Parkinson’s Disease: Management and Treatment

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Outline

- Parkinson’s Disease
  - Demographics
  - Diagnosis Characteristics
  - Pathophysiology
- Treatments
  - Levadopa
  - Anticholinergics: Amantadine
  - Dopamine Agonists
  - COMT Inhibitors
  - Selegiline
  - Rasagiline

What Is Parkinson’s Disease?

- Chronic, progressive neurodegenerative disease
- “Shaking palsy” first described in 1817
- Clinical diagnosis, not laboratory diagnosis
- 2 or more cardinal signs:
  - Bradykinesia
  - Rigidity
  - Tremor
- Slowly progressive
Epidemiology of PD

- **Incidence**
  - 20/100,000 in US
  - Approximately 60,000 new cases/year
  - 5 to 24/100,000 worldwide

- **Prevalence**
  - 300/100,000 in US and Canada
  - 1 million persons in the US
  - 500/100,000 persons >50 years
  - 1000/100,000 persons >65 years
  - Many cases remain undiagnosed

Related Disorders

- Secondary parkinsonism
  - Medication-related (eg, antipsychotics)

- Atypical parkinsonism
  - Progressive supranuclear palsy (PSP)
  - Multiple system atrophy (MSA)

- Diffuse Lewy body disease

Lewy bodies in a neuron from the substantia nigra in PD
**Possible Etiologies of PD**

- **Environment**
  - Pesticides
  - Herbicides
  - Rural living
  - Well water
- **Oxidative stress**
- **Mitochondrial dysfunction and inflammation**
- **Glutamate excitotoxicity**
- **Ubiquitin-Proteosome System (UPS) defects**


**Possible Etiologies of PD**

- **Genes**
  - Autosomal dominant inheritance is rare and includes:
    - α-synuclein
    - Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)
  - Autosomal recessive juvenile parkinsonism (AR-JP) has been associated with mutations in the parkin gene
    - Parkin gene mutations may account for PD in up to 50% of familial patients with AR-JP


**Manifestations at PD Onset**

- Tremor at rest
- Bradykinesia
- Rigidity
- Micrographia
- Hypophonia
- Masked face
- Slowed activities of daily living
- Decreased arm swing when walking
- Dystonia
- Hypomimia

Non-motor Symptoms of PD

- Cognitive impairment
- Depression
- Fatigue
- Anxiety
- Sleep disturbances
- Sensory symptoms
- Bladder urgency
- Constipation
- Impaired olfaction
- Seborrheic dermatitis


Cardinal Features of PD

- Tremor (resting)
- Rigidity
- Bradykinesia/Akinesia
- Postural Instability

Cardinal Features of PD

- Tremor
  - 50% of patients present with tremor as an initial symptom
  - Most often it begins in one hand, but may appear in legs, jaw or other areas
  - Spreads to both sides as disease progresses
  - Occurs in motion classically described as “pill rolling”
Cardinal Features of PD

- **Rigidity**
  - Increased resistance to movement when a joint is passively flexed and extended
  - “Lead-Pipe” rigidity
    - Uniformly increased resistance to movement
  - “Cogwheel” rigidity
    - Variable, jerky resistance

- **Bradykinesia/Akinesia**
  - Bradykinesia, slowness of movement
    - Slowness in carrying out and stopping movements
    - Delay in starting movement
  - Akinesia, absence of movement
    - Example: Freezing of Gait (FOG)

- **Postural Instability**
  - Occurs in more advanced stages of PD
  - Due to loss of postural reflexes
  - Least specific motor symptom
  - Patients become prone to falls
**Natural History of PD**

**Without treatment**
- PD progresses over 5 to 10 years from mildly symptomatic state to rigid, akinetic state in which patients cannot care for themselves
- Death often occurs from complications of immobility (e.g., pneumonia, pulmonary embolism)

**Hoehn and Yahr Stages**

<table>
<thead>
<tr>
<th>Stage 1</th>
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<tbody>
<tr>
<td>Tremor, rigidity, or bradykinesia on one side; minimal functional impairment</td>
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<table>
<thead>
<tr>
<th>Stage 2</th>
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<tr>
<td>Features of Stage 1 become bilateral</td>
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<thead>
<tr>
<th>Stage 3</th>
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<tbody>
<tr>
<td>Bilateral symptoms progress but are still mild to moderate with a mild loss of balance</td>
</tr>
<tr>
<td>Patient can still function independently</td>
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<thead>
<tr>
<th>Stage 4</th>
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<tbody>
<tr>
<td>Bilateral symptoms become more severe with significant loss of balance</td>
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<td>Patient requires substantial assistance</td>
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<tr>
<th>Stage 5</th>
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<tbody>
<tr>
<td>Bilateral symptoms are severe</td>
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<tr>
<td>Patient restricted to a bed or wheelchair</td>
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</tbody>
</table>

