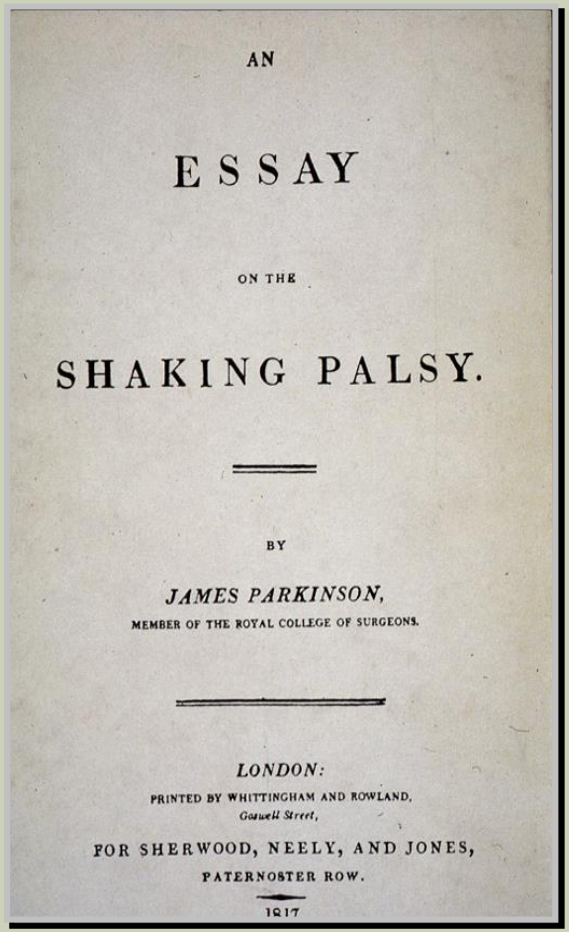
LEARNING OBJECTIVES

The Course Participant will:

1. Be familiar with recent theories concerning the pathogenesis of Parkinson's Disease (PD)
2. Understand clinical and neuroimaging criteria for the diagnosis of PD
3. Be proficient in choosing medication for symptomatic treatment of motor symptoms
4. Understand the role of surgical treatment (Neuromodulation) in PD

PARKINSON'S DISEASE BACKGROUND



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817

- First described as "shaking palsy" by James Parkinson in 1817
- 1 million patients in the United States
- Tremor, stiffness, slowness
- Difficulty with gait, speech

Olanow CW et al. *Neurology*. 2001;56 (suppl 5):S1-S88. National Parkinson Foundation Web site. www.parkinson.org. Marttila RJ, Rinne UK. *Acta Neurol Scand*. 1991;84(suppl 136):24-28. DeStefano AL et al. *Am J Hum Genet*. 2002;70:1089-1095.

PATHOGENESIS OF PD:

Which statement is TRUE?

a) Nicotine use increases the risk of developing PD.

b) Women are less likely than men to acquire PD.

c) Patients with an affected first-degree relative should undergo genetic testing in order to determine the proper treatment.

ETIOLOGY OF PARKINSON DISEASE

Environmental or endogenous toxins

etiology

Single or multiple genes

Pathogenesis

free radicals

mitochondrial dysfunction

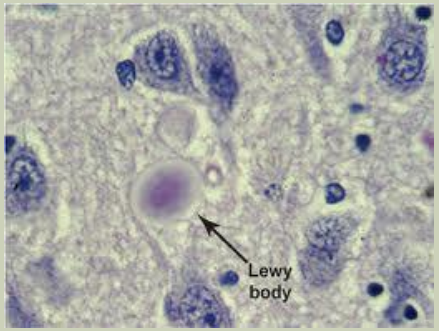
oxidative stress

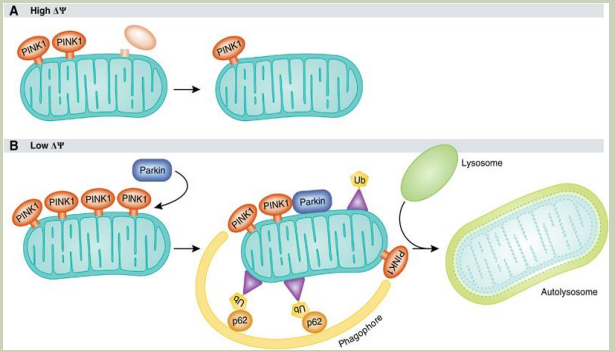
protein aggregation

Parkinson's disease(s)

