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

Incidence of PD Increases With Aging

<table>
<thead>
<tr>
<th>Age</th>
<th>No. PD Cases</th>
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<tbody>
<tr>
<td>30-39</td>
<td>0</td>
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<tr>
<td>40-49</td>
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<tr>
<td>50-59</td>
<td>0</td>
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<td>60-69</td>
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<td>70-79</td>
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N=588
Conceptual Diagram of PD Phases: Significant Pathology Occurs Prior to Motor Symptom Emergence

% Remaining Dopaminergic Neurons

Presymptomatic phase

Early nonmotor symptoms

Specific symptoms

Time (years)

Onset

Diagnosis

Dopaminergic neuron loss in PD

Nonmotor

Motor

Sleep

Olfactory*

Mood

Autonomic system

Early nonmotor symptoms

Specific symptoms
Parkinson’s Disease

Characteristic Motor Deficits

• **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

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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
    • Tasmear
    • Comtan
MAO-B Inhibitors (MAO-I-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

- Tasmor (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 by 1.4 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”