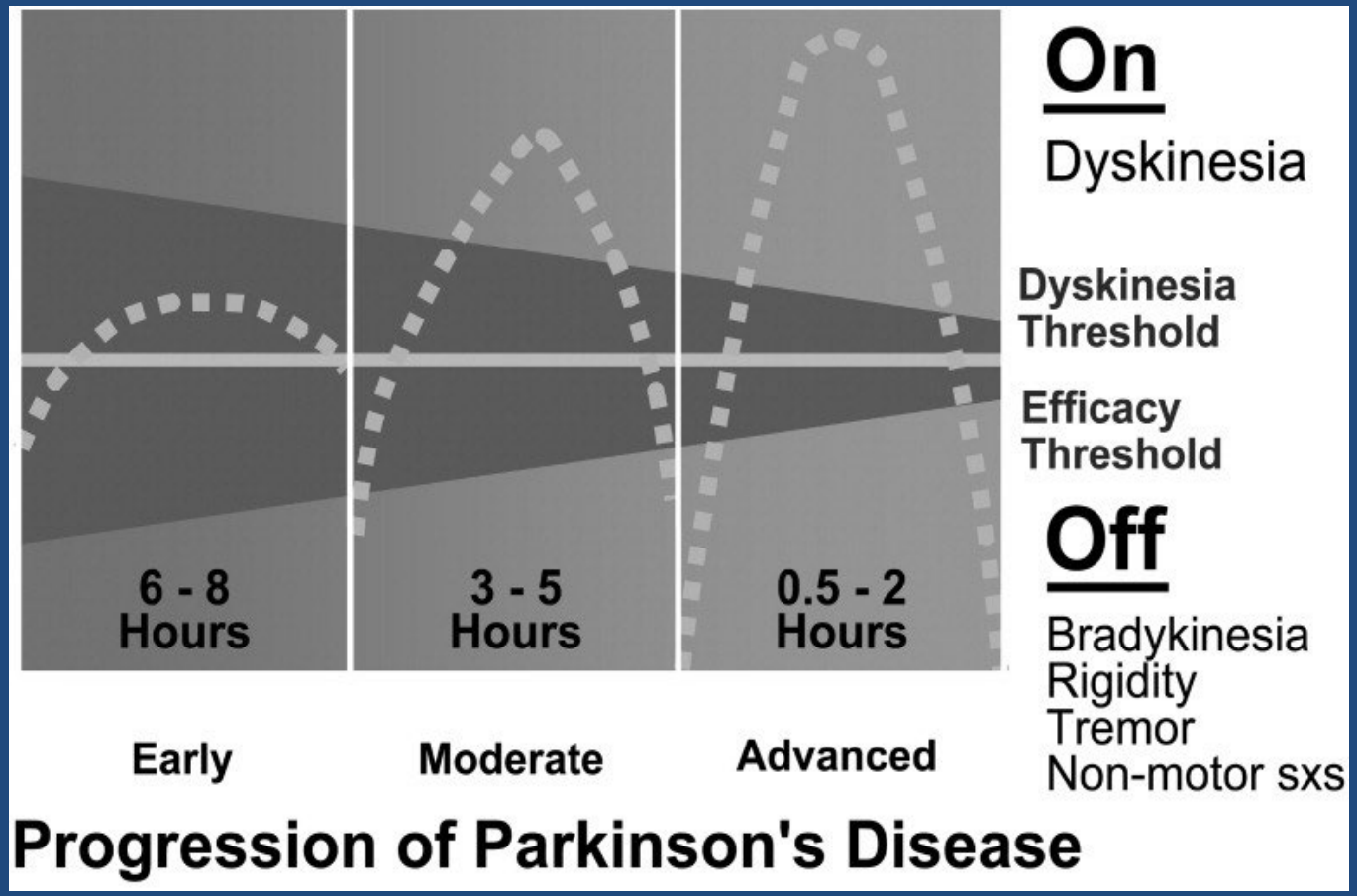
# When to Start What

- Treatment should start anytime function is impaired by physical manifestations of PD.
- Levodopa remains most effective symptomatic therapy.
- Delayed use of levodopa may delay onset of dyskinesias and response fluctuations, particularly in young onset (<40)
- LD vs. DA agonist: controversial
  - No difference in quality of life after 6 years

# Complications of Medical Therapy

- 50% after 5 years, 80% after 10 years
  - Dyskinesia
  - Wearing off
  - Freezing
  - Dystonia
  - On/Off

# Motor fluctuations and dyskinesias in Parkinson's disease: Clinical manifestations




Movement Disorders, Volume: 20, Issue: S11, Pages: S11-S16, First published: 08 April 2005, DOI: (10.1002/mds.20458)

