Key Concepts and Issues in Parkinson's Disease in 2016

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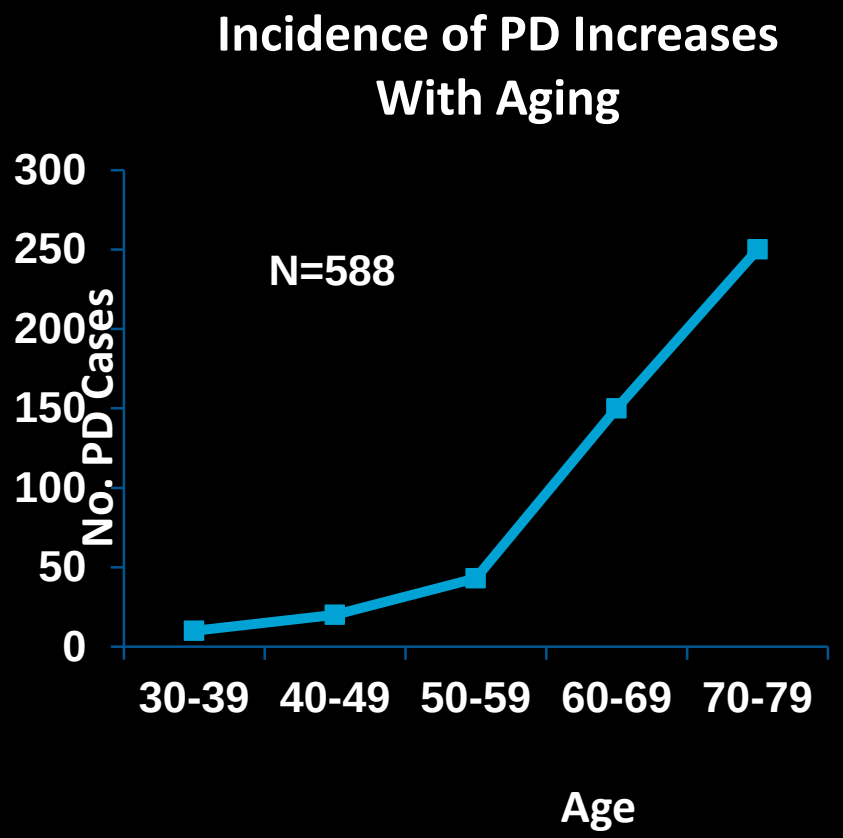
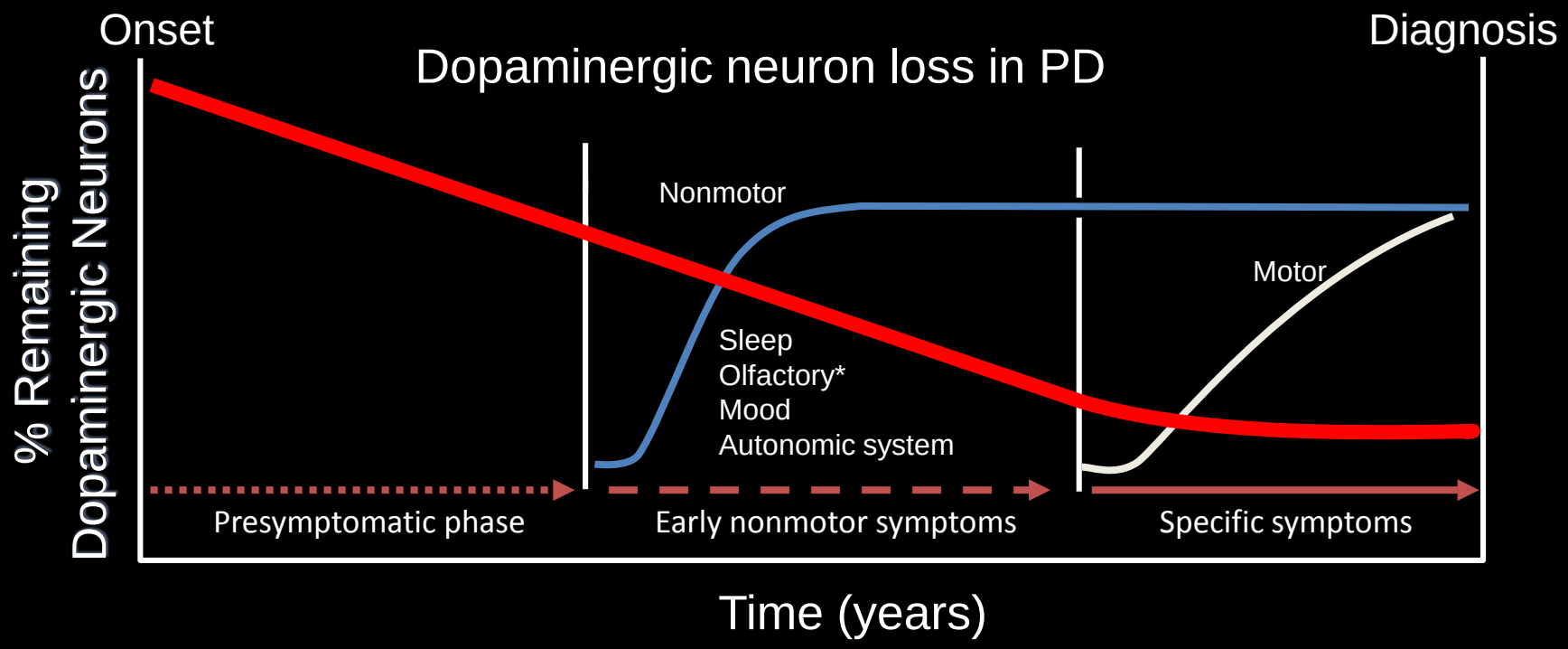
Epidemiology and Incidence of Parkinson's Disease (PD)

