PARKINSON'S DISEASE

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Financial Disclosures

- Dr. Amy Amara has the following relative financial disclosures:
  - *Consultant Grey Matter Technologies &*
  - *Jazz Pharmaceuticals*

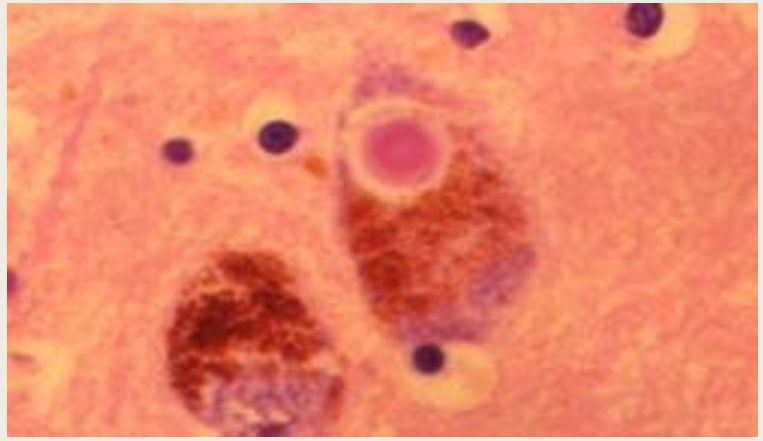
- Dr. Amy Amara will not be discussing the off-label or investigational use of products

Objectives

- Understand the Clinical Features of Parkinson’s Disease
- Recognize Non-Motor Symptoms of Parkinson’s Disease
- Discuss Treatment Options for Motor and Non-Motor Symptoms of Parkinson’s Disease

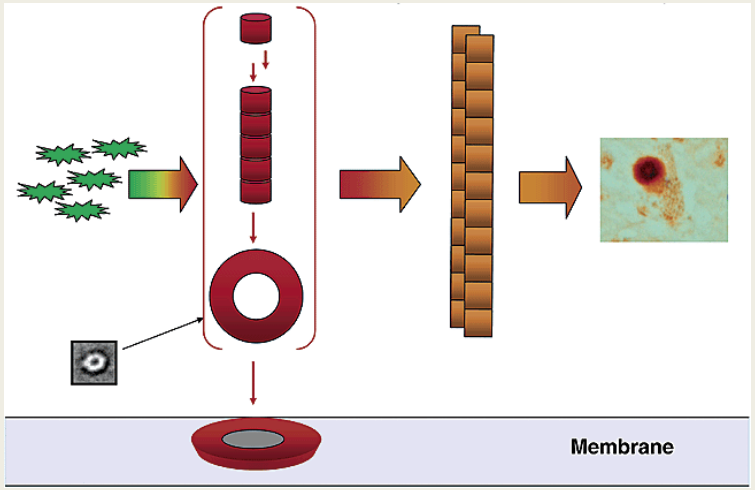
Outline

- Parkinson's Disease **Pathology**
- Clinical Features
  - *Motor symptoms*
  - *Non-motor symptoms*
- Treatments
  - *Medication*
  - *Non-medication*
- Non-motor symptoms treatments

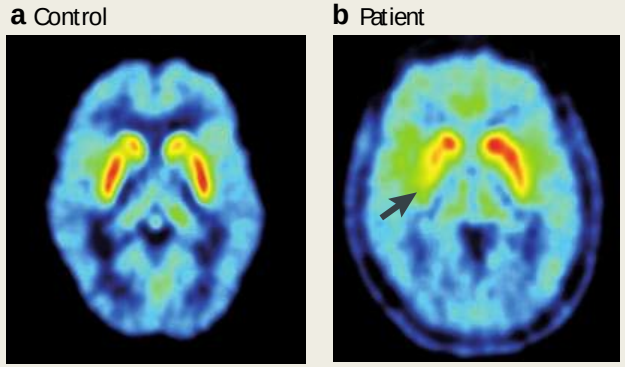


PD Pathology

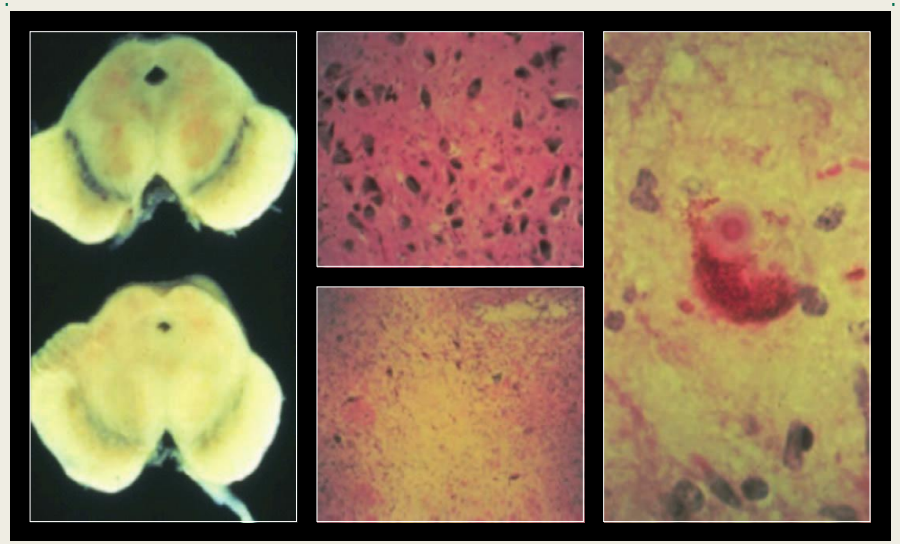
- Proposed mechanism: Excess alpha-synuclein forms aggregates that are neurotoxic
- These form the main component of Lewy bodies
- Neuronal death in substantia nigra—loss of pigmented cells



