Parkinson’s Disease:
Moving Toward Improved Understanding and Treatment

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Disclosures
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Learning Objectives
• Explain the pathophysiology of Parkinson’s disease, including the motor and non-motor symptoms.
• Summarize new data on current and emerging therapies for Parkinson’s disease
• Apply available modalities to patient cases using evidence-based medicine
• Describe the impact of OFF periods on patient daily life
• Formulate strategies for improving education regarding OFF periods in patients with Parkinson’s disease
Pathophysiology of Parkinson’s disease

Parkinson’s Disease

Parkinson’s disease is a progressive neurodegenerative disorder characterized by aggregates of misfolded α-synuclein called Lewy bodies. Parkinson’s disease has a complex clinical phenotype that includes motor and non-motor symptoms that vary not only in severity but also in terms of presence or absence from case to case.

Parkinson’s Disease – Substantia Nigra

[Images showing normal and Parkinson’s disease Substantia Nigra]
Dopamine Deficiency in the Nigrostriatal Pathway

Basal ganglia – “extrapyramidal system” includes substantia nigra, striatum (caudate and putamen), globus pallidus, subthalamic nucleus, and thalamus

Parkinson’s disease 60% - 80% reduction in dopamine producing neurons in the substantia nigra

Two output pathways from the striatum: indirect pathway in which dopamine (D2) has an inhibitory influence and the direct pathway in which dopamine (D1) has an excitatory influence

In the context of dopamine depletion the indirect inhibitory pathway mediated via D2 striatal receptors is thought to be overactive, whereas the direct inhibitory pathway mediated via D1 striatal receptors is underactive

As a consequence, the main pallidal-thalamic outflow pathway provides excessive inhibitory input to the thalamus, which causes suppression of thalamo-cortical-spinal pathway, causing slowness of movement (bradykinesia)

Clinical Diagnosis of PD Requires Only Motor Symptoms

First essential criterion:
• Slowing of physical movement (bradykinesia)

Plus at least one of the following:
• Tremor (4-7Hz)
• Muscle rigidity

Stage and Severity of Parkinson’s Disease

Hoehn and Yahr Stage

Stage 1 – unilateral involvement only, usually with no functional disability
Stage 2 – bilateral involvement without impairment of balance
Stage 3 – bilateral involvement with impairment of postural reflexes (balance)
Stage 4 – severely disabling disease; still able to walk with assistive device or stand unassisted
Stage 5 – confinement to bed or wheelchair, unless aided

Unified Parkinson’s Disease Rating Scale – part 3 motor exam, example for rigidity

0: normal: no rigidity
1: slight: rigidity detected only with activation maneuver
2: mild: rigidity detected without activation maneuver, but full range of motion easily achieved
3: moderate: rigidity detected without activation and full range of motion is achieved with effort
4: severe: rigidity detected without activation and full range of motion not achieved
Now let me tell you the rest of the story...

Non-motor symptoms of Parkinson’s disease

Neuropsychiatric:
apathy, anxiety, depression, psychosis, impulse control disorders
Cognitive impairment, ≤40% have MCI at diagnosis and 80% demented within 20 years of motor symptom onset
Olfactory loss ≤90%
Dysautonomia ≤70%
Sleep disturbances >30%

Parkinson’s as a Disease Model for Neuropsychiatric Symptoms
New Landscape of Parkinson’s Disease

Prodromal PD → Symptomatic PD → PD Dementia

PD diagnosed by motor symptoms

New ‘stages’ of Parkinson’s disease

Prodromal: pre-motor, hyposmia, RBD, cardiac sympathetic denervation

Symptomatic: motor symptom onset and progression

Dementia: progressive cognitive decline due to Lewy body disease or comorbidity
Key Points

- Parkinson's disease, in most cases, starts years before motor symptoms are present.
- Non-motor symptoms such as autonomic dysfunction, REM sleep behavior disorder, and loss of smell are biomarkers of early disease.
- Going forward, early recognition and disease modifying treatments will likely significantly lower the burden of PD.