Epidemiology

- PD is the second most common neurodegenerative disorder after Alzheimer's disease
- Affects 0.3% of worldwide population
  - 1%-2% of people aged >60 years
- Approximately 1 million people have PD in the United States (US)
- Prevalence predicted to almost double in US from 2005-2030 in individuals aged >50 years



Conceptual Diagram of PD Phases: Significant Pathology Occurs Prior to Motor Symptom Emergence

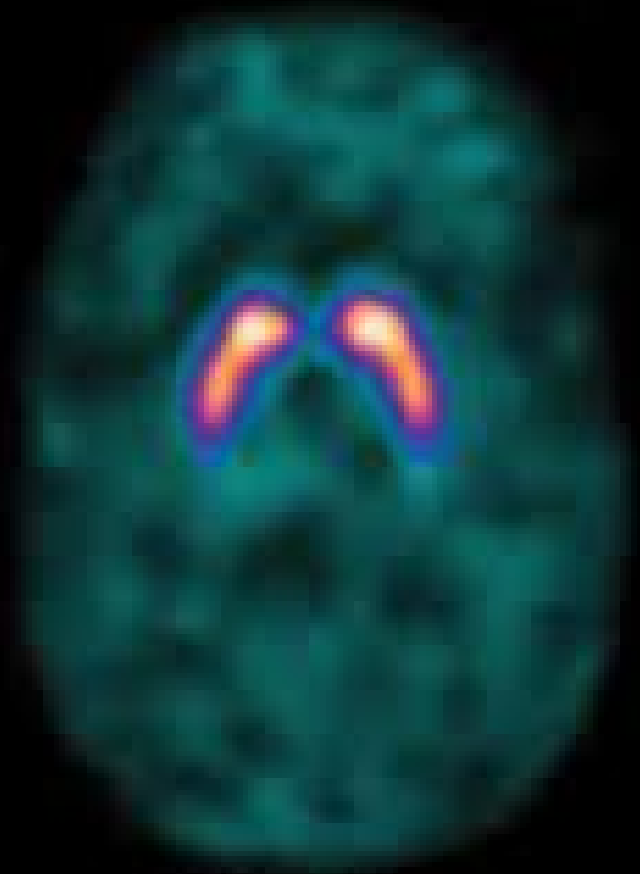


Characteristic Motor Deficits[1]