Volles and Lansbury, 2003



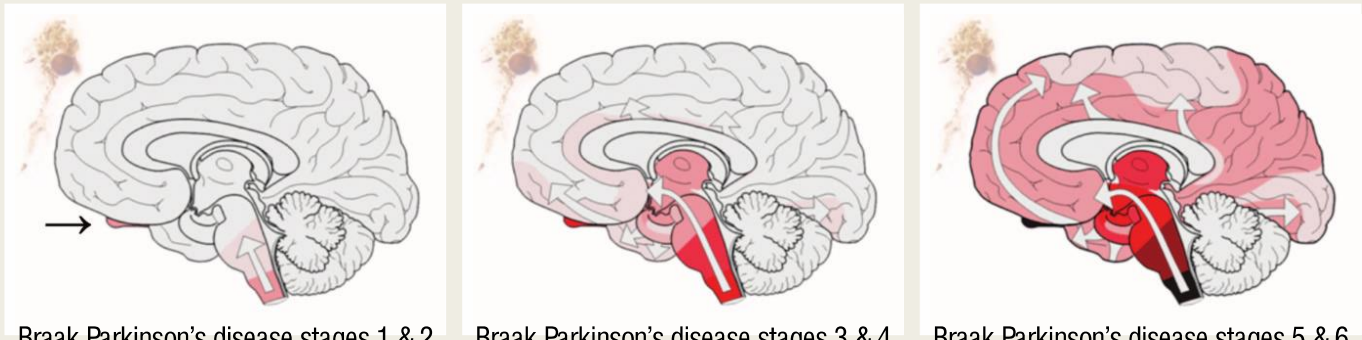
Redgrave et al. Nature Rev Neurosci. 11:760. 2010



Olanow et al. Neurology 72(Suppl 4):S1 2009

Braak Hypothesis

- Identification of α-synuclein (key component in Lewy bodies) allowed discovery of extent of PD pathology
- Braak hypothesis proposes a progression of pathology: starts in enteric nervous system→dorsal motor nucleus of vagus, olfactory nucleus→brainstem→substantia nigra→cortex



This hypothesis suggests that pathologic changes are first noted in the olfactory region and lower brainstem, and only later extend to involve dopamine neurons in the SNc (Courtesy of Heiko Braak).

Olanow et al. Neurology 72(Suppl 4):S1 2009

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Cardinal Motor Features

- Bradykinesia/Akinesia
- Rest Tremor
- Rigidity
- Postural Instability

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

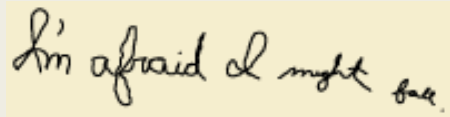
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Bradykinesia

- Slowness of movement (Akinesia=absence of movement)
- The most characteristic feature of PD
- Problem with initiating and executing movement
- Worsens over the course of the disease
- Takes longer to perform ADLs, slower movements and reaction times

BRADYKINESIA-MANIFESTATIONS

- Loss of Spontaneous Movement
  - *Fewer hand gestures*
  - *Decreased blinking frequency*
  - *Decreased swallowing frequency (→ drooling)*
- Reduced arm swing during walking
- Shuffling gait/shortened stride length
- Difficulty rising from a chair
- Hypophonic speech
- Hypomimia (masked facies)
- Impaired fine motor tasks (buttoning buttons)
- Micrographia



- Dysdiadochokinesia

Rest Tremor

- 4-6 Hz tremor at rest
- Asymmetric, often unilateral
- Usually most prominent in distal part of limb
- Supination/pronation/"pill-rolling" motion
- Often spreads from one hand to the other
- Can affect lips, chin, jaw, arms, legs
  - *Usually doesn't affect neck or voice*
- Affects 75% PD patients during disease course

Rigidity

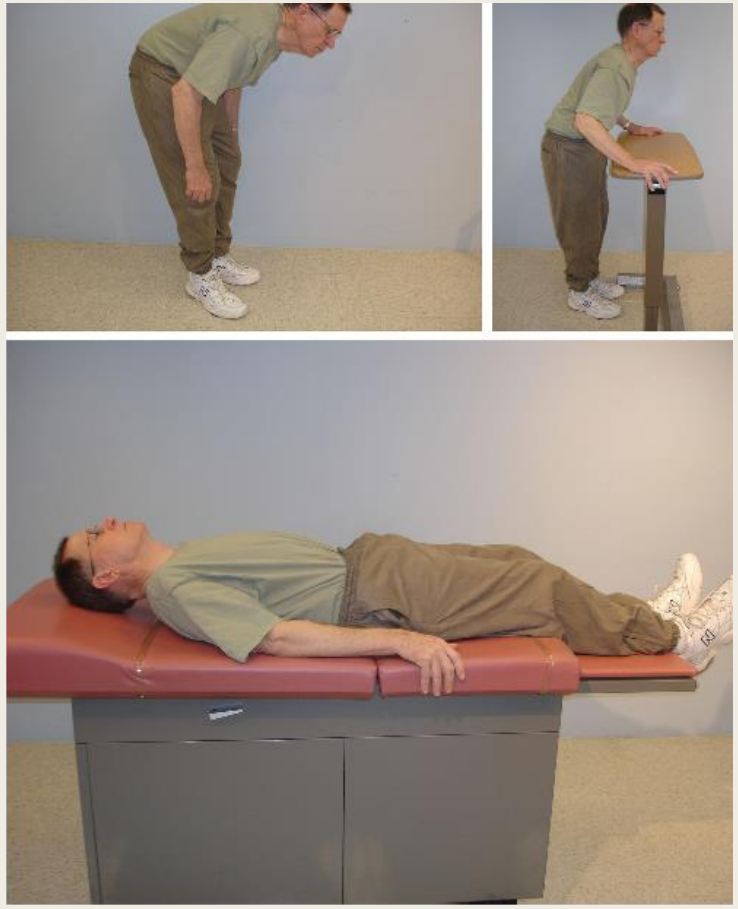
- Increased resistance present throughout the range of passive movement
- May be associated with cogwheeling (usually a manifestation of underlying tremor)
- May occur proximally or distally
- Usually asymmetric
- Froment's maneuver: movement in contralateral limb accentuates the rigidity
- Can be painful

