Objectives

- Clinical features of PD
- Pharmacological treatment of PD
- Surgical treatment of PD
Parkinson disease (PD)

- “Sporadic” progressive multisystem neurodegenerative disorder
- Motor symptoms & non-motor symptoms
- Pathology:
  - Loss of dopamine cells in midbrain (substantia nigra)
  - Autonomic degeneration
  - Degeneration of other central and peripheral neurological pathways
Lewy bodies in PD

*H and E*  
*Ubiquitin*

- α-synuclein, ubiquitin (about 90 different molecules)
- Brainstem → cortex

Diagnostic criteria for PD:
Motor signs

1. Bradykinesia
   - Slow movement initiation
   - Reduced amplitude and speed
   - AND 1 of the following:
     2. Rigidity
     3. Rest tremor
     4. Postural instability (appears much later)

UK Brain Bank, Adapted, Litvan, 2003
**MOTOR EXAM:**

UPDRS (Unified Parkinson Disease Rating scale)

<table>
<thead>
<tr>
<th>UPDRS Item</th>
<th>Assessment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinesia subscale</td>
<td>Score includes speed and amplitude of hand and leg movements</td>
<td>0 (not affected) to 36 (most severely affected)</td>
</tr>
<tr>
<td>Tremor subscale</td>
<td>Score includes severity of tremors affecting arms, legs, head</td>
<td>0 (not affected) to 32 (most severely affected)</td>
</tr>
<tr>
<td>Rigidity subscale</td>
<td>Score includes severity of stiffness in neck and limbs</td>
<td>0 (not affected) to 20 (most severely affected)</td>
</tr>
<tr>
<td>Walking and Postural stability</td>
<td>Score includes ability to walk, characteristics of walking</td>
<td>0 (not affected) to 20 (most severely affected)</td>
</tr>
</tbody>
</table>

**Hoehn-Yahr staging system**

- 0 No signs of disease
- 1 Unilateral disease
- 1.5 Unilateral + Axial involvement
- 2 Bilateral disease w/o balance impairment
- 2.5 Mild b/l disease (with balance impairment) but recovery on pull test
- 3 Mild to moderate b/l disease; some PI; physically independent
- 4 Severe disability; still able to walk or stand unassisted
- 5 Wheelchair bound or bedridden unless aided

**PD Non-motor symptoms**

- Sleep disorders
  - REM sleep behavioral disorder (RBD)
  - RLS
- Cognitive deficits
  - Dementia
- Mood disorders
  - Autonomic dysfunction
    - Orthostatic hypotension
    - GI sx
    - GU sx
    - Sexual sx
- Sensory symptoms

Differential diagnosis of PD

- Essential tremor
- Atypical Parkinsonism
  - Progressive supranuclear palsy (PSP)
  - Multiple system atrophy (MSA)
  - Corticobasal degeneration (CBD)
  - Vascular parkinsonism
- Alzheimer’s disease
- Lateral geniculate body degeneration
- Diffuse Lewy body disease
- Iatrogenic disorders
  - Antipsychotics
  - Metoclopramide (Reglan®)
- Others
  - NPH
  - Mass lesions
  - Trauma
  - Toxins - Manganese

123 I-Ioflupane SPECT scan (DaTSCAN)

- FDA approved in the US
- Parkinsonian neurodegenerative syndromes versus:
  - Essential tremor
  - Drug-induced parkinsonism
  - Vascular parkinsonism
  - Psychogenic parkinsonism
- Neurodegenerative parkinsonism/PD
  - Sensitivity ~ 80%
  - Specificity > 90%

