New Developments in Parkinson’s Disease Treatment

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PD is largely a Disease of Middle-Aged and Older Adults.

Only 5% to 10% of patients have symptoms before age 40 (young onset PD YOPD).
Epidemiology of PD

- 500,000 to 1 million patients in USA
- 40,000 to 60,000 new cases/year.
- Average age of onset is 60 years
- Affects up to 0.3% of the general population but 1% to 3% of those >65 years
- Prevalence increasing as the population ages.
Prevalence of PD

- 65-74 years: 14.9%
- 75-84 years: 29.5%
- >85 years: 52.4%
Economic Burden of PD

- National cost estimates to be as high as $25 billion/year.
- Based on study estimating annual direct and indirect cost of PD at $25,000/patients.
- Direct healthcare cost
  - Physicians
  - Medication
  - Hospitalization
Economic Burden of PD

- Indirect cost:
  - Lost productivity
  - Uncompensated informal care giving by family members.
- Economic burden will increase as population ages.
Longitudinal Course of PD

- Insidious, often unilateral onset of subtle motor features.
- Rest tremor, loss of arm swing, or slowing of movement
- Rate of progression varies; eventually symptoms worsen and become bilateral
- Postural Instability develops and marks the beginning of more severe disease.
- Treatment must be individualized and adjusted as the disease evolves.
Risk factors for PD

◆ Age is strongest predictor of increased risk of PD
◆ Other risk factors include:
  – Exposure to environmental toxins
  – Genetic factors
  – Family history of Parkinsonism
  – Male gender
◆ Premorbid parkinsonian personality characterized by traits of
  – introversion
  – rigidity
  – inflexibility
Role of Environmental Toxins in PD

- Data are inconclusive
- PD may be more common in those who have a history of exposure to insecticides, heavy metals, and herbicides.
- Lived in rural areas for prolonged periods
- Drank well water for many years.
Cell Death in PD

- Many potential mechanisms
  - Mitochondrial dysfunction
  - Oxidative stress
  - Excitotoxicity
  - Deficient neurotrophic support
  - Apoptosis
  - Immune mechanisms
Motor Abnormalities

- Tremor (at rest and in severe cases postural)
- Akinesia, bradykinesia
- Rigidity
- Postural instability
Diagnostic Criteria for PD

- At least 2 of these criteria are required
  - Bradykinesia
  - Muscular rigidity
  - Resting Tremor
Additional Diagnostic Criteria for PD

- Unilateral onset
- Persistent asymmetry affecting side of onset the most
- Progressive disorder
- Positive response to levodopa > 5 years
- Levodopa-induced chorea
Atypical Features indicating a Non-PD Diagnosis

- Remitting course
- Oculogyric crisis
- Supranuclear down or lateral gaze palsy
- Cerebellar signs
- Severe autonomic dysfunction suggesting diagnosis other than PD.
Atypical Features Indication a Non-PD Diagnosis

- Alzheimer’s disease-like dementia from onset of symptoms
- Early change of personality: apathy, disinhibition, or irritability.
- Early word-finding deficits or loss of fluency
- Pyramidal signs unexplained by other neurological findings or neurological disease.
Atypical Features Indicating a Non-PD Diagnosis

- Abrupt onset symptoms
- Stepwise course
- Motor neuron signs
- Postural instability with falling early in disease course
- Unilateral dystonia associated with apraxia or cortical sensory loss
- Lack of disease progression.
Increased Diagnostic Accuracy in PD

◆ CLINICAL
  resting tremor
  unilateral onset
  masked fascies

◆ PHARMACOLOGIC
  Dramatic and sustained response to levodopa treatment.
Neurodegenerative Diseases With Parkinsonian Features.

- Progressive supranuclear palsy
- Multiple system atrophy
  - Shy Drager Syndrome
  - Olivopontocerebellar degeneration
  - Striatonigral degeneration
- Corticobasal ganglionic degeneration
Other causes

- Medications:
  - Neuroleptics
  - Reserpine
- Vascular
- Trauma
- Hydrocephalus
- Toxins
Approach to Pharmacologic Treatment of PD

- Treatment planning must include
  - Short term and long-term symptom management
  - Management of potential adverse effects
- Timing of initial therapy is based on patient functional ability and physician philosophy
- Treatment evolves as illness progresses
- Dosage increase to maximize therapeutic response are necessary with disease progression
Pharmacotherapy of PD

Current armamentarium
- Amantadine
- Anticholinergic
- Monoamine oxidase type B (MAO-B) inhibitors
- Dopamine agonist
- Carbidopa/levodopa
- Catechol-O-methyltransferase (COMT) inhibitors
Levodopa Therapy Has Revolutionized Treatment of Parkinson’s Disease

- Most efficacious symptomatic drug
- Improves activities of daily living
- Improves survival
- Long-term use is associated with motor complications

Levodopa: Long-Term Concerns

- Motor fluctuations
  - Up to 50% of patients after 5 years of treatment
  - 70% or more of patients after 15 years of treatment
- End of dose wearing off phenomenon
- Unpredictable on-off fluctuations
- Dyskinesias
Incidence of Symptom Reemergence in Clinical Studies

Within 2 years after levodopa initiation, approximately 40% of patients developed symptom reemergence or wearing-off.