Rigidity: Postural Deformity

- Axial rigidity can lead to abnormal posture: anterocollis, scoliosis
- Flexed neck and trunk and flexed elbows and knees
- Usually occurs late
- Camptocormia: extreme flexion of thoracolumbar spine
- Pisa syndrome: tilting of trunk when sitting or standing

CAMPTOCORMIA

Bloch et al. *J. Neurol, Neurosurg, Psych*. 2006, 77: 1223



Jankovic, J. *J Neurol Neurosurg Psychiatry* 2008; 79:368

Pisa Syndrome

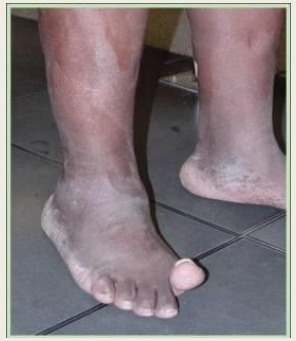
van de Warrenburg B P C et al. J Neurol Neurosurg Psychiatry 2007;78:329-330

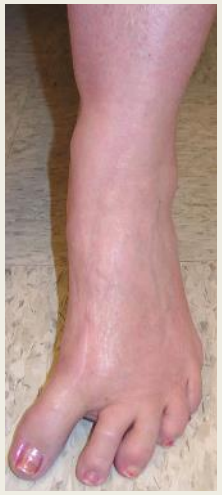
Postural Instability

- Usually the latest cardinal motor symptom to appear
- Loss of postural reflexes
- Leads to falls
- Most disabling symptom
- Least responsive to dopaminergic therapy
- Tendency to fall forward or backward due to inability to correct posture
- Festination (body getting ahead of the feet): ineffective short, rapid, accelerating steps; inability to stop

Dystonia

- Striatal hand (ulnar deviation of the hand, flexion of metacarpophalangeal joints, extension of proximal and extension of distal interphalangeal joints)
- Striatal toe (extension or flexion of toes)
- May occur as off phenomenon or may be a side effect of medications





Jankovic, J. *J Neurol Neurosurg Psychiatry* 2008; 79:368

Motor Complications

- Dyskinesias: abnormal writhing, hyperkinetic movements
  - *Long term complication of dopaminergic therapy*
- Wearing off: improvement from medications begins to wear off before next dose of medicine
- Dopamine dysregulation syndrome: crave more medication due to alterations in reward system

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Non-motor symptoms

- Common: 88% of patients complain of at least one non-motor symptom
- May precede onset of motor symptoms
- Likely mediated by dopaminergic and non-dopaminergic mechanisms
- Significant negative impact on quality of life and possible source of disability

