Joint Session with ACOFP and Cleveland Clinic: Managing Chronic Disease

Parkinson's Disease: Early Warning Signs, When to Refer

Hubert Fernandez, MD
Early (and Late) Signs of PD: When to Refer

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Disclosures

Consulting:
AbbVie, Acadia, Eli Lilly, Indus, Ipsen, Merz, Novartis, Pfizer, Sunovion, Voyager

Independent Contractor (including contracted research):
Acordia, Biogen, Kyowa Hakko, Michael J Fox Foundation, NIH/NINDS, Parkinson Study Group, Rhythm, Teva

Teaching and Speaking:
Medscape, Vindico Education
Who gets PD?
- Mean age of onset: 60-70, M>F
- Affects 0.3% of the population and 1% of those older than 60
- Over 1.5 million people in North America affected


PD Motor Symptoms
The Parkinson Family

- Idiopathic Parkinson’s Disease
- Secondary Parkinson’s Disease
- Essential Tremor
- Vascular
- Drugs
- Essential Tremor
- Progressive Supranuclear Palsy
- Multi-System Atrophy
- Other
- Essential Tremor
- Vascular
- Drugs
- Essential Tremor
- Progressive Supranuclear Palsy
- Multi-System Atrophy
- Other
- Essential Tremor
- Vascular
- Drugs
- Essential Tremor
- Progressive Supranuclear Palsy
- Multi-System Atrophy
- Other

A Brief History of Our Understanding of PD

- 1817: "An Essay on the shaking palsy"
- 2017: A Brief History of Our Understanding of PD

A Brief History of Our Understanding of PD

1817

1872

Charcot

late 1950s

dopamine

1817

1872

2017

HO

NH₂

HO

A Brief History of Our Understanding of PD

1817

1872

late 1950s

1960s

levodopa

Dramatic changes in our understanding of the pathology, genetics, and clinical management of PD
The evolving Parkinson disorder

• The cure remains elusive…
• Striatal dopamine loss + more
• “Multiple systems” disorder
• Better treatments available
• Patients are living longer

Non-motor signs and symptoms

• **Craniofacial** - masked facies, sialorrhea, anosmia, hypophonia, dysarthria, dysphagia
• **Sensory** - pain, paresthesias
• **Autonomic** - urinary disturbance, constipation, sexual dysfunction
• **Neuropsychiatric** - depression, anxiety, apathy, dementia, psychosis
• **Other** – fatigue, sleep disturbance, seborrheic dermatitis, eye abnormalities
Classical Progression of Parkinson Disease

≈ 0 to 4 years: “the good years”

Figure adapted from Nyholm D, et al. (2007) Parkinsonism Relat Disord. 13:515-517.

Very Early PD
Are there agents that can slow disease progression in PD?

**Disease Modifying Agents Recently or Currently Tested**

- Vitamin E
- CoQ10
- Riluzole
- GPI-1485
- Pramipexole
- Cogane
- CEP-1347
- TCH-346
- Creatine
- Rasagiline
- Inosine, Isradepine, Exercise!
Exercise!

- HMO, Seattle, Washington: 1740 adults 65 or older without cognitive impairment.
- After 6 years, participants exercising > 3 or more times a week had a 38% lower incidence of dementia.
- Subsequent literature: chorus not a debate.

Ann Intern Med, January 2006
Classical Progression of Parkinson Disease

≈ 4 to 7 years: parkinsonism

Figure adapted from Nyholm D, et al. (2007) Parkinsonism Relat Disord, S13-S17.
Mild to Moderate PD

Symptomatic Treatment of Early PD

- Carbidopa/levodopa (IR, CR, rapidly dissolving)
- Dopamine agonist (ropinirole, pramipexole, rotigotine, cabergoline)
- MAO inhibitors (selegiline, rasagiline, safinamide)
- Amantadine
- Anticholinergic drugs (trihexyphenidyl)
Treatment of PD with Levodopa

- Improves tremor, rigidity and bradykinesia in PD, particularly in early stages of PD
- Rapid onset, well tolerated
- Decreases mortality
- However, 80% of patients have motor complications after 5-10 years (major source of disability)

Levodopa superiority vs Dopamine Agonists

- Pramipexole vs Levodopa (UPDRS)
Dyskinesias: Sydney 15-Year Multi-Center Longitudinal Study

- 15 yr F/U: 94% dyskinesias, 96% "end-of-dose failure"
- Dyskinesias: non-disabling in the majority