- Montrastruc (N=29), 40%
- DATATOP (N=352), 42%
- Holloway (N=150), 38%
As the Disease Progresses, the Therapeutic Window Narrows*

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

- Smooth, extended response
- Absent or infrequent dyskinesia
- Diminished duration
- Increased incidence of dyskinesia
- Short, unpredictable response
- “On” time is associated with dyskinesias

Early Disease Advanced Disease

Levodopa Plasma Level

Early Disease: Fluctuating Plasma Levodopa Levels

Buffering by Striatal DA Terminals

Buffer Capacity

Relatively Constant Motor Function

Advanced Disease: Fluctuating Plasma Levodopa Levels

Buffering by Striatal DA Terminals

Buffer Capacity

Striatal Dopamine Levels Mirror Levodopa Serum Levels in the Periphery

*Artist’s representation of plasma levodopa and dopamine levels in disease progression
Strategies to Improve Symptom Reemergence

- Increase levodopa dose
- Fractionate levodopa dose
- Use controlled-release levodopa
- Use longer acting dopamine agonist
- Add COMT inhibitor
Current and Investigational Surgical Procedures for PD

- Ablative procedures
  - Thalamotomy
  - Pallidotomy
  - Subthalamotomy

- Deep Brain stimulation of the
  - Thalamus (Vim nucleus)
  - Globus Pallidus pars interna (GPi)
  - Subthalamic nucleus (STN)

- Restorative procedures
  - Fetal human nigral transplantation
  - Fetal porcine nigral transplantation
  - Trophic factors (e.g., glial-derived neurotrophic factor (GDNF
Thalamotomy

- Consistent and long-lasting improvements in contralateral tremor.
- May improve contralateral dyskinesias
- Widely available
- **Disadvantages**
  - No meaningful effect on bradykinesia and gait function
  - Bilateral lesions associated with risk for severe dysarthria, dysphagia and cognitive dysfunction.
Pallidotomy

━ Advantages
  – Consistent and dramatic improvement in contralateral dyskinesias
  – Mild improvement in parkinsonian features
  – Widely available.
Figure: Time course of response to unilateral Gpi pallidotomy
The bars show the values obtained during the OFF period (12 hours after last medication) for the total UPDRS (TOTAL), total motor (MOTOR) and total ADL (ADL) scores and during the ON period (1 hour after usual morning medication) for the ipsilateral (IPSI) and contralateral (CONTRA) dyskinesia scores at baseline (black), 1 week (grey), 3 months (stippled) and 6 months (white) after surgery in sequence. The motor and dyskinesia scores were evaluated blindly; the total UPDRS and ADL scores contain non-blinded data. Numbers of the left vertical axis apply...
Pallidotomy

- Destructive (lesioning procedure) associated with risk for cognitive dysfunction, dysphagia and dysarthria.
- Necessity for microelectrode recordings not definitively established
- Mechanism responsible for clinical benefit not defined
- Lesion may preclude use of future more effective therapy
Deep Brain Stimulation

- It is considered a “non-destructive” procedure
- Bilateral procedures associated with minimal risks
- Potential to stimulate targets that one may be hesitant to lesion
- Stimulation settings can be adjusted to maximize benefit and minimize adverse effects
- Stimulation of the STN and GPi benefit all cardinal features of PD
- Does not preclude future therapies that depend on the integrity of the basal ganglia.
Deep Brain Stimulation

**Disadvantages**

- Necessitates needle passage through the brain
- Mechanical and infectious adverse effects associated with impaired device
- Need to periodically replace battery
- Optimal target site not known
- Mechanism of action not known
- High cost
Axial slices: -4.5 and 6.0 mm
Investigational Strategies

- Deep brain stimulation
- Fetal nigral transplantation
- Glutamate antagonists
- New MAO-B inhibitors
- Grafting with genetically engineered cell lines
- Dopamine receptor uptake inhibitors
- Neuroprotective agents
- Neurotrophic factors