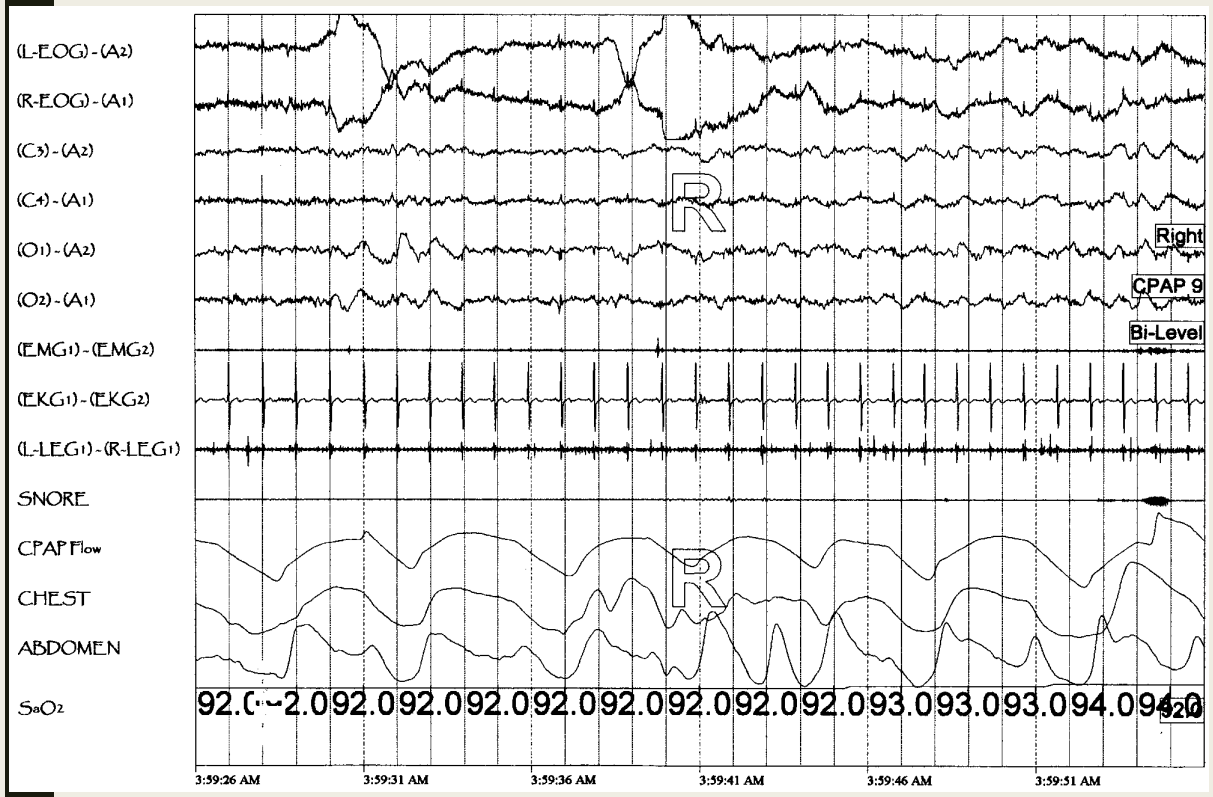
Nonmotor symptoms in PD

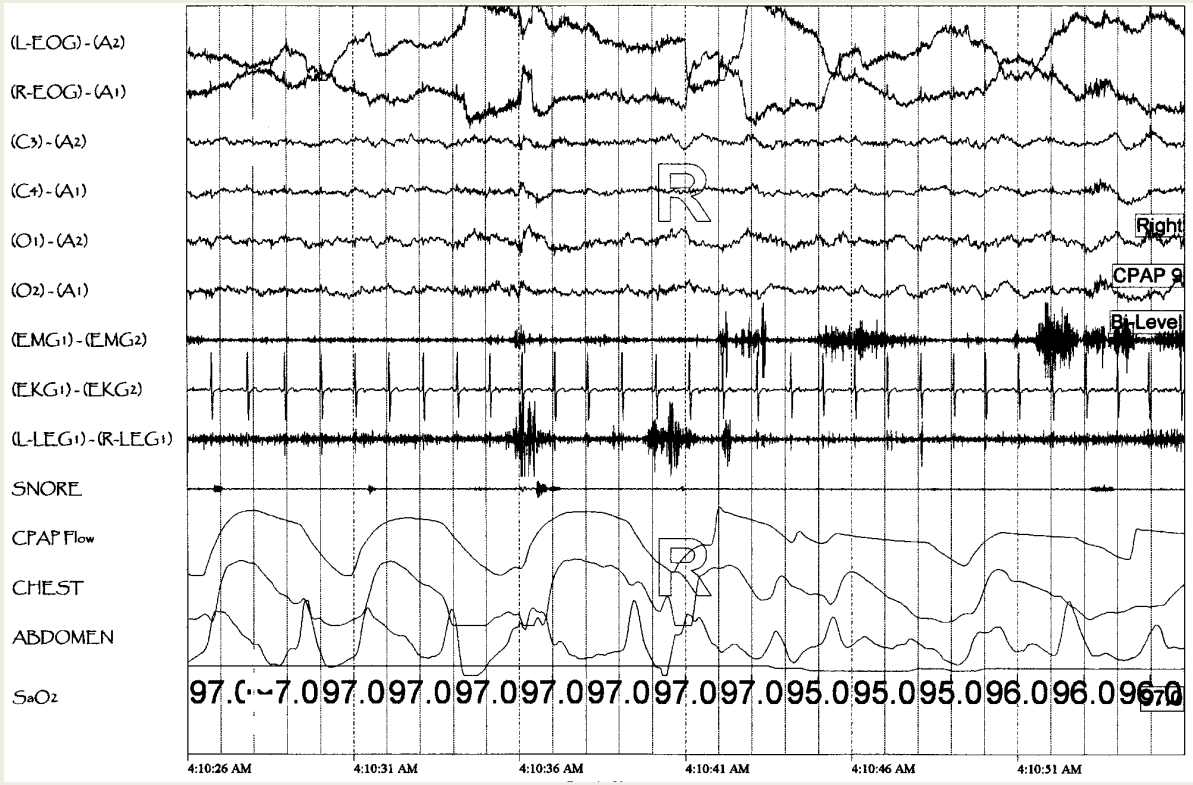
- Mood Disorders
  - *Depression, Anxiety, Apathy, Anhedonia, Impulse Control Disorders*
- Cognitive Dysfunction
  - *Dementia, Psychosis, Bradyphrenia, Apathy*
- Autonomic Dysfunction
  - *Cardiovascular, GI, Thermoregulatory, Urogenital*
- Sensory Symptoms
  - *Pain, Hyposmia*
- Sleep Dysfunction
  - *Sleep Fragmentation, difficulty rolling over, daytime sleepiness, parasomnias (RBD), leg jerks*

Prodromal non-motor symptoms

- Anosmia
- Constipation
- Depression
- REM Sleep Behavior Disorder (RBD):
  - *Parasomnia*
  - *Loss of atonia of REM sleep*
  - *Unpleasant, often violent, vivid dreams*
  - *Poses risk to patient and bed partner*
  - *65% of RBD patients develop neurodegenerative disorder at 7.5 years and 90% at 14 years.*

REM Sleep Behavior Disorder





Loss of normal paralysis of dream sleep

Leads to acting out dreams

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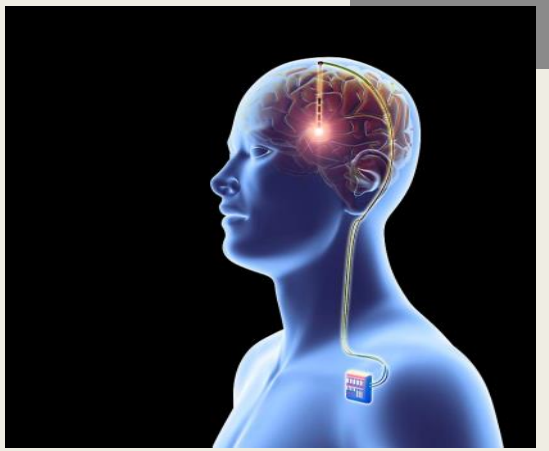


http://health-innovations.org/2015/03/23/eight-year-study-assesses-efficacy-of-dbs-on-pain-in-patients-with-parkinsons-disease/

Classes of Pharmacologic treatments for PD

- Levodopa
- Dopamine agonists
- catechol O-methyltransferase (COMT) inhibitors
- Monoamine oxidase (MAO)-B inhibitors
- Anticholinergics
- Amantadine