Current and emerging therapies for Parkinson’s disease

1. Prevention or delay of disease progression ('disease modifying')
2. Symptomatic monotherapy
3. Adjunctive therapies
4. Prevent or delay of motor complications
5. Motor complication therapies
Disease Modifying Interventions

Exercise – has insufficient evidence and considered investigational, but is widely recommended

No clinically useful interventions to prevent or delay disease progression (Fox SH et al 2018)

Notable negative studies – MAOIs, CoQ10, creatine, vitamin D, dopamine agonists

Promising candidates – BIIB054 (cinpanemab) targets abnormal alpha-synuclein, BIIB094 (LRRK2 ASO) antisense oligonucleotide helps reduce LRRK2 protein, small molecules may also be helpful, agents that down regulate inflammation especially via type-2 astrocytes

Symptomatic Monotherapy

**Efficacious – clinically useful**
- Dopamine agonists – non-ergot, ergot
  - Levodopa + peripheral decarboxylase inhibitor – immediate release, controlled release, extended release
  - Monoamine oxidase inhibitors – B-selective, eg, rasagiline, selegiline

**Likely efficacious – clinically useful or possibly useful**
- Anticholinergics
- Amantadine

Adjunctive Therapies

**Efficacious – clinically useful**
- Dopamine agonists
- Rasagiline

**Likely efficacious – clinically useful or possibly useful**
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- Amantadine
Deep Brain Stimulation

Potential benefits:
- Reduces motor signs of the disease
- Improves off time
- Improves dyskinesia, especially GPi DBS
- STN may allow dopamine reduction

Potential adverse effects:
- Speech and cognitive impairment
- Gait changes

Key Points
- Symptomatic therapies are predominantly focused on motor symptoms and are based on increasing dopamine levels
- Adjunctive therapies are used when patients are deemed to be "undertreated" with monotherapy
- Deep brain stimulation is a viable option for many and earlier use and broader application of this intervention is being explored
Motor complications of dopaminergic therapy

Levodopa Induced Dyskinesia

Hyperkinetic involuntary movements of upper and lower limbs, trunk, and less often facial muscles

May occasionally have dystonic posturing

~40% experience dyskinesia after 4-6 years of levodopa treatment

Dyskinesia is associated with longer duration of PD and higher levodopa doses

Dyskinesia is most likely at "peak" dose — high levodopa concentrations

On-off dopamine medication fluctuations
On-off Dopamine Medication Fluctuations

Most of end-of-dose deterioration (return of motor symptoms)
Occur in >50% of patients at 5 years and nearly 100% at 10 years
Disease duration, exposure to levodopa and cumulative dose, delayed or erratic gastric emptying, female sex, low body weight, and young disease onset
High protein meals interfere with absorption
Rare cases, can occur as early as 6 months after initiating dopaminergic therapy
Most associated with levodopa, but can occur with agonists
Non-motor fluctuations often occur in conjunction with motor fluctuations

Recognizing Off-Periods (and Other Complications of Therapy)

Ask patients to keep a symptom journal
Suggest they anchor journal entries by noting the time they take PD medications
Do off periods occur at every dosing interval? Or only after meals?
During what interval of time, relative to medication dosing, do off periods occur? Dose failure? End-of-dose wearing off?
Do any other (non-motor) symptoms occur during off periods?

Prevent or Delay of Motor Complications

Efficacious – clinically useful
- Dopamine agonists
Treatments for Motor Fluctuations

**Efficacious – clinically useful**
- Dopamine agonists
- Levodopa with peripheral decarboxylase inhibitors, several forms, standard, extended release, intestinal infusion
- COMT inhibitors, eg, entacapone
- MAO-B or MAO-B plus channel blockers
- Bilateral STN or GPi DBS
- Unilateral pallidotomy

**Likely efficacious – possibly useful**
- Istradefylline (adenosine A2A antagonist)
- Apomorphine SC

Treatments for Dyskinesia

**Efficacious – clinically useful**
- Amantadine
- Clozapine, but requires special monitoring
- Bilateral STN or GPi DBS
- Unilateral pallidotomy

**Likely efficacious – clinically useful**
- Intestinal infusion of levodopa

Key Points

- Motor complications of dopaminergic therapy include dyskinesia and on-off fluctuations
- Disease duration, rather than time of exposure to levodopa, is thought to be the main factor associated with the development of motor complications
- Motor complications are most typical of moderate to advanced disease
Case vignettes

63 year old right handed male with new onset rest tremor in left hand, mild bradykinesia and rigidity

- carbidopa/levodopa 25/100mg 1 tablet 3 times daily
- rasagiline 1 mg daily
- rotigotine transdermal patch
- trihexyphenidyl

72 year old right handed male with an 8 year PD hx, no tremor, moderate bradykinesia and rigidity, severe dyskinesia on standard levodopa Q3 hours

- amantadine
- rasagiline 1 mg daily
- surgery, eg, GPi DBS
- transition to extended release levodopa
56 year old right-handed female with PD onset at age 42, now with bilateral symptoms, severe on-off fluctuations and moderate dyskinesia on levodopa 5/day

- amantadine
- bilateral deep brain stimulation
- pramipexole extended release
- COMT inhibitor

Any Questions?

References