# Surgery for PD

- Deep Brain Stimulation (DBS)
  - Patient selection important
  - Does not alter course of disease
  - STN vs. GPi
- Other approaches under investigation
  - High frequency ultrasound
  - Gene transfer/therapy

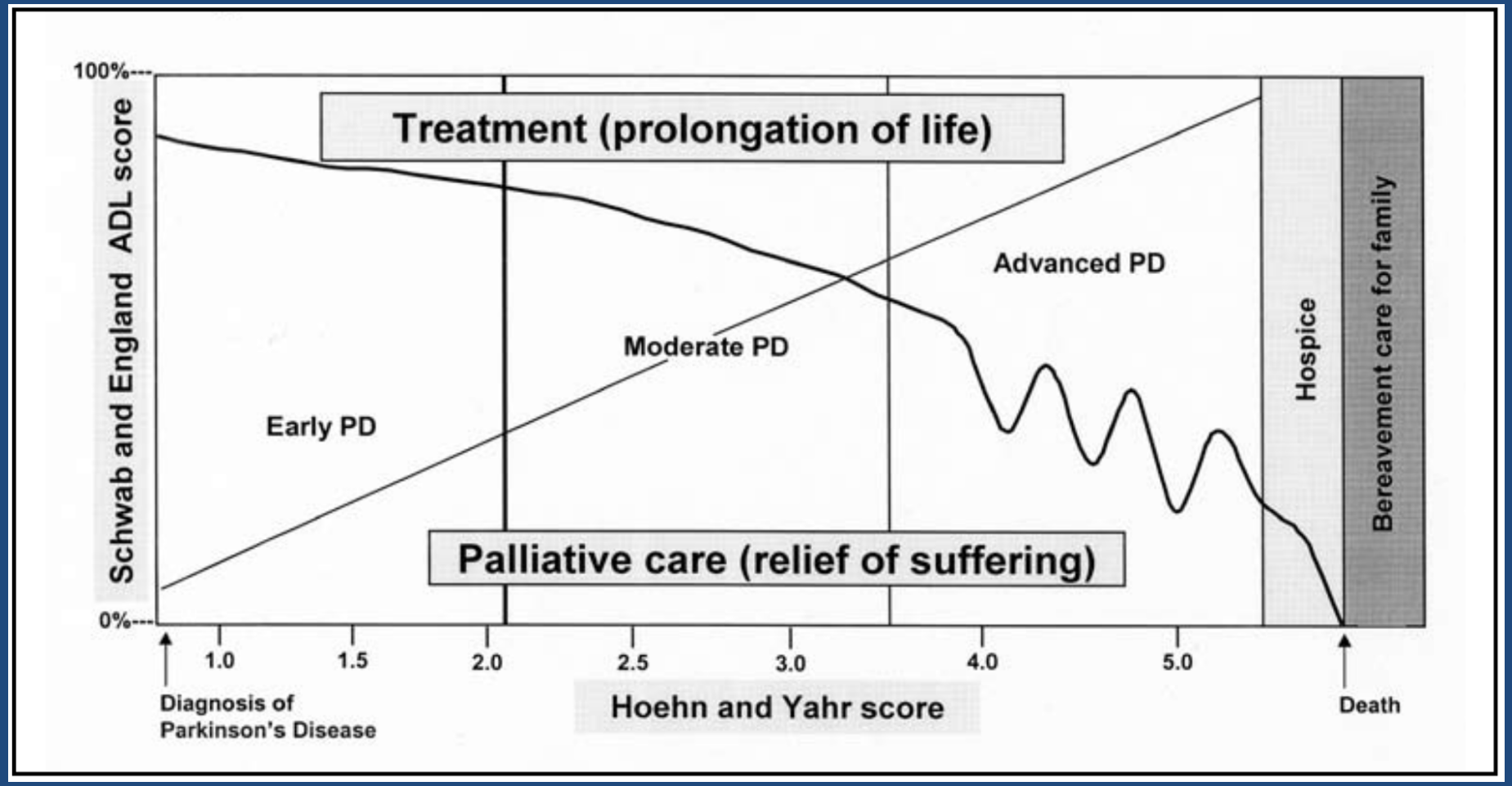
# Other Treatments

- Education of patient and family
- Support for patient and family
- Counseling (professional, legal and financial)
- PT, OT, SLP
- Exercise (including Yoga, Tai Chi, Dance)
- Relaxation Therapy
- Nutritional consultation
- Home Health Services
- Respite
- Palliative Care

# Complementary & Alternative Interventions

- Various supplements
  - Beware of amino acid compounds
- Chiropractors and/or massage therapy
- Acupuncture
- Yoga
- Stem cell treatments
  - Caveat emptor

# PD Model of Care




Bunting-Perry, L. (2006). Journal of Neuroscience Nursing, 38(2), 105-112