Levodopa

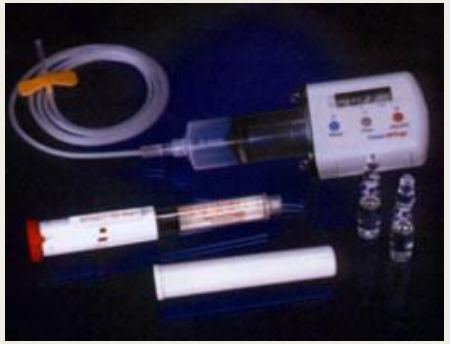
- Most clinically potent treatment available
- Administered with carbidopa to prevent peripheral conversion of L-dopa to dopamine
- Available formulations:
  - *Immediate release (Sinemet)*
  - *Controlled release (Sinemet CR)*
  - *Orally disintegrating (Parcopa)*
  - *Extended release (Rytary)*
  - *Levodopa carbidopa intestinal gel (Duopa)*
  - *Inhaled levodopa (Inbrija)-just FDA approved*

Carbidopa/Levodopa: Potential Side Effects

- Acute side effects:
  - *Nausea/Vomiting*
  - *Orthostasic hypotension*
  - *Hallucinations/psychosis*
- Long-term side effects:
  - *Levodopa-induced dyskinesias (LID)*

Dopamine agonists

- Ergots: bromocriptine, cabergoline, lisuride
  - *cardiac valve fibrosis (5HT2b receptor agonist)*
  - *Lisuride (5-HT2a and 2c agonist and 5-HT2b antagonist)*
- Pramipexole: IR and SR
- Ropinirole: IR and XR
- Rotigotine (patch)
- Apomorphine: short-acting, rescue
  - *SQ injection (penject)*
  - *continuous (pump)*
  - *Inhaled and intranasal*



Dopamine agonists: potential side effects

- Nausea/vomiting/Orthostatic hypotension
  - *Decreases as tolerance develops*
- Hallucinations
  - *Esp in elderly or cognitively impaired patients*
- Sedation, daytime sleepiness, “Sleep attacks”
- Lower extremity edema
- Weight gain
- Impulsive control disorders:
  - *gambling, hypersexuality, impulsive eating*

COMT inhibitors

- No effect as monotherapy, requires presence of levodopa
- Entacapone combined with carbidopa/levodopa=Stalevo
- Tolcapone: associated with liver failure
- Side effects are related to increased availability of levodopa in CNS
- Used to combat wearing off

MAO-B inhibitors

- Selegiline
- Rasagiline
- Zydis selegiline
- Safinamide (approved for “off” time as C/L adjunct)
- These are selective for MAO-B and less risk for hypertensive crisis assc with MAO-A inhibition→ excess tyramine
- Concern for risk of serotonin syndrome

Anticholinergics

- Trihexyphenidyl (Artane)
- Benztropine (Cogentin)
- Potentially useful in younger PD patients with preserved cognition and tremor predominant phenotype.
- Helpful for tremor and rigidity, less helpful for bradykinesia

Anticholinergics: Side Effects

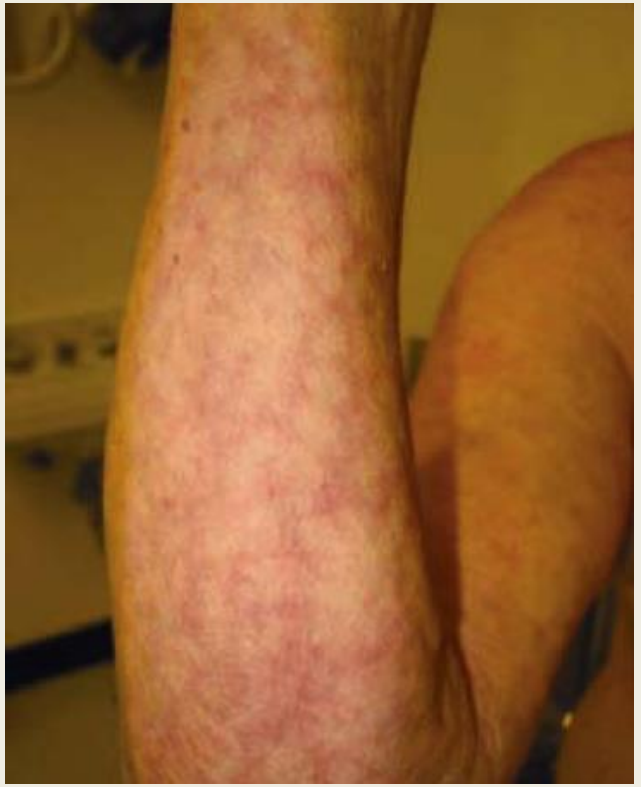
- Memory impairment
- Confusion/Hallucinations
- Sedation/Dysphoria
- Dyskinesias
- Dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, tachycardia
- Can exacerbate closed-angle glaucoma or prostatic hypertrophy