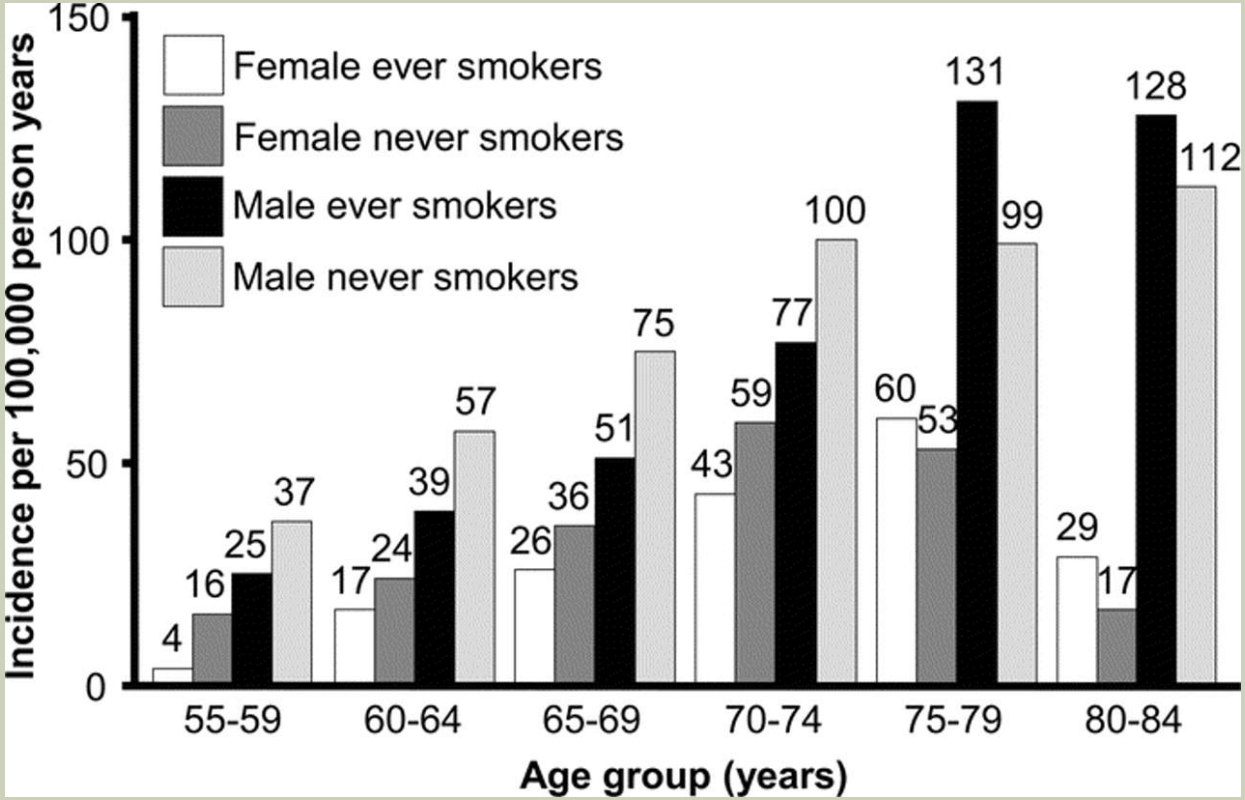
MONOGENIC CAUSES OF PD ARE RARE BUT SCIENTIFICALLY IMPORTANT

- Protein Aggregation
  - α-synuclein
- Mitochondrial maintenance
  - Parkin, PINK-1
- Lysosomal degradation
- LRRK2
  - -function unknown
  - 5% Ashkenazi Jews with PD





ENVIRONMENTAL FACTORS AGE, SMOKING, GENDER



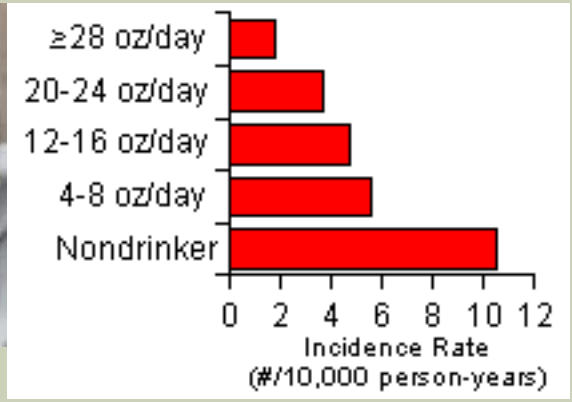
CAFFEINE REDUCES RISK OF PD

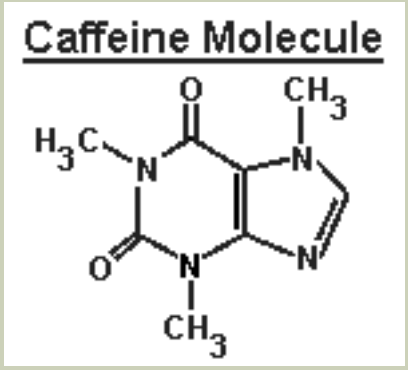
Both caffeine and nicotine interact within dopamine system

Drug develop opportunities:

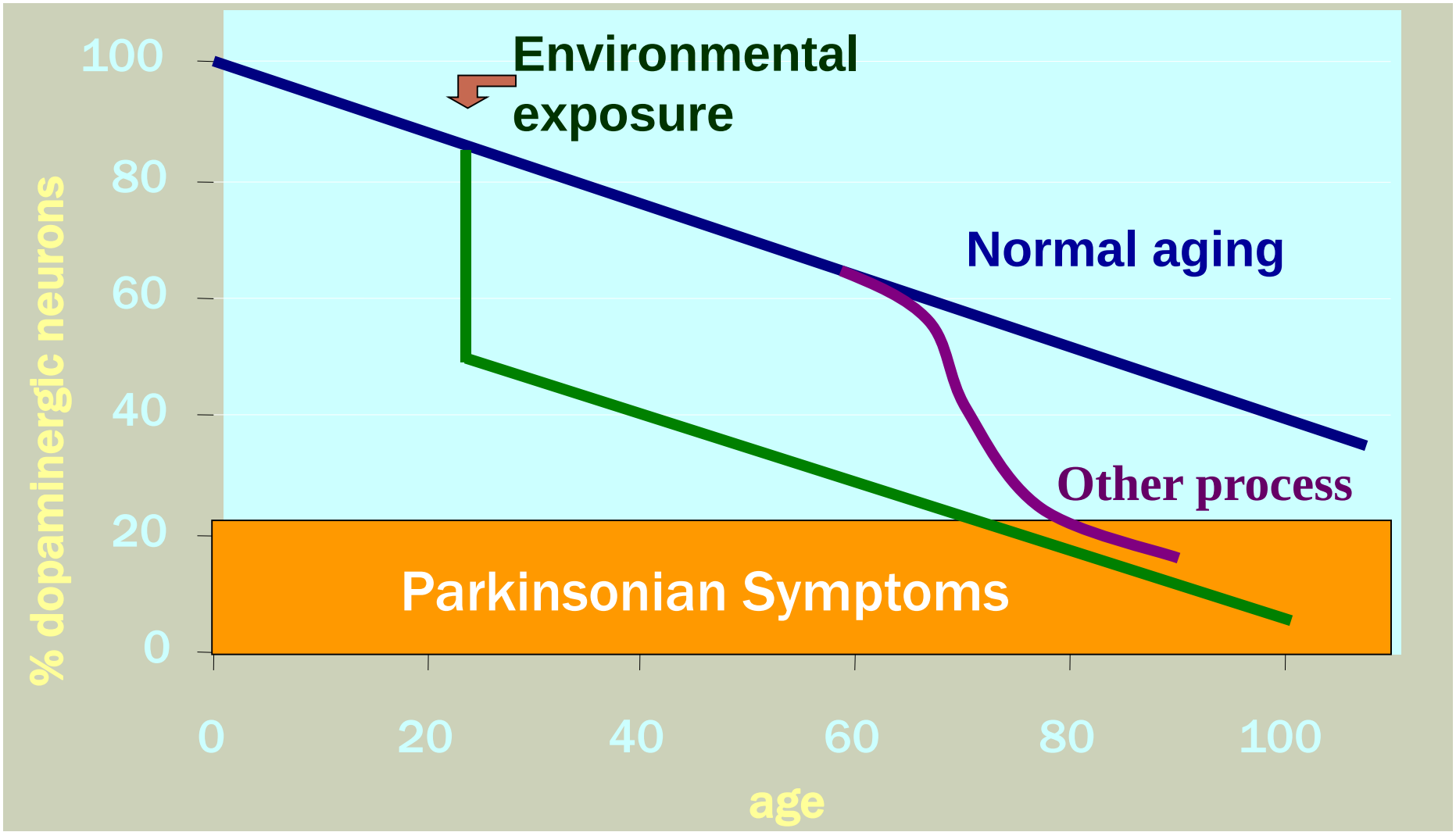
Adenosine receptor antagonists, under development

