Optimizing the Treatment of Parkinson's Disease: Patient-specific Considerations

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Outline
- Epidemiology of Parkinson's Disease (PD)
- Pathology
- Making the diagnosis of PD
- Clinical features of PD
  - Motor features
  - Non-motor features
  - Pre-motor features
  - Natural History of PD
- Treatment of PD
  - Non-pharmacologic treatment
  - Dopaminergic treatment
  - Motor fluctuations
  - Treatment of selected non-motor features of PD
  - Indicators for the need to refer to a specialist
  - Surgical and niche treatments for PD

London, 1817

Braak’s Hypothesis
Spread of Synucleinopathy

Pathology

Epidemiology of PD

Direct and indirect costs associated with PD exceed $20 billion annually in United States
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Making the Diagnosis of PD

- PD remains a clinical diagnosis based on recognition of the three cardinal signs:
  - Rest tremor
  - Bradykinesia
  - Limb rigidity
- DaTscan is a diagnostic tool which can indicate if nigral dopaminergic degeneration is present or not, but it is not specific for PD, and patients should receive a neurologic consultation before considering DaTscan.
- DaTscan is generally recommended when suspicion exists for neuroleptic induced or psychogenic parkinsonism or when an atypical tremor is present.

Motor Features of PD

- Resting tremor
  - 70% of patients
  - "Pill-rolling" tremor in hands
  - Can involve lips, chin, jaw, legs
- Bradykinesia
  - 80% to 90% of patients
  - Most disabling symptom of PD
- Rigidity
  - >90% of patients
  - "Cogwheel" (fluctuating) or "lead pipe" (continuous)
- Postural instability
  - Indicative of advanced-stage PD
  - Frequent cause of falls

Associated Motor Features

- Stooped posture
- Small handwriting
- Decreased arm swing
- Cramping
- Difficulty swallowing
- Changes in facial expression
- Shuffling

Non-motor Features of PD

- Psychiatric disorders
  - Depression in up to 40% of patients
  - Anxiety in ~30% of patients
- Cognitive disorders
  - Mild cognitive impairment
  - Dementia in 15% to 40% of patients
- Sleep abnormalities
  - >70% of patients
  - REM sleep behavior disorder
- Autonomic dysfunction
  - Constipation
  - Orthostatic hypotension
- Sensory
  - Olfactory dysfunction
- Miscellaneous
  - Fatigue and weight loss

Pre-motor Features

- Constipation, anosmia, REM sleep behavior disorder, depression
- Presence of alpha-synuclein in colonic mucosa is controversial
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Natural History of PD

Progression of Motor Symptoms

Non-pharmacologic Treatment

Non-dopaminergic Drug Treatment for PD

Dopaminergic Treatment of PD
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**Levodopa**

- By far the most clinically effective drug for the symptoms of Parkinson’s disease, introduced in 1975 as carbidopa/levodopa
- Helpful in alleviating all of the three cardinal symptoms (tremor, rigidity, bradykinesia)
- When started early in the disease it can produce a dramatic and smooth clinical response lasting years
- Uptake and conversion to dopamine allows storage and release in a physiologic fashion

**Impact of Levodopa on Mortality**

![Impact of Levodopa on Mortality](image)

**Levodopa Dose Response**

![Levodopa Dose Response](image)

**Levodopa Adverse Effects**

![Levodopa Adverse Effects](image)

**Levodopa’s Limitation is Short Half-life**

- Short half-life of levodopa leads to pulsatile stimulation of DA receptors which alters BG signaling resulting in dyskinesia

**Levodopa Recommendations**

- As levodopa is the most effective drug for PD, it should be used in almost all patients at some point in the disease
- Always use the lowest dose of levodopa that is sufficient to control PD symptoms
- To minimize the risk of nausea, avoid 10/100 preparation; generally one needs a 1:4 ratio of carbidopa to levodopa
- Always give levodopa a minimum of 3 times daily to reduce plasma levodopa fluctuations
- Consider treatment with carbidopa/levodopa extended release due to longer half-life
Dopamine Agonists

- Symptomatic efficacy is moderate (second in power to levodopa)
- Because of their long half-lives, these drugs produce more physiologic receptor stimulation and have been shown to delay the onset of dyskinesia
- Slow upward dose titration is the key to achieving adequate doses for full efficacy; side effects may prevent optimal dosing
- When used in addition to levodopa in fluctuators, they result in a 2-3 hour reduction in off time per day

Available Dopamine Agonists

<table>
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<th></th>
<th>Ropinirole</th>
<th>Pramipexole</th>
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<td>0.25 – 8 mg TID</td>
<td>0.125 – 1.5 mg TID</td>
<td>0.24 mg once daily</td>
<td>0.375 – 4.5 mg once daily</td>
<td>2-8 mg daily</td>
<td>2-6 mg SC PRN</td>
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Agonist Side Effects

- Sedation
- Sleep attacks
- GI side effects (nausea and vomiting)
- Orthostatic hypotension
- Leg edema
- Compulsive behaviors (impulse control disorders)