Amantadine

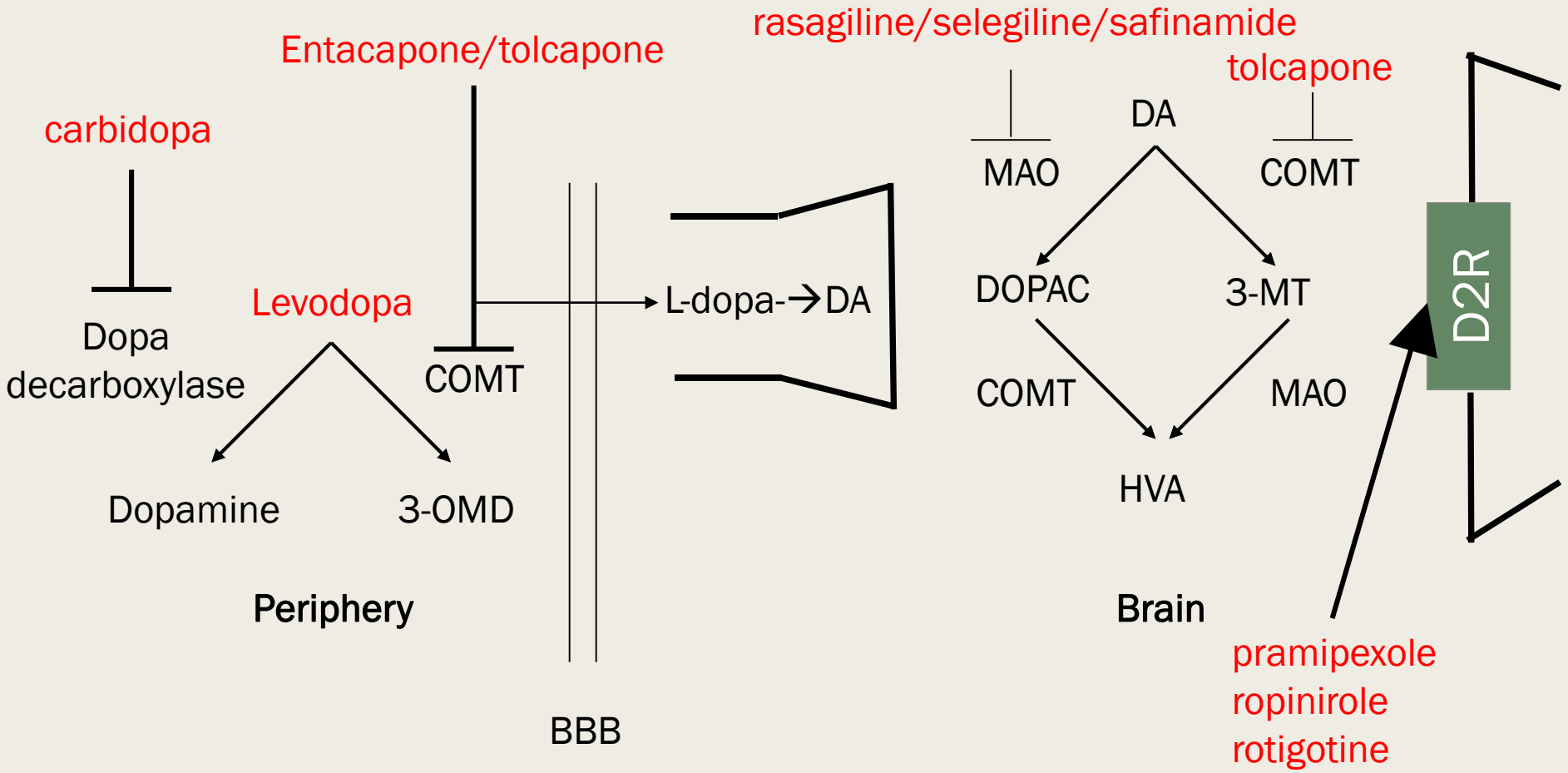
- Unknown mechanism of action in PD
- Improves
  - *Akinesia*
  - *Rigidity*
  - *Tremor*
- Improves dyskinesias
- Effect may be transient

Amantadine: Potential Side Effects

- Confusion
- Hallucinations
- Insomnia
- Nightmares
- Ankle Edema
- Livedo Reticularis
- Dry mouth/blurry vision
- Headache



PD medication mechanisms

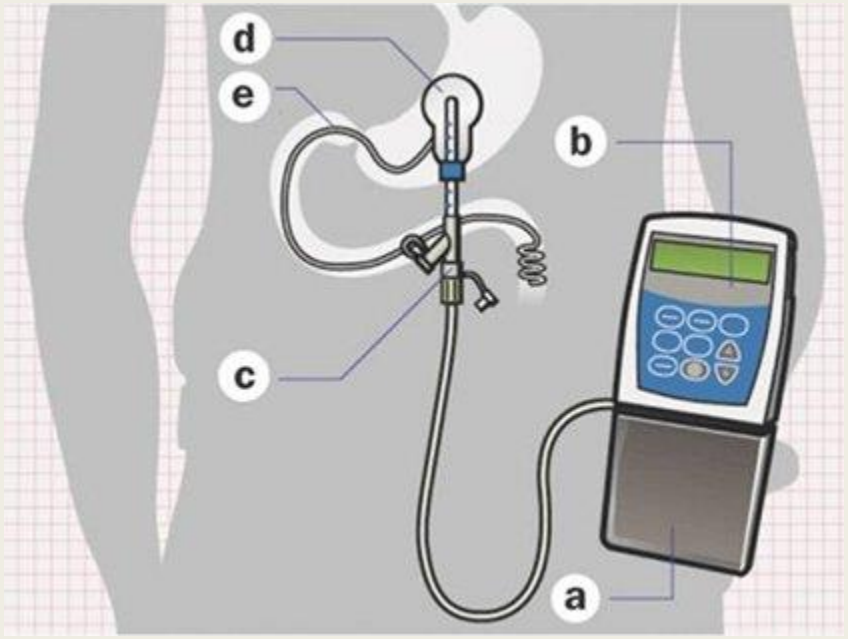


BBB: blood brain barrier; COMT: Catechol O-methyltransferase; 3-OMD: 3 O-methyldopa; DOPAC: dihydroxyphenylacetic acid; 3-MT: 3-methoxytyramine; HVA: homovanillic acid; MAO: monoamine oxidase; D2R: dopamine receptor

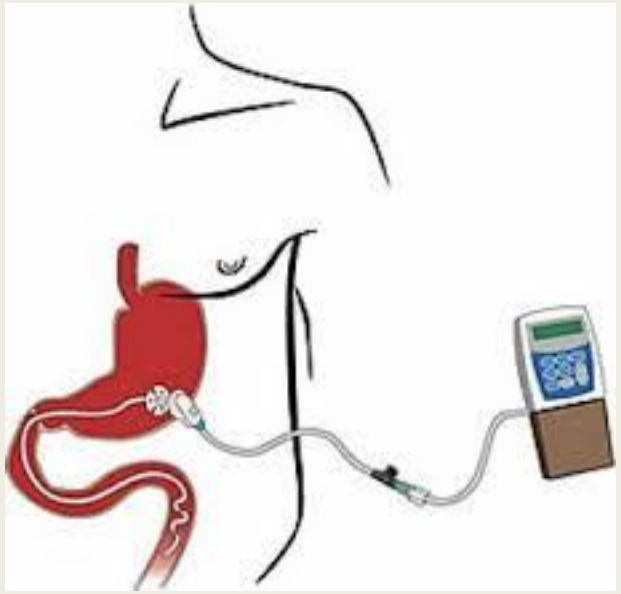
Adapted from Olanow, Stern, Sethi, *Neurology* 2009, 72 (suppl 4): S1

