Updates in Parkinson’s Disease

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NO DISCLOSURES
Objectives

- Be able to recognize nonmotor and motor manifestations of Parkinson’s disease
- Be able to recognize the pros/cons of different treatment strategies to optimize motor function
- Be able to recognize advanced surgical options
AN ESSAY ON THE SHAKING PALSY.

CHAPTER I. DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.
Parkinson’s disease

Parkinson's Disease

Normal

Substantia nigra
The Parkinson’s Complex

- Parkinsonism
- Substantia Nigra
- Pons
- Basal Forebrain
- Medulla
- Amygdala
- Hypothalamus
- Olfactory bulb
- Spinal Cord (intermediolateral column)
- Peripheral Autonomic Nervous System (heart, intestinal tract, bladder)
- Neocortex
- Olfactory Cortex
- Temporal Cortex

Symptoms of Parkinson’s disease

<table>
<thead>
<tr>
<th>Features of Parkinson’s Disease</th>
<th></th>
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<tbody>
<tr>
<td><strong>Motor</strong></td>
<td></td>
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<tr>
<td>Bradykinesia</td>
<td></td>
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<tr>
<td>Rigidity</td>
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<tr>
<td>Tremor</td>
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<tr>
<td>Postural Instability</td>
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## Symptoms of Parkinson’s disease

### Features of Parkinson’s Disease

<table>
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<tr>
<th>Motor</th>
<th>Nonmotor</th>
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<tbody>
<tr>
<td>Bradykinesia</td>
<td>Alteration in memory, mood, and thinking</td>
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<tr>
<td></td>
<td>(neuropsychiatric)</td>
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<tr>
<td>Rigidity</td>
<td>Sleep Disorders</td>
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<tr>
<td>Tremor</td>
<td>Autonomic Symptoms</td>
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<tr>
<td>Postural Instability</td>
<td>Gastrointestinal Symptoms</td>
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<td></td>
<td>Sensory Symptoms</td>
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Question: What impacts patients’ quality of life the most when surveyed?

A. Motor
B. Non-motor
C. Both equally
Question: What impacts patients’ quality of life the most when surveyed?

A. Motor
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Tenets of Best Medical Treatment

- **Individualized** care
- Based on comprehensive assessment of both motor and nonmotor symptoms
- Understanding the importance of life individual circumstances
- Accounting for severity of disease
Foundation of current pharmacologic treatment strategies

• Current methods are aimed at treating the downstream effects of the disease process
• The goal of treatment is to increase the amount of dopamine
• Drugs targeted at other neurotransmitters
Does Levodopa eventually stop working?

A. Yes
B. No
A. Yes
B. No

Does Levodopa eventually stop working?
Levodopa

- Early introduction of levodopa is associated with early appearance of levodopa related motor complications
  - These complications include dyskinesias and wearing off
  - Younger patients appear to be at higher risk
- In 4-6 years, about 40 percent will develop manifestations of this phenomenon
  - However, in the majority the motor complications were mild and not disabling

Ahlskog JE et al, Movement Disorders, 2001
Treatment of Motor complications
Initiation of dopaminergic therapy

• In early 2000s, studies indicated that treating with dopamine agonist before levodopa delays the onset of motor complications
• Recently, long term usefulness of this strategy has been challenged
• Lancet 2014
  – Randomly assigned 1620 people with early PD to levodopa-sparing therapy (DA or MAOBI) or levodopa
  – 7 years of follow-up, self-reported scores on scales measuring mobility and QoL showed small but persistent benefits of starting treatment with levodopa rather than the other drugs
Levodopa - Pros and Cons

- Starting levodopa at diagnosis was associated with a better quality of life.
- Early levodopa therapy MAY normalize basal ganglia physiology
- Fewer neuropsychiatric side effects

- Early levodopa may be associated with motor complications
Medical Management of PD