Impulse Control Disorders

- Work by blocking breakdown of dopamine inside the brain thus enhancing the effect of both endogenous and exogenous dopamine
- Rasagiline, selegiline and safinamide currently available
- Rasagiline and selegiline produce symptomatic effects in monotherapy and when used with levodopa
- Safinamide has anti-glutaminergic properties and reduces dyskinesia in animal models, but this finding was not confirmed in humans

COMT Inhibitors

- By blocking peripheral degradation of levodopa, these drugs potentiate the effect of levodopa and lengthen its half-life
- Entacapone and tolcapone are available, but tolcapone almost never used due to idiosyncratic liver toxicity

MAO-B Inhibitors

- By blocking peripheral degradation of levodopa, these drugs potentiate the effect of levodopa and lengthen its half-life
- Entacapone and tolcapone are available, but tolcapone almost never used due to idiosyncratic liver toxicity
Motor Fluctuations

- Almost universal in advanced Parkinson's disease
  - 40% of patients on levodopa for 4-6 years
  - 70% of patients on levodopa for >9 years
- The chief cause of motor disability in this disorder
- Common manifestations: "wearing-off" effect, "skipped-dose" or "no-on" effect, "on-off" phenomenon
- Related to variations in levodopa absorption, distribution and metabolism


Management of Motor Fluctuations

- The wearing-off effect is best managed by more frequent, but not overlapping, levodopa dosing
- The "skipped-dose" effect is due to administration of subthreshold amounts of levodopa; the size of the dose should be raised until 80% of doses actually kick in
- The "on-off" effect is caused by dietary protein or too frequent administration of small levodopa doses
- Adjunctive drug therapy with MAO-B inhibitors, COMT inhibitors, amantadine, or dopamine agonists may be helpful

Carbidopa/Levodopa Extended Release

Healthy volunteers, C/L extended release, 2 caps of 245 mg

Orthostatic Hypotension

- Orthostatism is common in PD due to degeneration of the post-ganglionic autonomic nerves resulting in reduced release of norepinephrine
- Non-pharmacologic measures include liberalizing dietary salt and sleeping with the head of the bed elevated
- Pharmacologic therapy consists of
  - Fludrocortisone
  - Midodrine (agonist of norepinephrine receptors)
  - Droxidopa (pro-drug of norepinephrine)
Hallucinations and Delusions

- Positive psychotic features are common in advanced PD, particularly when dementia is also present
- Typical neuroleptics and most “atypical” antipsychotics must be avoided due to the risk of worsening PD motor symptoms
- Quetiapine and clozapine are atypical antipsychotics which at usual doses do NOT worsen PD and which may be effective for psychosis
- Pimavanserin is a new antipsychotic specifically indicated for PD psychosis with no anti-dopaminergic activity that works by reducing serotonergic tone

Pimavanserin

- A serotonin inverse agonist
- Dosed as 17 mg two tablets once daily
- Full effect may take 6 weeks to fully wash in
- Common side effects are nausea and peripheral edema

Pimavanserin Efficacy

When to Refer to a Specialist

- Management of early PD is straightforward and consists of
  - Recommendation for regular exercise
  - Annual dermatologic examinations
  - Treatment with levodopa/carbidopa, preferably long-acting forms given a minimum of three times daily
- General neurology referral is appropriate early in the course of PD to ensure dopaminergic drugs of differing classes have been considered
- As PD advances, motor complications and non-motor features develop which may require movement disorders specialist involvement
- Consider referring patients to a movement disorder specialist for clinical trial participation

Surgery for PD

- Originally developed in the 1960s, surgery is now offered to patients with established levodopa-responsive PD for whom drug treatment is no longer adequate
- Most commonly employed technique is deep brain stimulation of the subthalamic nucleus (STN) or globus pallidus (GPI)
- Most often, these procedures are performed bilaterally to achieve best results
- Patients undergoing STN stimulation usually need to reduce oral dopaminergic medication postoperatively, while GPI stimulation may not require drug dose reduction
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**Surgical Selection Criteria**
- Advanced PD having failed reasonable medical management
- Persistent favorable response to levodopa (just marred by dyskinesia or motor fluctuations)
- Good gait and balance in the on state
- Normal or essentially normal cognition (dementia is exclusionary)
- Depression (if any) is well controlled by medication
- Adequate support system and ongoing accessibility to a specialized center for device programming

**Motor Block Phenomena**
- Motor blocks are sudden, often unpredictable inhibitions of voluntary movement
- Most commonly, these affect gait and result in sudden “freezing”
- Freezing is most frequent when the patient enters doorways or enclosed spaces
- Can occur with peak, trough or mid-range brain levodopa levels
  - Off-state freezing of gait (FOG) is most common and treatable by reducing off states
  - On-State FOG is highly resistant to drug treatment

**Visual Cueing**
- Several studies have pointed out that a variety of visual and auditory cues may help overcome FOG
- The mechanism of action of these devices is unknown

**Summary**
- Parkinson's disease is a common neurodegenerative disease of the elderly that will be increasingly common as the population ages
- The disease is complex because of its myriad clinical features which include both motor and non-motor symptoms
- Dopaminergic treatment with levodopa is the mainstay of treatment of the motor aspects of the disease
- Practitioners should be alert to the worsening of symptoms that result from disease progression which necessitates drug dosage adjustment
- Referral to a movement disorders neurology specialist is recommended when complex features arise or to consider clinical trial participation