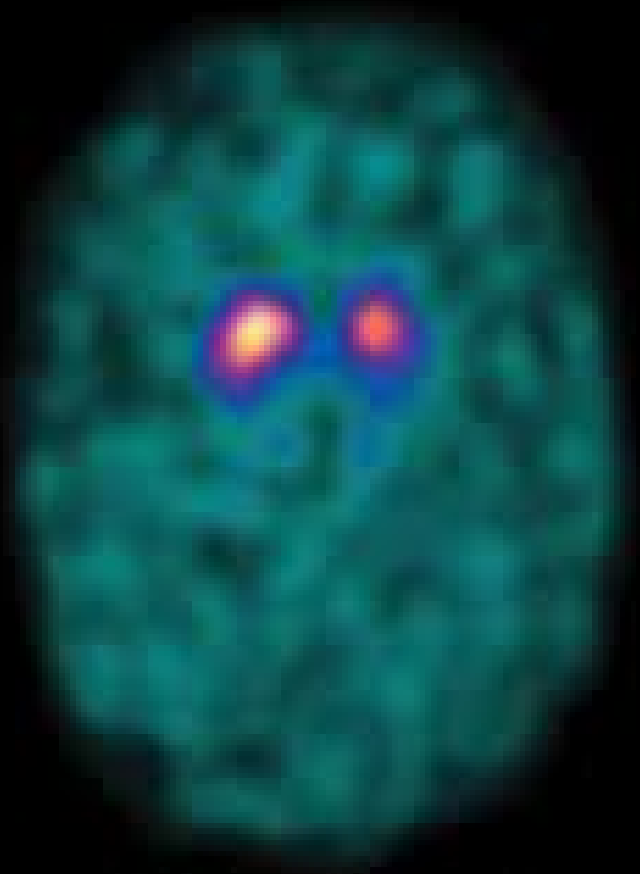
- Tremor
  - Involuntary tremulous motion
- Rigidity
  - Stiffness caused by involuntary increase in muscle tone
- Bradykinesia/akinesia
  - Slowness or absence of movement
- Postural instability
  - Poor balance, loss of postural reflexes, gait disorder

1 Paulson, Stern. In: Watts, Koller, eds. *Movement Disorders*. 1997.

DaTSCAN™



DaTscan Normal



DaTscan Abnormal

Non-Motor PD Features

- Sleep disorders
  - REM Sleep Behavior Disorder (RBD)
  - Periodic Limb Movements of Sleep (PLMS)
  - Restless Leg Syndrome
  - Sleep Apnea
- Autonomic dysfunction
  - Neurogenic orthostatic hypotension
  - Bowel and bladder dysfunction
  - Temperature regulation/Sweating
  - Cardiac sympathetic denervation
- Sensory abnormalities
  - Pain, numbness, aching
  - Visual disturbances
- Dermatological changes
  - Seborrhea
  - Skin cancer
    - Malignant melanoma
- Olfactory dysfunction
  - Very early sign in PD
- Cognitive dysfunction
  - Executive dysfunction
  - Dementia
    - Lewy Body disease
- Psychiatric disorders
  - Affective disorders
    - Depression
    - Euphoria/Mania
  - Psychosis
    - Paranoia
    - Delusions
    - Obsessive Compulsive behaviors

Pain in Parkinson’s Disease

Pain and Sensory Symptoms in PD

- Dr. James Parkinson in 1817 noted “rheumatic pain” in the extremity first affected by tremor
- Dr. Charcot in 1877 noted “neuralgic pains” in PD.
- In one study 40-50% of PD patients experience numbness, tingling, burning aching and pain
- In another study, 9% of PD patients presented with painful sensations

Pain in Parkinson's Disease

- Musculoskeletal
  - Underlying conditions exacerbated by PD
- Radicular
  - Nerve root or peripheral neuropathy
- Dystonia
  - Painful muscle cramps related to l-dopa dosing
- Central pain
  -formication,burning, tingling, strange aching
- Akathitic pain
  - Restlessness, can be related to medication status, usually occurs in OFF state

Pain and Sensory Symptoms in PD

- Pain in PD often correlates with motor state
- Prevelance is 28-83%. After systemic causes excluded it is 40%
- Shoulder pain is a well known presenting symptom in PD (approximately 40%)
  - Misdiagnosed as “frozen shoulder”
    - Leads to unnecessary surgery in some cases
    - Often Improves with adequate PD treatment (and PT)
- Pain related to dystonia (cramping) only occurs in PD patients
  - More common in younger patients as an “off” symptom
- Pain can mimic other neuropathic syndromes (back pain, herniated disc, burning and aching)
  - Leads to extensive and non-fruitful work-ups
  - Often resolves when patient is “on”

Medications

Medical Management Of Parkinson's Disease

General Guidelines

- Each patient is assessed and treated individually
- Initiate symptomatic treatment when patient begins to experience functional disability
- Treat the most bothersome symptoms
- Levodopa-sparing strategies should be considered to limit long-term motor complications
  - When needed, dopaminergic drugs with long half lives are preferred (decreased pulsatile stimulation)