Ioflupane Binds to DaT on Nigrostriatal Neurons

www.GEHealthcare.com
Pharmacological treatment of motor symptoms

Medications for PD

A. Dopaminergic drugs
1. Levodopa (oral preparations and extenders)
2. Dopaminergic agonists
3. Newer agents

B. Non-dopaminergic drugs
1. Amantadine (glutamate antagonist)
2. Monoamine oxidase B inhibitors
3. Newer agents

Medications for PD

Dopaminergic drugs:
1. Levodopa + carbidopa
   - Sinemet®
   - Sinemet CR®
2. COMT inhibitors
   - Entacapone
   - (Tolcapone)
3. Levodopa +carbidopa + entacapone
   - Stalevo®
4. Dopamine agonists
   - Pramipexole (Mirapex®)
   - Ropinirole (Requip®)
   - Rotigotine (Neupro®)
   - Apomorphine

Non-dopaminergic drugs:
- Amantadine
- MAO-B inhibitors
   - Rasagiline (Azilect®)
   - Selegeline

2 basic questions

• Q 1. When do you start treatment for PD?
  • At earliest sign of functional impairment
• Q2. What drug do you choose?
  • Age
  • Stage of PD:
  • Efficacy and side-effect profile
  • Evidence based guidelines
  • Clinical observation and experience
  • Affordability

Levodopa
L-Dopa metabolism

![L-Dopa metabolism diagram]

Carbidopa-levodopa preparations

- Sinemet ® (10/100, 25/100, 25/250)
- Sinemet CR® (10/100, 50/200)
- Stalevo® (50, 75, 100, 125, 150, 200)
  - Carbidopa-levodopa-COMTAN 200mg
- Parcopa® (10/100, 25/250)
  - Orally disintegrating

Levodopa prolongs life expectancy

Rajput, Parkinsonism and related disorders,

- 934 patients followed for 32 years after onset of PD
- 215 had PD onset before 1973 and had limited access to LD
- 565 had PD onset after 1973 unrestricted LD access
Levodopa vs Placebo

PSG, NEJM, 2004

-N=311/361 completed study
-UPDRS scores significantly worse in Placebo and in lower L-dopa arms
-Dyskinesias worse in higher dose group

Motor Fluctuations and Dyskinesias

Jankovic, Movement Disorders, Vol 20, Suppl 11, 2005

• Motor complications after long-term use
  – Wearing off
  – Dyskinesias

• Non-motor complications:
  – Neuropsychiatric
  – Orthostatic hypotension

Levodopa + Entacapone increases "on" time

PSG, Ann Neurol, 1997

Levodopa + Entacapone:
• Increased "on" time
• Reduced "off" time
• Reduced L-dopa dose
Dopaminergic agonists

- Pramipexole (regular, ER, max 4.5 mg daily)
- Ropinirole (regular, XL, max 24 mg daily)
- Rotigotine (transdermal patch, 2mg-8 mg daily)
- Apomorphine (injectable: 2mg-6 mg max daily)

PSG, JAMA 2000

Pramipexole v Levodopa (CALM-PD)
**CALM-PD study**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pramipexole (%)</th>
<th>L-Dopa (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>32.4</td>
<td>17.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>9.3</td>
<td>3.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>14.6</td>
<td>4.0</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>6.0</td>
<td>10.0</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>36.4</td>
<td>36.7</td>
<td>ns</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25.5</td>
<td>24.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

PSG, *JAMA* 2000

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**Ropinirole vs Levodopa study**

- 5 year double-blind randomized study
- 30 centers (Canada, Europe, Israel)
- N =268, Ropinirole arm vs L-dopa arm
- Supplemental L-dopa, as needed
- Primary endpoint was dyskinesia


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**Ropinirole vs L-dopa study**

![Graph showing progression of dyskinesia with Ropinirole and L-dopa](image)

Ropinirole vs L-dopa adverse effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>N=500</th>
<th>N=1,645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>104</td>
<td>264</td>
</tr>
<tr>
<td>Somnolence</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>


Rotigotine transdermal patch v placebo


- N=277
- 2,4,6 mg patches
- Significant improvement in UPDRS II,III
- Side-effects comparable to other DA agonists; application site rxn

24 weeks

Dopaminergic agonists (DA agonists)

- More potential side-effects than L-dopa in older patients
  - Hallucinations
  - Pedal Edema
  - Postural hypotension
  - Somnolence, sleep attacks