**Clinical Features of PD**

- **Autonomic Dysfunction**
  - Orthostatic hypotension, constipation, dysphagia, sweating, urinary dysfunction

- **Neuropsychiatric Disturbances**
  - Depression, dementia, hallucinations, sleep disturbances, somnolence (sleepiness)
  - 30% – 40% of patients develop depression

**Stages of PD**

- **Early stage**
  - Mild symptoms
  - ADL not jeopardized
  - "Honeymoon period"
  - Treatment adequately controls symptoms

- **Moderate stage**
  - Fluctuating response to LD
  - Symptoms affect ADL
  - More intensive treatment needed

- **Advanced stage**
  - Symptoms resist all available treatment
  - Disability
  - Motor complications
  - Freezing
  - Falls
  - Cognitive decline
  - Death

**References**

Natural History of PD

- Decline may be rapid during first years of disease
- Possible risk factors for PD progression:
  - Older age at onset
  - Longer disease duration
  - Clinical phenotype
  - Dementia

Poewe et al. Neurology. 1996;47:S146-52

Morbidity and Mortality in PD

- Increased morbidity and mortality
  - Mortality rates vary due to heterogeneity of PD populations
  - Worse with dementia
  - Better when treated
- Most common causes of death:
  - Pulmonary infection/aspiration
  - Pulmonary embolism
  - Complications of falls/fractures
  - Urinary tract infection


Quality of Life in PD

- Health-related quality of life (QOL) influenced more by mental than physical factors
- Considerably affected by:
  - Symptoms of PD and disease progression
  - Side effects of drug therapy
    - Motor fluctuations and dyskinesias

Chrischilles et al. Parkinsonism-Relat Disord. 2002;8:199-209
Neurotransmitters and Movement

- Two main neurotransmitters involved in PD
  - Dopamine
  - Acetylcholine

Dopamine Synthesis and Metabolism

Adapted from Adler et al., Parkinson’s Disease and Movement Disorders. Totowa, NJ: Humana Press; 2000:64.

Neurotransmitters and Movement

- Dopamine facilitates movement
  - Dopamine binding to both D1 and D2 receptors results in increased thalamic activity

- Dopamine blocks acetylcholine transmission
  - Decreased dopamine results in increased cholinergic activity causing some PD symptoms
Neurodegeneration

- Loss of dopaminergic neurons in the substantia nigra begins years before symptoms arise.
- 60%-80% of dopaminergic nigral neurons have been lost by the time clinical features of PD emerge.
- As a dopamine deficiency occurs, direct pathway activity is reduced and indirect pathway activity is increased.

Dopaminergic Cell Loss

- PD patients have a higher yearly rate of dopaminergic cell loss compared to people without the disease (6-13% versus 0-2.5%).

Possible causes for dopaminergic cell loss:
- Oxidative stress inside nigral cells.
- Damage to mitochondria
  - Mitochondria damaged by free radicals cannot produce enough energy for cell activity.
- Apoptosis cascade
  - Programmed cell death
  - Possibly triggered by free radicals.
- Loss of neural growth factors
  - Deficiencies of: BDNF, GDNF, FGF2 in the substantia nigra of PD patients.
Lewy Bodies

- Abnormal intracellular cytoplasmic inclusions (unusual protein clusters)
- Characteristic of PD

Goal of Therapy

Adequately control the symptoms of Parkinson’s disease while minimizing the adverse effects of drug therapy for as long as possible

Treatment Interventions

- Preventive treatment
  - No definitive prevention available
- Symptomatic treatment
  - Pharmacological
  - Surgical
- Non-motor management
- Restorative—experimental only
  - Transplantation
  - Neurotrophic factors
Unmet Needs in PD Treatment

- Effective symptom control with few side effects
- Neuroprotection
- Avoid and/or treat
  - Motor fluctuations and dyskinesia
  - Cognitive dysfunction
  - Gait and balance difficulty
- Convenient dosing regimen (once daily; no titration)
- Improve quality of life


Neuroprotective Therapy in PD

- Protect or rescue vulnerable nigral neurons
- Slow or stop disease progression
- Should be initiated as soon as diagnosis of PD is made
- Should be directed at:
  - Etiologic factors
  - Pathogenetic factors