Surgical Therapies: Levodopa/Carbidopa Intestinal Gel

- Continuous infusion of LCIG 16 hours per day
- Reduces off time and increases on time
- Provides more steady state dopamine levels



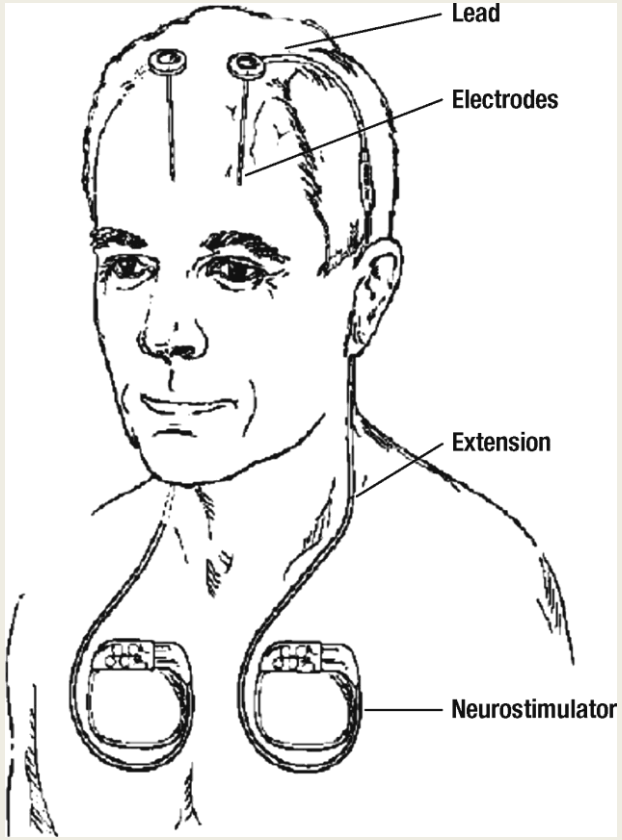
Richards, L. Nature Rev. Neurol. 5: 354, 2009



http://www.parkinsonsresource.org/education/duodopa/

Surgical Therapies: Deep Brain Stimulation (DBS)

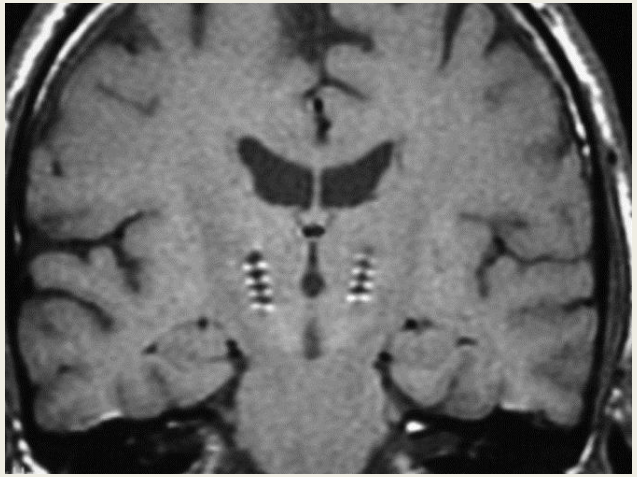
- Electrode implantation in the brain
- Superior to best medical therapy for PD motor symptoms
- Tremor, rigidity, bradykinesia and dyskinesia improve
- Often less helpful for balance
- Helps symptoms responsive to levodopa

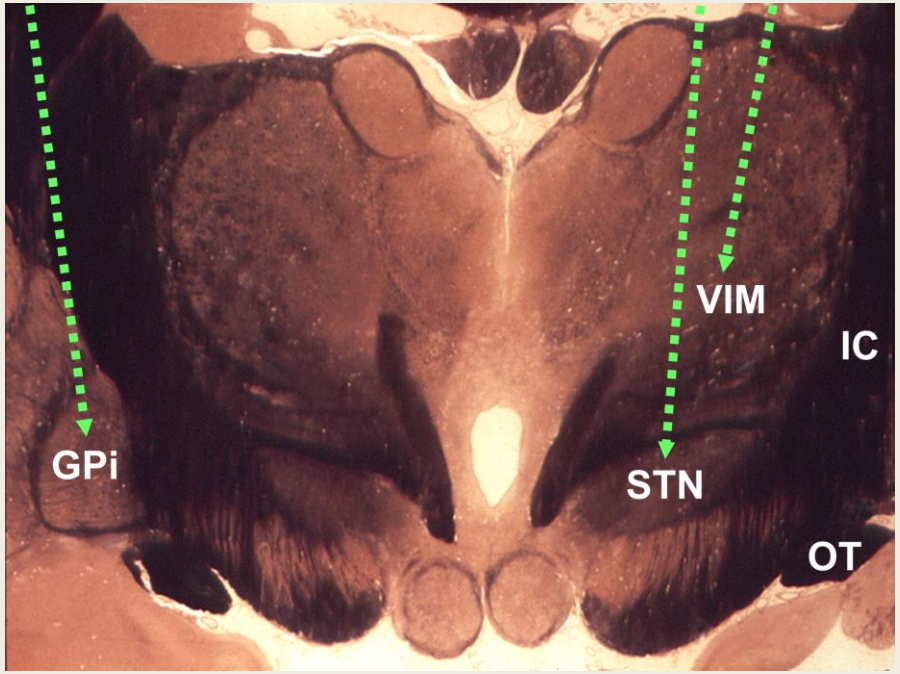


Olanow et al. Neurology 72(Suppl 4):S1 2009

DBS targets for PD

- Subthalamic nucleus (STN)
- Globus pallidus interna (GPi)
- Ventral intermediate nucleus of thalamus (VIM)