Periphery

Blood-brain barrier

Brain

Neuron

L-DOPA

AADC

DA

DA

Dopamine receptors

Dopamine agonists
Available Dopamine Agonists

- Pramipexole (*Mirapex*)
- Ropinirole (*Requip*)
- Rotigotine (*Neupro Patch*)
- Apomorphine (injection)
- Extended Release formulations provide more continuous dopaminergic stimulation and improved compliance
Dopamine agonists

- Can be used as the sole therapy in mild to moderate disease
- Used as adjunctive therapy in more advanced disease
- Levodopa is typically required in 2-5 years after diagnosis
Dopamine Agonists - Pros and Cons

- Fewer motor complications

- Side effects include hallucinations, confusion, somnolence or sleep attacks, low blood pressure, edema, and impulse control
Medical Management of PD

Periphery

Blood-brain barrier

Neuron

Brain

L-DOPA

AADC

DA

MAO-B inhibitors

Dopamine receptors
MAOB Inhibitors

- Rasagiline (Azilect)
- Selegeline (Eldepryl, Zelapar)
- Safinimide (xadago)
- It is generally felt that MAOB inhibitors are less effective
- Used as sole therapy in mild disease and adjunctive therapy in moderate disease
- Due to a long half-life, once daily dosing is possible with a side effect profile similar to placebo
Non-Dopaminergic Therapy

- Anticholinergic agents (examples of which are trihexiphenidyl)
- Mainly effective for drooling and tremor
  - Unfortunately not as effective for rigidity, bradykinesia, and balance
- Side effects include confusion, dry mouth, constipation, urinary retention, and cognitive impairment
- Amantadine is another medication useful for tremor and dyskinesia
Medical Treatment of Advanced Disease - Fluctuations and Dyskinesias

- Incidence of fluctuations and dyskinesias increase with advancing disease

*Mazzella L et al., Parkinsonism and Related Disorders, 2005*
Treating fluctuations

**Periphery**
- L-DOPA
- COMT inhibitors
- 3-OMD

**Blood-brain barrier**
- L-DOPA
- AADC

**Brain**
- DA
- MAO-B inhibitors
- COMT inhibitor*

**Neuron**
- Dopamine receptors
- DA
Apomorphine

- Injectable dopamine agonist used for unpredictable severe wearing off periods
- Rapidly effective when injected under the skin
- Reaches full potency in 10 minutes—lasts 60 minutes
- Side effects of lightheadedness, nausea, dyskinesia, hallucinations, and injection site reaction
Levodopa + carbidopa capsule, containing IR + ER pellets

ADVANCE-PD (2013)
- Randomized, double blind, placebo controlled study of 393 fluctuating PD patients comparing IR levodopa to Rytary
- PD patients had at least 2.5 hours of “off” time underwent open label IR treatment, followed by 6 weeks open label Rytary dose conversion, then all randomized to 13 weeks double blind IR vs ER vs placebo
- Primary endpoint: Off time
- Results: Rytary reduced daily OFF time by 1.17 hours compared to IR levodopa
  - Reduced dosing frequency (3 per day vs 5 x /day)
  - FDA approved 2015
Treatment of Motor Fluctuations
Inbrija (Dopaminergic Therapy)

- Inhaled levodopa
- FDA approved 12/2018 for the treatment of OFF periods in PD
  - 351 patients enrolled, randomized to placebo; 60mg or 84mg dose
  - Assessed at 12 weeks
  - Use up to 5 times per day for Off periods
  - Primary endpoint: Change in UPDRS iii, 30 min post dose
  - Results: Ibrija improved UPDRS scores by nearly 4 points compared to placebo (between-group difference -3.92 [-6.84 to -1.00]; p=0.0088)
  - Onset of action as early as 10 minutes, duration approx 60 min
  - Caution: lung disease; apparatus
• Pill with multilayer films containing IR + IR/ER LD
• Phase II study of 34 PD patients showed AP-CD/LD was safe and reduced OFF time by 45% (nearly 2 hours) and reduced total number of levodopa doses (Lewitt et al. MovDisor. 2014)
• Phase III study (ACCORDANCE)
  – 462 patients
  – Open label: 6 weeks of stabilization of levodopa dose, 6 weeks of conversion to AP
  – Randomized to double blind, 13 week tx with IR levodopa OR AP
• Primary endpoint: change in OFF time
• Phase 3 study completed enrollment
Amantadine: Robust evidence for dyskinesia suppressing effects