Nicotinic Acetylcholine Receptor agonists

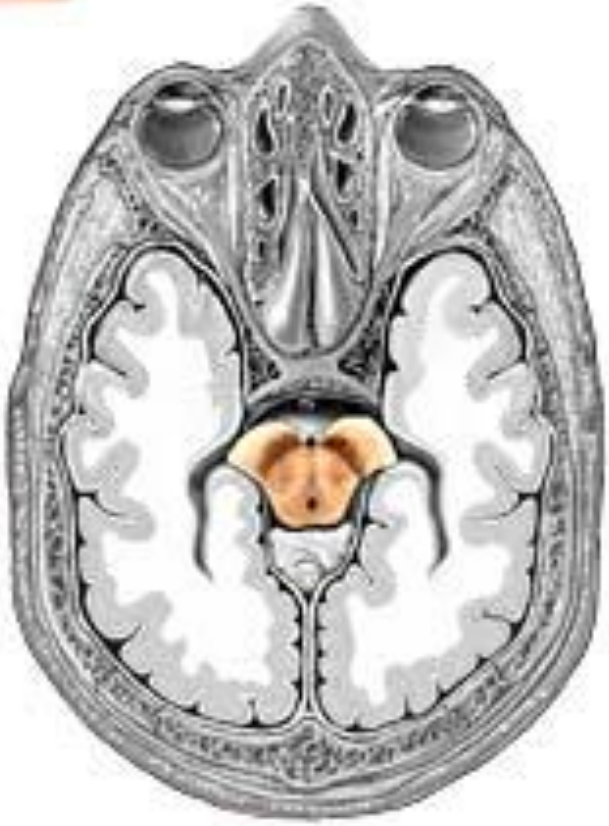




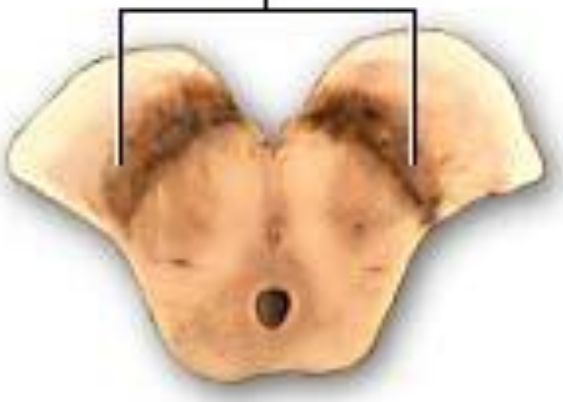
OTHER ENVIRONMENTAL RISKS



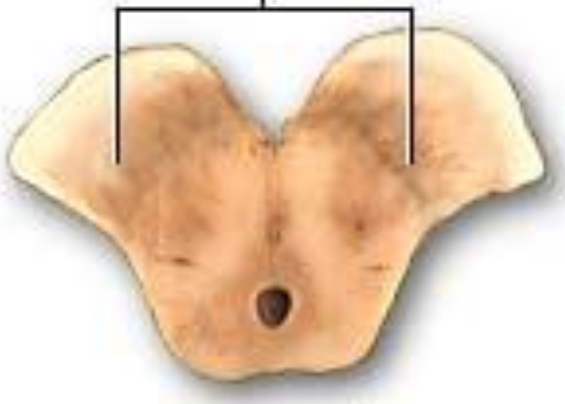
Cut section of the midbrain where a portion of the substantia nigra is visible



Substantia nigra



Diminished substantia nigra as seen in Parkinson's disease



A.D.A.M.