Pharmacologic Treatment Options for Motor Symptoms of Parkinson's Disease

- MAO-B Inhibitors
  - Azilect
  - Zelapar
  - Eldepryl
- NMDA receptor antagonist
  - Amantadine
- Anticholinergics
  - Artane
  - Cogentin
- Dopamine receptor agonists
  - Requip (IR,XL)
  - Mirapex (IR,ER)
  - Apokyn
  - Neupro patch
- Levodopa
  - Carbidopa/levodopa IR
  - Carbidopa/levodopa CR
  - Parcopa
  - Stalevo
    - Carbidopa/levodopa/entacapone
  - Rytary
  - Duopa-Carbidopa/levodopa Intestinal Gel
  - Catechol-O-Methyltransferase Inhibitors
    - Tasmar
    - Comtan

MAO-B Inhibitors (MAOI-B)

- Eldepryl (selegiline)

  -Zelapar (selegeline)
- Azilect (rasagiline)

Dopamine Receptor Agonists

- Parlodel (bromocriptine)
- Requip (ropinirole)
  - Requip XL (once a day)
- Mirapex (pramipexole)
  - Mirapex ER (once a day)
- Apokyn (apomorphine)
  - Only parenteral Parkinson's drug
- Neupro (rotigotine)-24 hour benefit
  - Patch allows continuous dopaminergic stimulation via transdermal delivery

L-DOPA

Levodopa

- Immediate Release

  Sinemet (carbidopa/levodopa)

  - 10/100, 25/100, 25/250
- Controlled Release

  (Sinemet CR, carbidopa/levodopa CR)

  - 25/100 and 50/200
- Orally Disintegrating

  (PARCOPA)

  - 10/100, 25/100, 25/250
- Stalevo (carbidopa, l-dopa, entacapone)
  - Stalevo 50, 75, 100, 125, 150, 200
- Rytary
  - 4 dosing strengths available
    - 23.75/95, 36.25/145mg, 48.75mg/195mg, 61.25mg/245mg
- Duopa-levodopa intestinal gel

COMT INHIBITORS

- Tasmar (tolcapone)
- Comtan (entacapone)

Rytary™

- Sustained release tablet of carbidopa/levodopa with long half-life
- Pivotal trials demonstrated efficacy as monotherapy (early PD)and as add-on therapy in fluctuating patients (reduced off time by 1.8 hours)
  - Also superior to carbidopa/levodopa/entacapone in reducing off time by1.4 hours
  - Administered 2/3 as often as carbidopa/levodopa IR(from 5 times/day to 3.5 times per day)
- Head to head comparisons of risk of dyskinesias and motor fluctuations vs. IR have not been done

Duopa™
(Carbidopa/levodopa Intestinal Gel)

- Aim is to achieve a more continuous
  l-dopa delivery (blood and brain levels)
  - Bypass the stomach and erratic gastric emptying that contributes to unreliable responses
- A stable concentrated CD/LD gel (20mg l-dopa/5mg carbidopa) administered via gastrostomy tube and J-tube using a small programmable external pump to precisely provide the required dose in a narrow therapeutic window
- Provides stable continuous l-dopa with reduced dyskinesias and motor fluctuations

Medications to Avoid in Parkinson's Disease

- Dopamine Receptor Blocking Agents
  - Most Typical and Atypical Neuroleptics
    - Haldol, Zyprexa, Risperdal, Aripiprazole, Geodon, etc.
      - In emergencies, Haldol is only parenteral drug available
    - Preferred drugs are Seroquel and Clozaril (must follow WBC) and Pimvaserin (soon to be released)
  - Antiemetics
    - Compazine, Reglan, Phenergan (dopamine blocking agents)
    - Preferred drug is Zofran (iv or po)

ON THE HORIZON

- Rescue Drugs
  - Sublingual Apomorphine (APL-130277)
  - Inhaled Levodopa (CVT 301)
- Continuous Transdermal Carbidopa/Levodopa
  - levodopa/carbidopa pump-patch (ND0612)
    - Passive chemical diffusion
  - Carbidopa/levodopa Accordion Pill
    - Gastric retentive technology
- Disease Modifying (NET-PD)
  - Inosine (precursor of urate)
    - May slow progression and reduces risk of PD

Mottos To Live By

"Never eat at a diner named Joe's Greasy Spoon"

"Never cheer for the opposing team at Wrigley Field"

"Never obtain Parkinson's disease advice from a Politician"

"Never become complacent about Parkinson's disease"