Glutamate antagonists

New formulations of Amantadine (Gocovri – FDA approved 2017; Osmolex 2018)

- RCT of 126 PD with dyskinesia randomized to ER Amantadine vs Placebo
- Primary endpoint: Dyskinesia rating scale
  - Results: At 12 weeks, ER formulation reduced dyskinesia by -20.7 for ER vs -6.3 placebo (treatment difference -14.4, 95% confidence interval -20.4 to -8.3, P < .0001); ER formulation improved OFF Time by 0.6 hours
  - Note: No direct comparison between ER and immediate release
Surgical/Advanced Treatment of PD

- Levodopa Intestinal Infusion (Duopa)
- Deep Brain Stimulation
- MRI guided focused ultrasound
Levodopa Intestinal Infusion (Duopa)

- Intrajejunal infusion (bypasses gastric emptying problems → less variable plasma concentrations than oral formulations)
- Available in Europe since 2004
- FDA approved 2015 for advanced PD
  - 12 week, double blind, sham controlled trial
  - Randomized 71 pts with advanced PD to LCIG vs oral C/L
  - Primary endpoint: OFF time
  - Results: showed a mean reduction in Off time of 4.04 hours vs 2.14 hours in placebo group; effects maintained for up to 24 months
- Option for advanced PD patients not interested in pursuing DBS
  - Keep in mind: Adverse events related to Duopa therapy have been cited to occur ~ 80%
• 1997: FDA approved thalamic DBS for ET and PD
• 2002: FDA approved STN and Gpi DBS for PD
• When compared to best medical therapy, DBS:
  – "On time" 4.6 hours per day
  – Higher rate of clinically meaningful motor improvement and improved quality of life (PDQ39)
• So what’s new?
  – Timing of surgery; target selection, surgical procedure, new technical developments
Can early intervention preserve functional capacity?

EARLY-STIM trial (2013)

Effects of DBS at mid stage rather than later stage PD

- 251 PD patients with symptom onset 4 years or more but motor complications < 3 years; average disease duration of 7.5 years, randomized to STN DBS + BMT vs BMT alone
  - Results: PDQ 39 improved by 26% in DBS group and worsened by 1% in medical therapy group
  - Secondary outcomes: UPDRS III improved by 53% DBS vs 4% BMT and Med reduction 39% in stim group vs INC 21% in BMT
  - AE: depression more frequent in DBS group


**Neurostimulation for Parkinson's disease with early motor complications.**

MRI-guided Focused Ultrasound for PD

- FDA approved for ET 2016
- FDA approved for tremor predominant PD 12/2018
  - 27 patients with tremor-predominant PD
  - Randomized in double blind, sham-controlled trial
  - Results: tremor scores improved 62% with FUS vs 22% with placebo; UPDRS motor scores improved 8 points with FUS vs 1 point with sham procedure

Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial.


• Things to consider
• Pros
  – Does not require surgical incision or generalized anesthesia
• Cons:
• Treatment effects and side effect profile/risk same as other “lesioning” procedures
  – Irreversible
  – Cannot be adjusted
  – Cannot be performed on both sides
Future Treatments

- Subcutaneous Apomorphine
- Continuous subcutaneous levodopa pump
Are there any disease modifying medications for Parkinson’s disease

- Yes
- No
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- Yes
- No
Disease Modification in Parkinson’s Disease: Current Approaches, Challenges, and Future Considerations

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Parkinson’s disease cause both motor and nonmotor symptoms which impact patient’s quality of life
Motor fluctuations require multifaceted approach, with various medications- balancing benefits and side effects
Advanced surgeries in the form of Intestinal infusion of Levodopa and Deep brain stimulation for treatment of advanced disease
Great deal of research focused on neuroprotective therapies, improved surgical techniques, and better delivery of levodopa