- Impulse control disorders
  - Gambling, spending, binge-eating, hypersexuality

- 2-3.5 fold increased when treated with agonists (Weintraub, et al. Arch Neurol 2010 (67)

• More potential side-effects than L-dopa in older patients
  - Hallucinations
  - Pedal Edema
  - Postural hypotension
  - Somnolence, sleep attacks
Non-dopaminergic drugs

- Monoamine oxidase B inhibitors
  - Rasagiline (0.5 mg-1 mg daily)
  - Selegiline (5 mg bid)
  - Zelapar® (orally disintegrating Selegiline, 1.25 mg-2.5 mg daily)
- Amantadine (100 mg bid-tid)
  - Adjunct medication for dyskinesias

Delayed start trial of Rasagiline

- N=1176, delayed start cross-over trial
- Early de novo PD
- Symptomatic benefit with both 1 mg and 2 mg of rasagiline
- Disease modifying effect with 1 mg (but not 2 mg of drug) ??


NEUROLOGY TODAY

FDA Committee: Rasagiline Rejected as ‘Disease Modifying’ for Parkinson Disease

The discordance between the effects of 1 mg and 2 mg of rasagiline probably led to this conclusion

Neurology today November 3, 2011
PD: motor fluctuations

- Dyskinesia
- Narrowing therapeutic window
- Bradykinesia
- Time

Pharmacological treatment of motor complications: “wearing off” & dyskinesias

- CR preparations
- COMTAN
- MOA B Inhibitors
- Dopaminergic agonists
- “Fractionation” of levodopa
- Amantadine
  - 100 mg bid-tid
  - Side effects:
    - Pedal edema
    - Hallucinations
    - Blurred vision
    - Avoid in CHF

Salat & Tolosa, J of Parkinson’s Disease 3 (2013)

Deep Brain stimulation for PD
DBS for PD for motor symptoms

- Implantation of electrodes in the globus pallidus (GPI) or subthalamic nucleus (STN)
- Current delivered by battery into brain electrodes is thought to disrupt and modulate abnormal motor activity and improve motor function
- The exact mechanism of action isn’t completely understood

DBS Programming for bradykinesia, tremor, and rigidity in PD

- Voltage
- Frequency
- Pulse Width
- Selection of contacts

Deep brain Stimulation (DBS) vs best medical therapy

- N = 255 randomized pts
- DBS arm 116/121; BMT 108/134
- Significant improvement in motor function (UPDRS 3), PDQ 39 (Qol scale) in DBS group at 6 mos
- More adverse effects in DBS group (neurocognitive, gait and balance, bleeding, infection, 1 death from ICH)

Weaver, FM, et al. JAMA, 2009
DBS in PD

– Selection of appropriate candidate
– Accurate implantation of electrodes
  • Skilled neurosurgeon
– Effective programming
  • Skilled neurologist

DBS in PD: candidate selection

– Demonstrable levodopa response
  • Exclude other parkinsonian conditions
– Significant motor fluctuations despite best medical therapy
– No dementia
– Adequately controlled psychiatric symptoms
– Ambulatory
– Acceptable surgical risk/comorbidities
– Reasonable expectations

Deep brain stimulation

Mnemonic: DBS in PD
• Does not cure
• Bilateral DBS usually needed for gait
• Smooths out on-off fluctuations
• Improves
  – tremor, rigidity, dyskinesia;
  – akinesia and postural instability responds least
• Never improves L-dopa unresponsive sx
  – (Severe tremor is an exception)
• Programming requires diligent, frequent followups
• Decreases meds, does not eliminate them

* Continuum, AAN, Feb 2007
Complications of DBS

<table>
<thead>
<tr>
<th>Surgery related</th>
<th>Hardware related</th>
<th>Stimulation related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure &lt;1% to 3%</td>
<td>Device malfunction</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Hemorrhage &lt; 4%</td>
<td>Lead fracture</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Superficial infection 2% - 25%</td>
<td>Lead migration</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Permanent deficit &lt; 6%</td>
<td>Lead disconnection</td>
<td>Compulsive laughter</td>
</tr>
<tr>
<td>Misplaced leads 12.5%</td>
<td>Lead erosion</td>
<td>Cognitive changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mania</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anxiety</td>
</tr>
</tbody>
</table>