Medications to Avoid in PD

- Medications that worsen Parkinsonism
  - *Most antipsychotics*
  - *Metoclopramide*
  - *Anti-emetics (promethazine, prochlorperazine)*
  - *Tetrabenazine, deutetrabenazine, valbenazine*
- Use caution with medications that can impair cognition
  - *Anticholinergics, diphenhydramine*

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Treating Mood Disorders in PD

- *Depression, Anxiety, Apathy, Anhedonia*
- *Treatments:*
  - Antidepressants: choice based on concurrent symptoms
    - *Anxiety*
    - *Insomnia (mirtazapine)*
    - *Bupropion has dopamine activity*
  - Anxiolytics
    - *Benzodiazepines can be used, but can exacerbate depression, cognitive dysfunction*

Treating Cognitive Dysfunction in PD

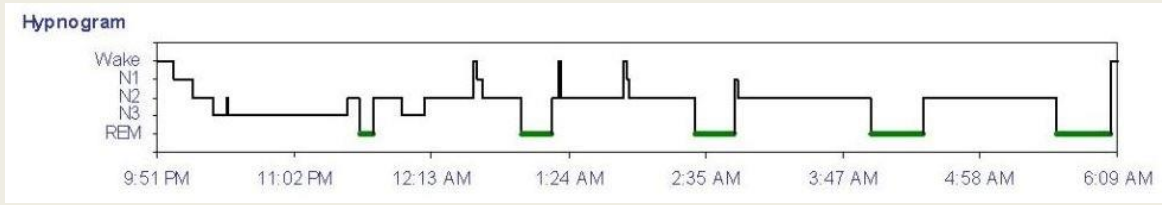
- Mild cognitive impairment; dementia; apathy; bradyphrenia
- Rivastigmine: FDA approved for treating PDD
  - *Transdermal and oral formulations*
  - *Cholinesterase inhibitors*
- Can also use donepezil or memantine
- Non-pharmacological therapies: Exercise

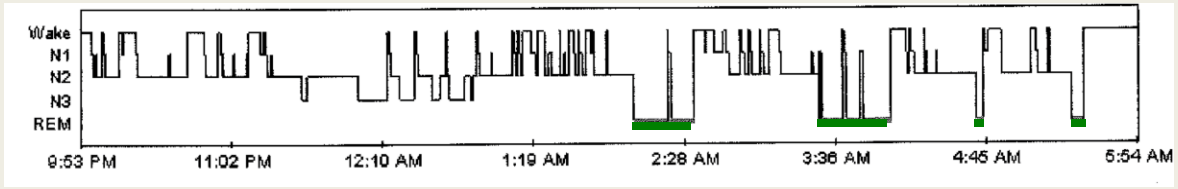
Treating Psychosis in PD

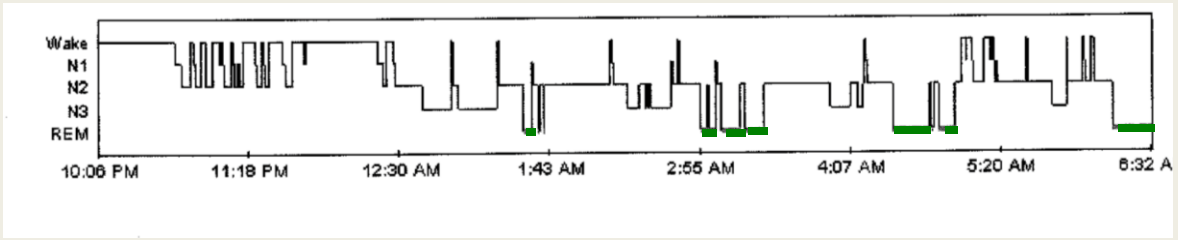
- Hallucinations, illusions, Capgras syndrome, delusions
- Pimavanserin: FDA approved for PD psychosis
  - *Serontonin (5-HT_{2A}) inverse agonist and antagonist*
  - *Concern for increased cardiovascular mortality*
  - *Check QT interval*
- Quetiapine
- Clozapine
- Avoid typical anti-psychotics due to worsening Parkinsonism

Treating Sleep Dysfunction in PD

- *Sleep fragmentation:*
  - Rule out non-PD causes (i.e. sleep apnea)
  - Improve motor symptom control during the night
  - Sleep aids have unwanted side effects
  - Exercise







http://www.globalhealingcenter.com/natural-health/9-reasons-exercise-best-medicine

Sleep Hygiene recommendations

- Maintain a consistent bedtime and waketime
- Avoid TV/Reading/Electronics in bed
- Don’t watch the clock
- Get out of bed if unable to sleep
- Avoid daytime activities at night
- Minimize alcohol

Treating Sleep Dysfunction in PD

- *Excessive daytime sleepiness*
  - Investigate night-time sleep
  - Adjust medications (dopaminergic effects)
  - Strategic napping
  - Exercise

http://www.globalhealingcenter.com/natural-health/9-reasons-exercise-best-medicine

Treatment of REM Sleep Behavior Disorder

- *Emphasize safety*
  - No weapons in bedroom
  - Move tables/lamps away from bed
  - Padded bed rails
  - Mattress on floor
  - Bed partner in separate room
  - Sleeping bag

RBD: Pharmacologic Therapies

(no FDA approved therapies)

- Clonazepam (0.25-2.0 mg)
  - *Can completely suppress behavior but doesn't restore REM atonia*
- Melatonin (3-9 mg)
  - *Partially restores EMG atonia*
- Rivastigmine-can lead to balance trouble
- Levodopa
  - *Suppresses REM*
- Donepezil
  - *Suppressed RBD in case series of 3 patients*
- Dopaminergic medications (pramipexole)

Summary

Parkinson’s disease is a heterogeneous disorder with motor and non-motor symptoms

Symptomatic treatments for PD motor symptoms are effective, but no cure or disease modifying treatment is available

Non-motor symptoms can be as disabling as the motor symptoms of PD