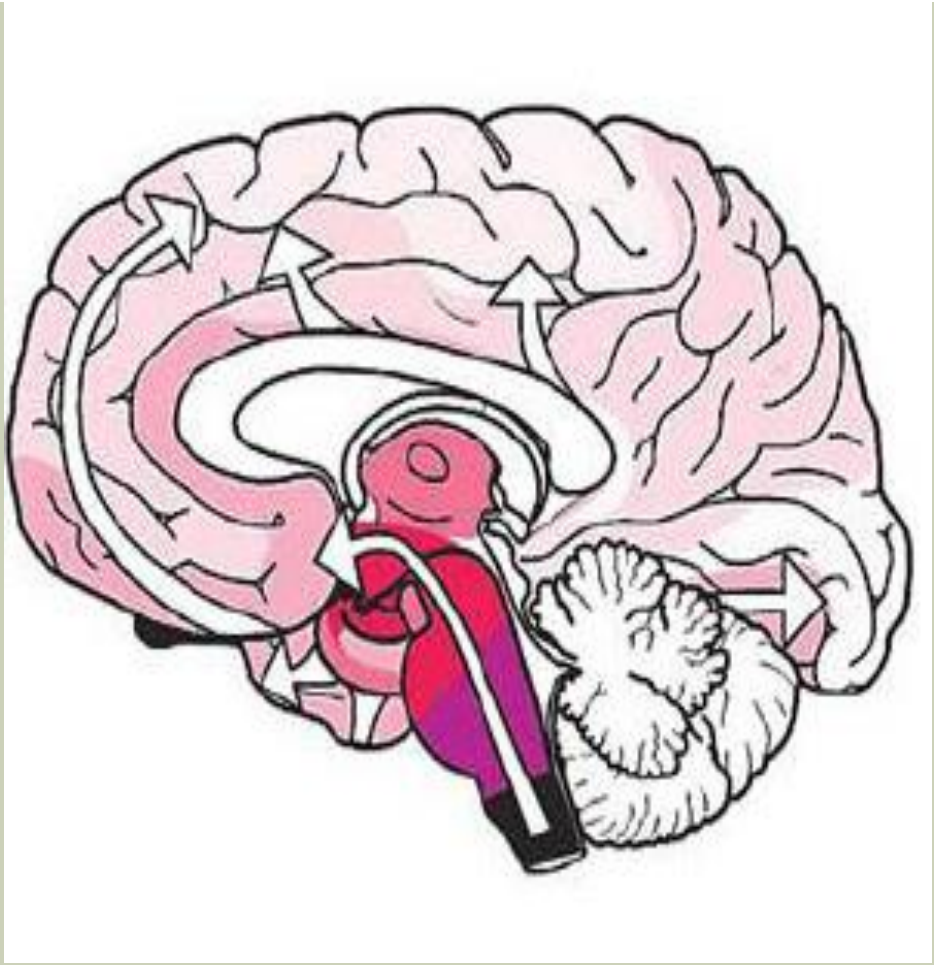
PARKINSON'S DISEASE PROGRESSION BRAAK STAGING

Memory, concentration

Movement Symptoms

Depression, sleep disorders

Autonomic symptoms



Braak H et al. *J Neurol*. 2002;249(suppl 3):III/1-III-5

DIAGNOSIS: PD CAN BE BEST DIAGNOSED

Which statement is TRUE?

The diagnosis of Parkinson's Disease:

a) requires MRI imaging to exclude ischemic neurovascular disease.

b) may be confirmed by nuclear medicine radio-pharmaceutical imaging.

c) is strictly a clinical diagnosis based on characteristic tremor.

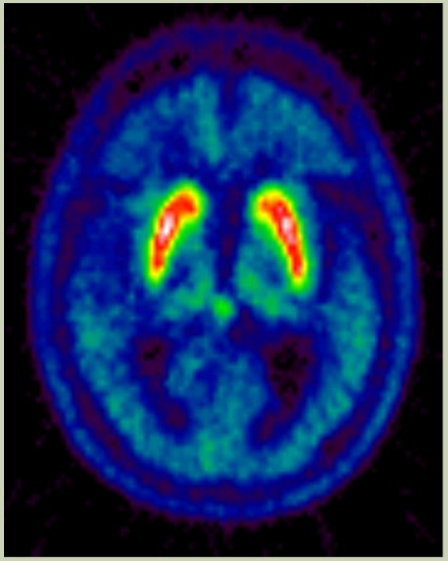
MANIFESTATIONS AT PD ONSET

- Tremor at rest
- Bradykinesia
- Rigidity
- Micrographia
- Hypophonia
- Masked face
- Stooped, shuffling gait
- Slowing of activities of daily living
- Decreased arm swing when walking

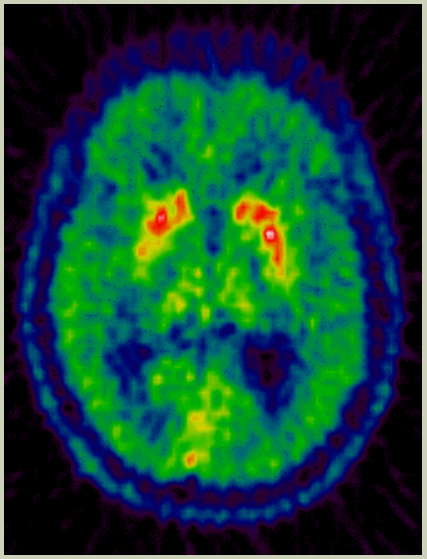
Barbosa et al. *Psychiatr Clin North Am.* 1997;20:769-90.
Playfer. *Postgrad Med.* 1997;73:257-64.

NUCLEAR MEDICINE IMAGING

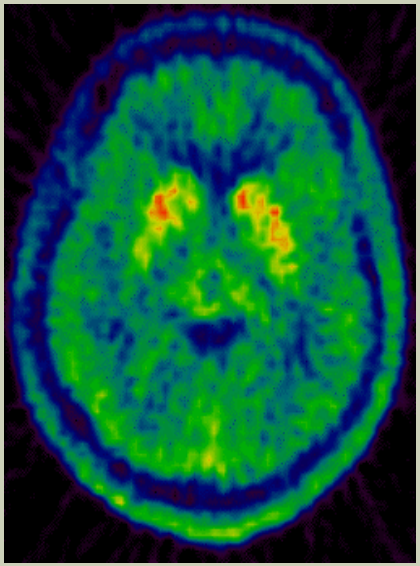
Loss of cells in the Substantia Nigra lead to less dopamine in other parts of the basal ganglia



Normal Subject



Early Parkinson's Disease



Later Parkinson's Disease

MEDICAL TREATMENT OF PD:

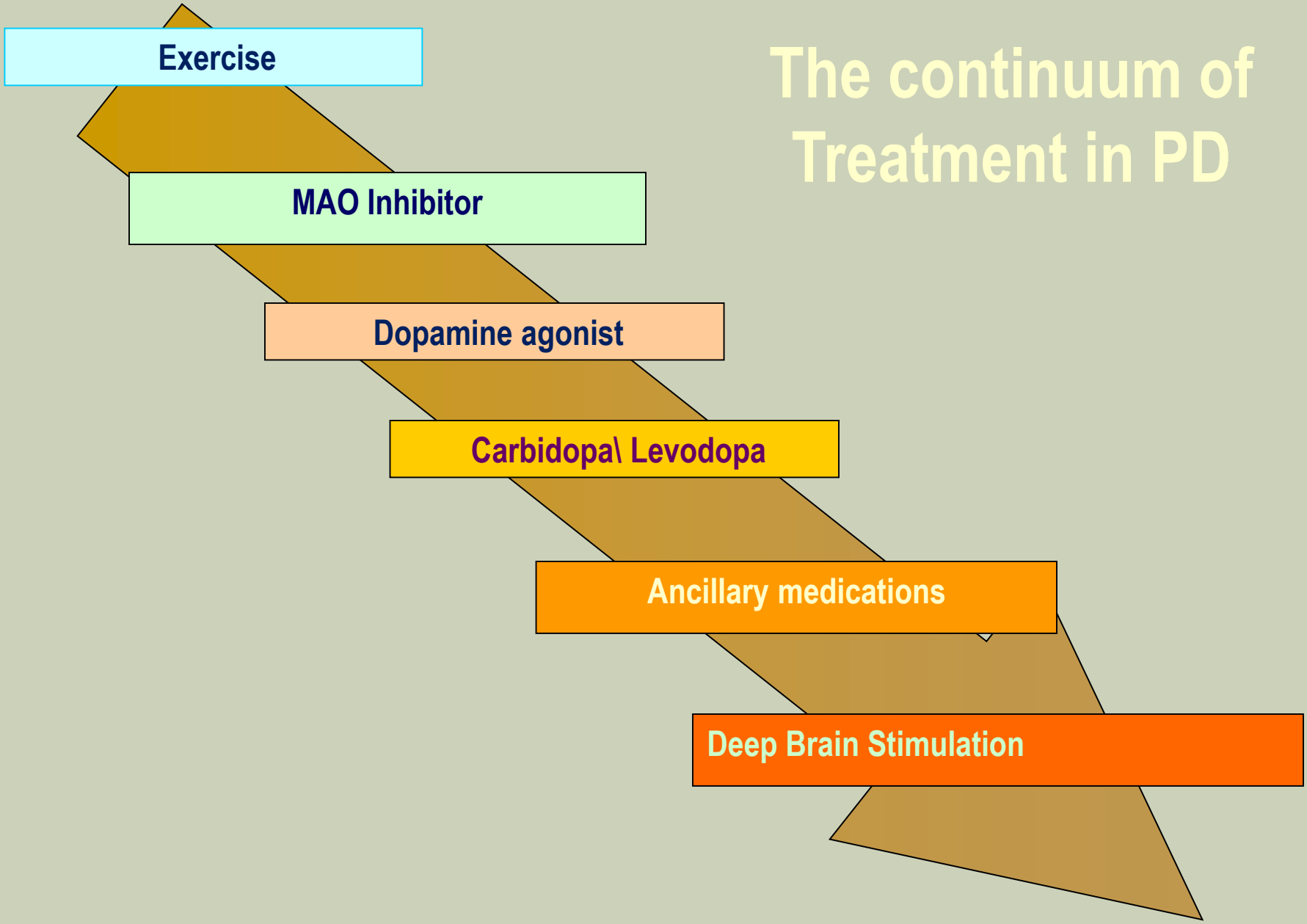
Which statement is TRUE?

a) Levodopa should never be used as the initial treatment since it may loose its effectiveness in 5-8 years.

b) Levodopa is always used in combination with Carbidopa.

c) Dopamine agonists can be effective but are currently limited to oral administration.

The continuum of Treatment in PD

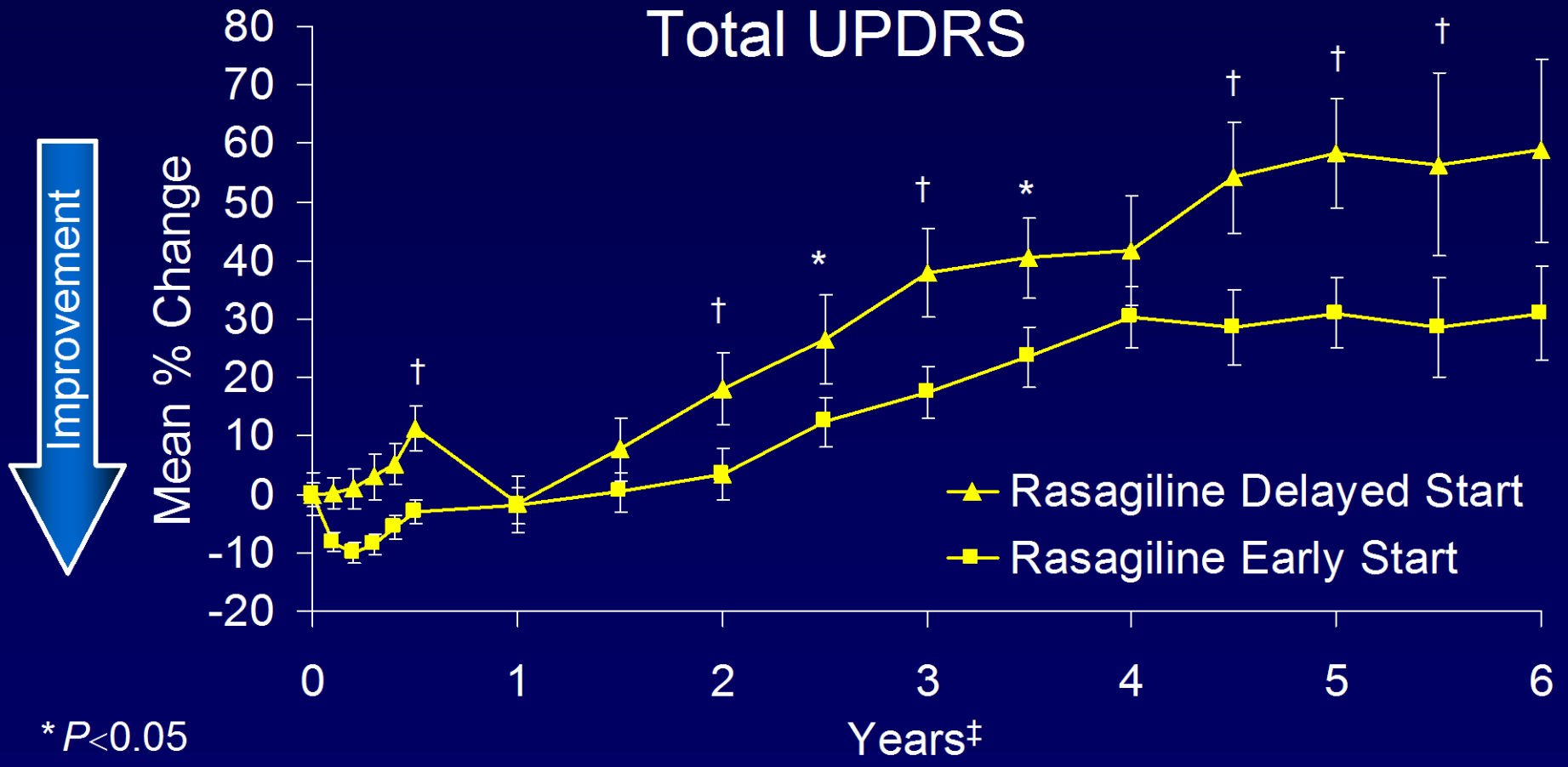


MAO-B INHIBITORS

- Selegeline
  - Standard formulations
  - Orally absorbed (Zelapar)
- Rasagaline (Azilect)
  - Better evidence for neuroprotection
  - Not converted to amphetamine

TEMPO

Long-Term Efficacy: Early vs Delayed Therapy



* $P<0.05$

† $P\leq0.01$

‡N=177 for all time points except for 5.5 y (N=153) and 6.0 y (N=101)

Hauser et al. *Neurology*. 2005;64:A107.