American Academy of Neurology (AAN) Level of Recommendations

- A = Established as effective, ineffective, or harmful for the given condition in the specified population
- B = Probably effective, ineffective, or harmful for the given condition in the specified population
- C = Possibly effective, ineffective, or harmful for the given condition in the specified population
- U = Data is inadequate or conflicting; given current knowledge, treatment is unproven
- Selegiline for early mild PD symptoms (Level A)
- Levodopa or dopaminergic agonists are both equally effective (Level A):
  - Levodopa: more motor improvement
  - DA agonists: less dyskinesias

### Neurology, 2006

#### Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review)

- Entacapone and rasagiline reduce off time (Level A)
- Pramipexole, ropinirole and tolcapone reduce off time (Level B)
- Carbidopa/levodopa CR and bromocriptine do not reduce off time (Level C)
- Amantadine reduces dyskinesia (Level C)
- Apomorphine, cabergoline, and selegiline reduce off time (Level C)

**Initiation of treatment in PD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Stage</th>
<th>Cognitive Psychiatric symptoms</th>
<th>Avoid in Comorbid conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>“Older” &gt;65</td>
<td>Any</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dopaminergic Agonists</td>
<td>“Younger” &lt;65</td>
<td>Usually mild-moderate (H and Y &lt;3)</td>
<td>Avoid</td>
<td>-</td>
</tr>
<tr>
<td>MAO B Inhibitors (Rasagiline)</td>
<td>At any age</td>
<td>Any</td>
<td>-</td>
<td>With certain drugs</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Avoid in the “elderly” &gt;75</td>
<td>Primarily for dyskinesias</td>
<td>Avoid</td>
<td>CHF, renal failure</td>
</tr>
</tbody>
</table>
Practice Parameters

• Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves motor function, reduced off time, dyskinesias, and medication usage (Level C)

AAN Practice Parameters, 2006

Non-motor symptoms in PD

• Erectile difficulty
  – Sildenafil 50 mg daily (level C)
• Constipation
  – Polyethylene glycol (level C)
• PLMS
  – Levodopa/carbidopa (Level C)
• Excessive daytime somnolence
• Fatigue
• Orthostatic hypotension
• Urinary incontinence
• REM disorder
• Anxiety
• Insomnia

Level U
**A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease**

*Neurology* 2012;78:1229–1236

- SAD PD study group
- N=115
- 12 wk, placebo controlled double blind trial of antidepressants in PD
- Significant improvement in HAM-D scores
  - Paroxetine 30-40 mg per day
  - Venlafaxine XR 150-225 mg per day

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**Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review)**

Report of the Quality Standards Subcommittee of the American Academy of Neurology

*M. Miyasaki, MD; R. S. Sch existed, MD; V. Van, MD; B. Revill, MD; M. C. P. C. Grinvald, MD; K. Hornak, MD; L. P. Beisary, MD; G. Stein, MD; W. S. Weingeist, MD*

- BDI, HAM-D screening scale (level C)
- MMSE (level B)
- (Amitryptyline for depression (level C)
  - Caveat: older study, usually not first line )
- Clozapine for psychosis (level B)
- *Rivastigmine for dementia (level B)*
  - Mean dose 9 mg daily

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**Non-pharmacological treatment**

(at all stages of disease)

- Education
- Exercise
  - Vigorous exercise
    - Pedaling
  - Dancing
  - Tai Chi
- PMR
  - PT
  - Balance and fall prevention
  - Speech therapy
  - LSVT
  - Caregiver support


Non-dopamine targets and candidate drugs

Summary

Dopaminergic & non-dopaminergic drugs, Non-medical therapy, DBS, future therapies

Normal Movement, Functional Improvement

Dyskinesias

Bradykinesia

Time

Thank you!