Possible Neuroprotective Agents Under Investigation

- MAO-B inhibitors
  - Selegiline, rasagiline
- Dopamine agonists
  - Ropinirole, pramipexole
- Trophic factors
  - GDNF, fibroblast growth factor, GM-1 Ganglioside, neuroimmunophilins
- Anti-inflammatory drugs
  - COX II inhibitors
- Anti-glutamatergics
  - Riluzole, remacemide
- Bioenergetics
  - Coenzyme Q10

Unmet Needs in PD Treatment: Neuropsychiatric Issues

- Cognitive impairment and dementia
- Hallucinations and psychosis
- Agitation
- Anxiety
- Sleep disorders

Unmet Needs in PD Treatment: Autonomic Dysfunction

- Orthostatic hypotension
- Constipation/urinary problems
- Thermoregulation and sweating
- Sexual dysfunction
- Pain/dysesthesias
- Dysphagia
- Seborrhea/blepharitis
- Sleep disturbances

Parkinson’s Disease: Therapeutic Options

- Carbidopa/Levodopa
- Anticholinergics
  - benztropine, trihexyphenidyl
- Antiglutaminergic agents
  - Amantadine
- Dopamine agonists
  - pramipexole, ropinirole, bromocriptine,
  - pergolide, apomorphine
- COMT inhibitors
  - entacapone, tolcapone
- MAO-B Inhibitors
  - selegiline, Zelapar, rasagiline
Levodopa (Sinemet®)

- Dopamine precursor
- First trial in PD patients 1961
- Most effective symptomatic therapy; “gold standard”
- Almost all patients will require at some point
- Administered with carbidopa to reduce peripheral conversion to dopamine
- Dosage schedule varies from patient to patient
- Most common early, acute side effects: nausea, vomiting, postural hypotension

Levodopa Metabolism

Motor Complications Associated With Levodopa Therapy

- Smooth clinical response for up to 3 to 5 years
- After “honeymoon,” slow “wearing off” of clinical benefit from LD dose
  - Motor fluctuations (“ON-OFF” response, delayed ON, dose failure)
  - Dyskinesias

References:
As the Disease Progresses, the Therapeutic Window Narrows*

Symptoms and side effects occur as the levodopa therapeutic window diminishes*

*Artist’s interpretation of plasma pharmacokinetic curves and the narrowing therapeutic window


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Causes of Motor Fluctuations

- Diminished capacity of striatal nerve terminals to store and release dopamine
  - Striatal function becomes dependent on plasma LD levels
  - Pathological modification of striatal receptors
    - Related to nonphysiologic delivery of LD in a pulsatile mode
- Risk Factors
  - Higher doses of LD
  - Early onset (age <40 years) of PD


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Non-motor Fluctuations

- Sensory/pain
  - Tingling sensation
  - Tightening sensation
- Mental (cognitive/psychiatric)
  - Anxiety
  - Fatigue
  - Irritability
- Autonomic dysfunction
  - Drenching sweats
  - Facial flushing
  - Dry mouth

- Akathisia
- Diffuse pain
- Depression
- Slow thinking
- Hallucinations
- Dyspnea
- Dysphagia
- Constipation

Anticholinergics

- Used to treat PD since mid-1800s
- Most useful for treating tremor
  - Typically used in younger patients (<70 years of age) in whom tremor is the dominant clinical symptom
- Not indicated for older patients, those without tremor, or those with dementia
- Commonly used agents include benztropine and trihexyphenidyl
- Most important central side effects are cognitive
- Peripheral side effects are muscarinic


Amantadine (Symmetrel®)

- Antiviral agent; limited antiparkinsonian activity
  - May increase dopamine release or inhibit its reuptake
  - May act as dopamine receptor agonist
  - May be weak NMDA antagonist
- Monotherapy in early PD to delay need for LD
  - Considered only “likely efficacious”
- Adjunct to LD in advanced PD to decrease dyskinesias
- Side effects: hallucinations, confusion, insomnia, nightmares


Amantadine

- Modest symptomatic benefit in tremor, rigidity and bradykinesia (200-300 mg/day)
- Can reduce levodopa-induced peak-dose dyskinesias
- May augment dopamine release, inhibit reuptake and stimulate dopamine receptors
- Adverse effects: dry mouth, confusion, hallucinations, agitation and leg swelling