DOPAMINE AGONISTS

- Oral
  - Pramipexole (Mirapex)
  - Ropinerole (Requip)
- Injectable
  - Apomorphine (Apokyn)
- Transdermal
  - Rotigitine – (Neupro)

DOPAMINE AGONISTS

Advantages

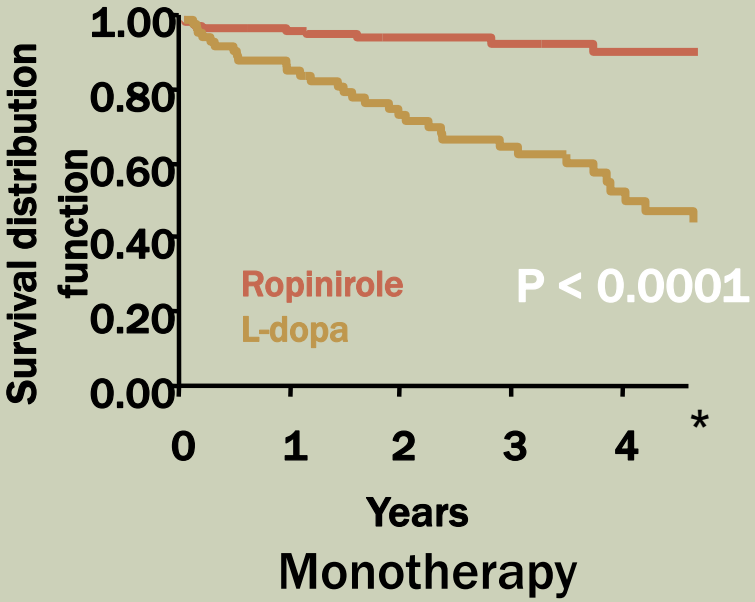
- Long duration of effect
- Do not cause dyskinesia
- Allow reduction of levodopa and smooth out fluctuations
- Can improve sleep/depression/sensory sx's

Disdavantages

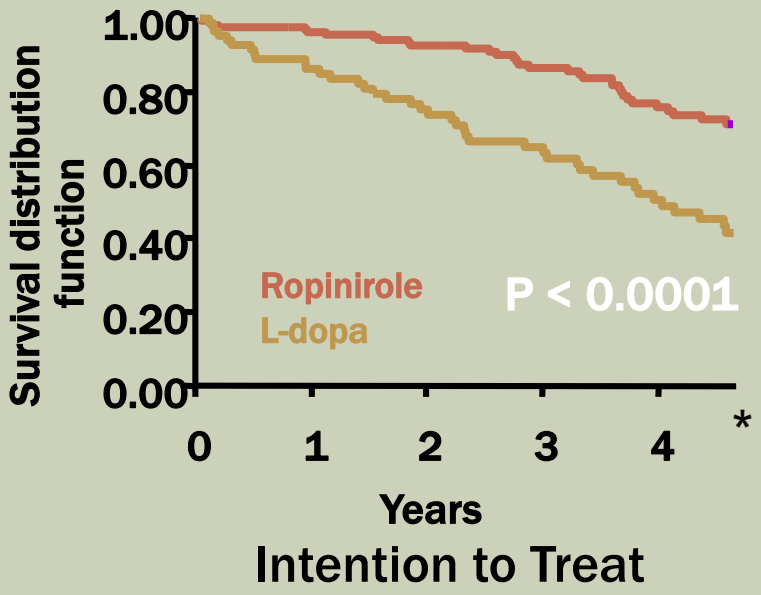
- Numerous side effects
  - Drowsiness
    - Sleep attacks (rare)
  - Low blood pressure
  - Leg swelling
  - Visual illusions
  - Compulsive behavior
    - Gambling
    - Sex addiction
    - Eating

DOPAMINE AGONISTS REDUCE DYSKINESIA:

EITHER AS MONOTHERAPY OR IN COMBINATION WITH LEVODOPA



Monotherapy



Intention to Treat

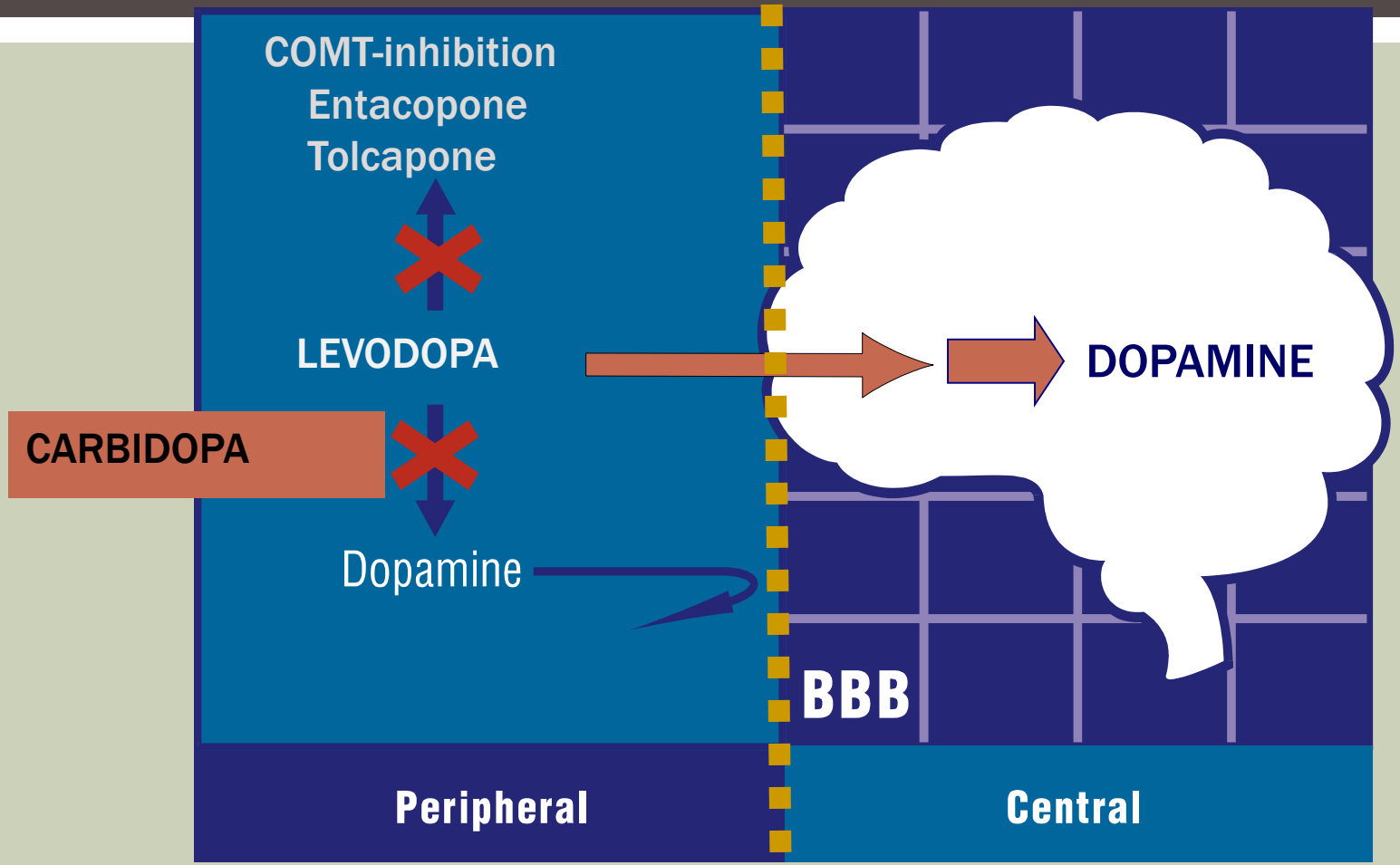
CARBIDOPA/LEVODOPA

- Advantages
  - Most potent
  - Few side effects
  - Almost always necessary
  - Inexpensive
- Disadvantages
  - Short duration/frequent dosing needed
  - Poor absorption by gut
    - Interference by food
    - Erratic effects
  - Stored and converted by brain cells
  - Causes dyskinesia

WHEN TO START LEVODOPA?

- Different answer for everyone
- Sometimes it may be the first drug prescribed and sometimes not
- Considerations
  - Can movement symptoms be adequately controlled without it?
  - Patients age and age of onset
  - Presence of other medical conditions

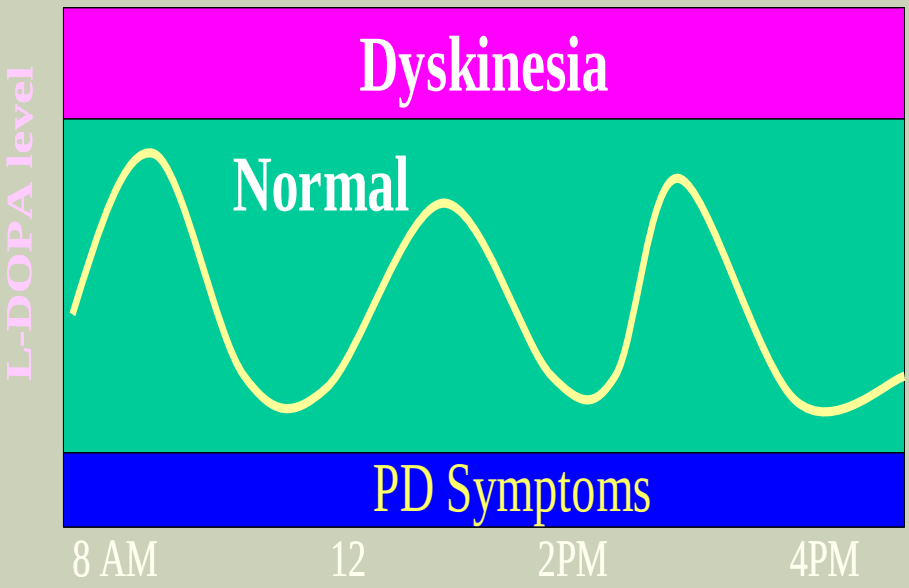
LEVODOPA

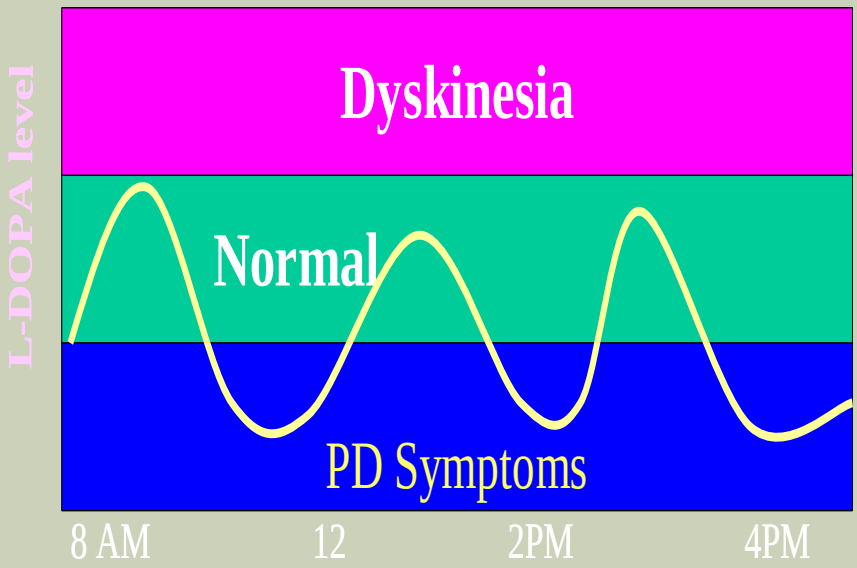

COMT-inhibition
Entacopone
Tolcapone
LEVODOPA
CARBIDOPA
Dopamine
DOPAMINE
BBB
Peripheral
Central