**Dopamine Agonists**

- Act directly on dopamine receptors without metabolic conversion
  - Longer t$_{1/2}$ than L-Dopa
- Monotherapy may delay motor complications
- Adjuncts to LD in advanced PD, lower dosage of LD
- Earliest were ergot derivatives (bromocriptine, pergolide)
  - Newer non-ergot derived agonists (ropinirole, pramipexole) are relatively selective for D$_2$ and D$_3$ receptors
- May be associated with more acute side effects than LD
  - Neuropsychiatric effects more frequent with agonists
  - Associated with somnolence, sleep attacks, hallucinations, peripheral edema
- Pergolide has been associated with valvular heart disease

References:

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**Catechol-O-Methyltransferase (COMT) Inhibitors**

- Inhibit peripheral metabolism of LD, prolonging response and decreasing required LD dose
- Increase "ON" time, decrease "OFF" time, improve motor scores
- Entacapone taken with each LD dose; no liver function monitoring required
- Tolcapone administered tid; liver function monitoring required
- Associated with dopaminergic side effects: primarily dyskinesias, diarrhea

References:

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**COMT Inhibitor AEs**

- Nausea
- Vomiting
- Hallucinations
- Confusion
- Diarrhea
- Urinary discoloration
- Abdominal pain
Monoamine Oxidase-Type B (MAO-B) Inhibitors

- Selectively inhibit central MAO-B, which degrades striatal dopamine
- Symptomatic benefit consistent with increased dopamine
- Class members include:
  - First-generation: selegiline
  - Second-generation: rasagiline

Selegiline

- **Indication**
  - Approved as adjunct therapy to levodopa
  - Used off label as monotherapy in early disease
- **Dose**
  - 10 mg/d in divided doses

Selegiline in Early PD

- Probability of Reaching End Point
- Placebo* vs. Selegiline*
- * With or without tocopherol (vitamin E)
- †Endpoint = need to begin levodopa therapy
- P < 0.0001
- Hazard ratio = 0.43
Rasagiline
A Novel, Second Generation MAO-B Inhibitor

- Once daily
- No titration
- Highly selective in vitro
- Potent, irreversible inhibition of MAO-B
- Propargylamine structure, no amphetamine metabolites

Metabolites of Rasagiline and Selegiline

[Chemical structures of Rasagiline and Selegiline with their metabolites]

Rasagiline: Second Generation MAO-B Inhibitor – Clinical Differences

- Rasagiline
  - Greater MAO-B potency
  - Once daily dosing no titration
  - Monotherapy side effect profile similar to placebo
  - FDA approved
    - Initial monotherapy
    - Adjunctive therapy
  - Evidence supporting adjunctive therapy by MDS and AAN
  - Possible slowing of disease – TEMPO 12 Month

- Selegiline
  - Twice daily dosing
  - Side effects possibly related to amphetamine metabolites
  - Not approved for monotherapy
    - FDA approved
      - Adjunctive therapy
    - Low level of evidence supporting use as adjunctive therapy by AAN and MPS
    - DATATOP did not prove neuroprotection

References:
Youdim. Presented at the 7th International Congress of Parkinson’s Disease and Movement Disorders; 2002 November 10; Miami, FL.
TEMPO: Percent of Patients on Rasagiline Without Additional Dopaminergic Therapy

At 2 years, 46% of the patients remaining in the study are adequately controlled by rasagiline treatment only.

Rasagiline treatment only

<table>
<thead>
<tr>
<th>Years of Treatment with Rasagiline</th>
<th>No. of Patients Remaining in Study</th>
</tr>
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<tbody>
<tr>
<td>Start</td>
<td>400</td>
</tr>
<tr>
<td>1</td>
<td>350</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>250</td>
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<tr>
<td>4</td>
<td>200</td>
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<td>5</td>
<td>150</td>
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<tr>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
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TEMPO: Percent of Patients on Rasagiline Without Additional Dopaminergic Therapy


Treatment of Orthostatic Hypotension

- Volume + Sodium Replacement
- Florinef 0.1mg QD-BID
- Midodrine 2.5 mg TID-10mg, TID
- Mestinon 30mg, BID-TID
- Droxidopa (Northera) 100mg-600mg, TID
Parkinson's disease: new risk factor for melanoma

Epidemiology of PD and melanoma

- Danish registry cohort study
  Atypical cancer pattern in patients with Parkinson's disease
  - 14,088 Parkinson's disease patients
  - 21 years follow-up
- PD patients had a 2x increased risk for melanoma

Epidemiology of PD and melanoma

- US survey of dermatologists
  - 862 patients with melanoma and 862 age- and gender-matched controls queried for PD history
  - With melanoma: 25 had history PD (2.9%)
  - Without melanoma: 11 had history PD (1.3%)
- Prevalence of PD significantly higher among patients with melanoma compared to controls (p=0.014)