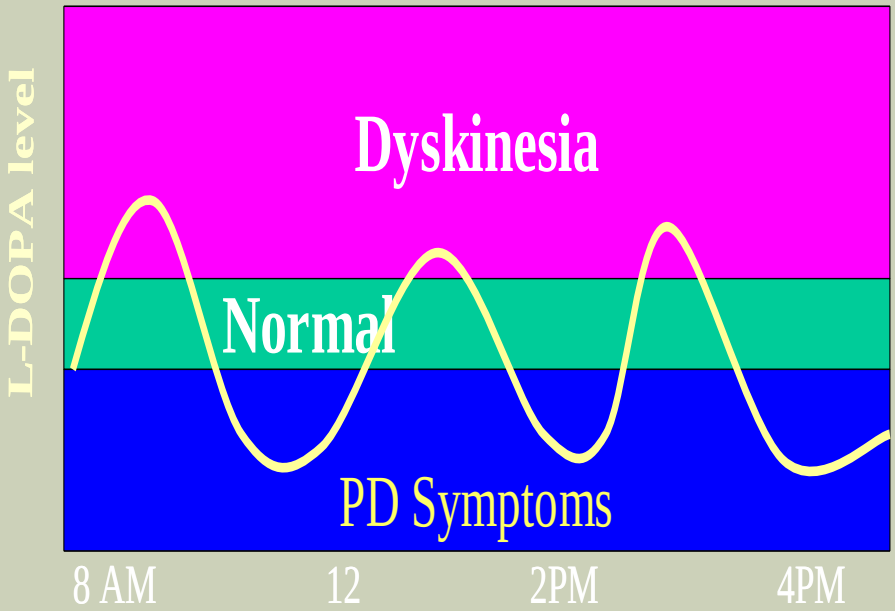
STAGES OF LEVODOPA EFFECT

- Stage 1: “Honeymoon”-works great
- Stage 2: “Wearing off” –end of dose
- Stage 3: Dyskinesia- at peak dose
- Stage 4: Motor fluctuations
  - Less time in ideal “zone”
  - Effects become erratic and unpredictable

Development of motor fluctuations and dyskinesia







SURGICAL TREATMENT OF PD:

Which statement is TRUE?

a) Deep Brain Stimulation (DBS) is reserved for cases which do not respond to Levodopa.

b) Surgical treatment should only be considered under an FDA-approved experimental protocol.

c) Surgical treatment has been shown to increase quality of life compared to medical treatment alone in patients with fluctuations response to Levodopa.

WHAT IS DBS-HOW DOES IT WORK?

- Uses high frequency electrical stimulation
- System has three components
  - Electrical signal generator (implanted under collarbone)
  - Connecting wire
  - Electrode (implanted in the brain)
- Masks abnormal brain signals
- Helps restore balance between the direct and indirect pathway

DBS CAN DECREASE MOTOR FLUCTUATIONS

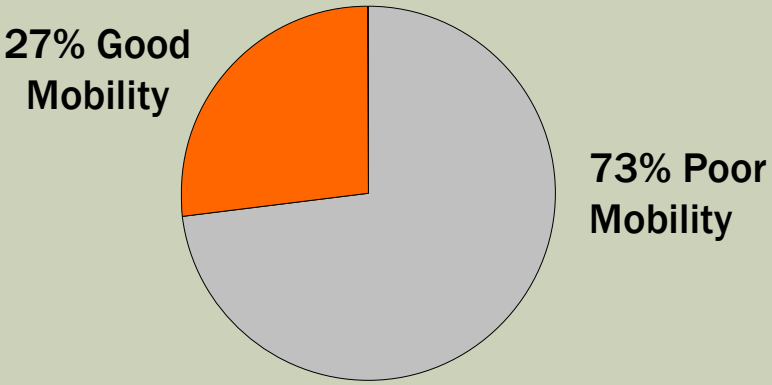
- Does not depend on increasing dopamine
- With Parkinson's disease, the brain circuits that control movements work abnormally.
- Deep brain stimulation helps these circuits to work in a more normal manner, which is thought to "restore" motor function.

WHAT ARE BENEFITS OF DBS?

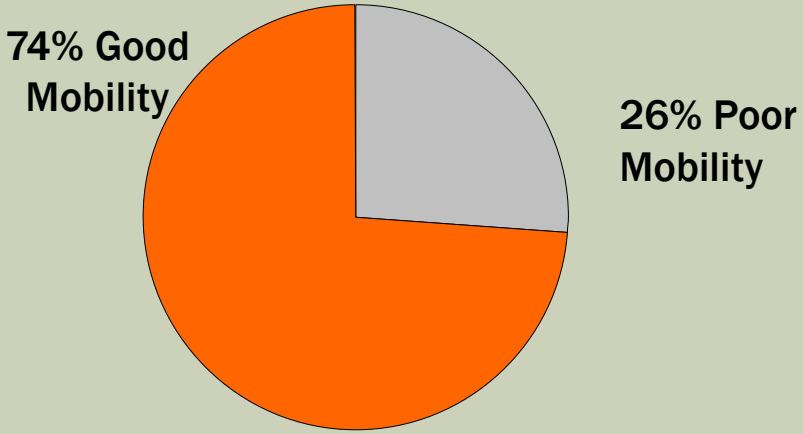
- Improvement in all cardinal symptoms
  - Balance may not show same degree of improvement
- Improvement in motor fluctuations
  - 25-75% increase in on-time without dyskinesia
  - 50% reduction in medications (STN DBS)
  - Improved sleep if off-time is occurring at night

BENEFITS OF DBS
INCREASE PERIODS OF GOOD MOBILITY*

Before DBS



After DBS



Good mobility: "on" time without dyskinesia
Poor mobility: "off" time and "on" time with dyskinesia

*Source: The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med.* 2001;345:956-963.

TARGETS IN THE BRAIN FOR DBS

- Globus Pallidus (GPi)
  - Studies show similar effectiveness to STN but results tend to be less dramatic
  - Blocks dyskinesia without reducing meds
    - Good choice for patients who have beneficial effects of levodopa on cognition and mood
    - May be better for older patients

TARGETS IN THE BRAIN FOR DBS

- Subthalamic nucleus (STN)
  - Most dramatic effects-particularly in younger patients
  - 50% reduction in medication
  - Improves tremor, rigidity, and bradykinesia
  - Dyskinesia improves as levodopa dose is lowered
  - May have cognitive and mood effects

DBS CAN EFFECTIVELY CONTROL TREMOR

- Tremor can be relatively resistant to medical treatment compared to other PD symptoms

STN STIMULATION

SUMMARY

- PD diagnosis can be aided by DAT scans
- Carbidopa/levodopa remains the most potent medical treatment
- New therapies are needed to control disease progression
- Surgical treatment DBS can be treatment of choice in carefully selected patients