Hely et al, 2005

Patient perception of dyskinesias in PD

<table>
<thead>
<tr>
<th></th>
<th>Early Untreated</th>
<th>Treated No dyskinesias</th>
<th>Treated Dyskinesias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>52</td>
<td>102</td>
<td>105</td>
</tr>
<tr>
<td>Number of male</td>
<td>33 (63.5%)</td>
<td>53 (52.0%)</td>
<td>71 (67.6%)</td>
</tr>
<tr>
<td>Current age (in years) (SD)</td>
<td>62.4 (12.7)</td>
<td>65.4 (13.9)</td>
<td>64.1 (9.3)</td>
</tr>
<tr>
<td>Age at diagnosis (SD)</td>
<td>60.4 (12.6)</td>
<td>60.5 (11.6)</td>
<td>53.8 (9.7)</td>
</tr>
<tr>
<td>Time followed in our clinic (months)</td>
<td>10.98 (20.71)</td>
<td>37.6 (33.2)</td>
<td>77.3 (53.7)</td>
</tr>
<tr>
<td>Number of new pts to clinic</td>
<td>23</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>UPDRS III score</td>
<td>19.7 (9.79)</td>
<td>21.9 (9.5)</td>
<td>24.8 (12.1)</td>
</tr>
<tr>
<td>UPDRS Q32</td>
<td>0</td>
<td>0</td>
<td>1.5 (0.96)</td>
</tr>
<tr>
<td>UPDRS Q33</td>
<td>0</td>
<td>0</td>
<td>1.0 (0.92)</td>
</tr>
<tr>
<td>Lang Fahn Dyskinesia Scale score</td>
<td>0</td>
<td>0</td>
<td>5.6 (4.9)</td>
</tr>
</tbody>
</table>

Hung et al, 2009
Hung et al., 2009

Level of Concern about Dyskinesia

<table>
<thead>
<tr>
<th>Group</th>
<th>Early Untreated</th>
<th>Treated</th>
<th>Treated with Dyskinesias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>not concerned</td>
<td>mildly concerned</td>
<td>extremely concerned</td>
</tr>
<tr>
<td>Group II</td>
<td>mildly concerned</td>
<td>very concerned</td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>not concerned</td>
<td>mildly concerned</td>
<td>very concerned</td>
</tr>
</tbody>
</table>

Patient’s preference: Dyskinesia or Parkinsonism

<table>
<thead>
<tr>
<th>Group</th>
<th>dyskinesia</th>
<th>parkinsonism</th>
<th>Undecided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>dyskinesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hung et al., 2009
Dopamine Agonists

- Mirapex (pramipexole)
- Requip (ropinirole)
- Neupro (rotigotine)

- Once a day dosing
- Generic available
- Improves depression
- Dopamine agonists have been shown to delay motor complications

Dopamine agonist versus levodopa
Dopamine Agonists: Problems

- May not control symptoms as well as levodopa
- Long titration period
- Associated with more side effects, esp. in older people
- Associated with “sleep attacks” and leg swelling/edema
- Associated with compulsive and impulsive behavior

Ropinirole vs L-dopa as Initial Therapy: Adverse Events*†

<table>
<thead>
<tr>
<th>Condition</th>
<th>REQUIP (n=179)</th>
<th>Levodopa (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>17.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>27.4%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25.1%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

* Reports of AEs occurring in ≥10% of either group in study population over 5 years.
† Patients often had more than 1 adverse event.
CALM-PD Outcomes: Adverse Events

**Total Cohort**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pramipexole</th>
<th>Levodopa</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>32.4%</td>
<td>17.3%</td>
<td>.003</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>17.9%</td>
<td>8.0%</td>
<td>.01</td>
</tr>
<tr>
<td>Generalized Edema</td>
<td>14.6%</td>
<td>4.0%</td>
<td>.002</td>
</tr>
</tbody>
</table>


Rasagiline for early monotherapy

- One dose; no titration
- Great tolerability; including elderly
- No sleep attacks; minimal** reports of compulsive or impulsive behavior

**Food interaction warning**
- Potential drug interaction
- No head-to-head trial vs. agonists or selegiline

**Shapiro, Chang, Munson, Okun, Fernandez, 2006**
Classical Progression of Parkinson Disease

\[ \approx 7 \text{ to } 10 \text{ years: dyskinesias} \]

Moderate PD with Mild Dyskinesias

Figure adapted from Nyholm D, et al. (2007) Parkinsonism Relat Disord, 13-517.
Motor Complications

- Motor fluctuations
  - End-of-dose deterioration
  - Delayed onset of response
  - Drug-resistant “offs”
  - Random oscillation (“on-off” phenomenon)
  - Freezing (unpredictable inability to initiate or finish a movement)
- Dyskinesias (abnormal involuntary movements)
- Peak-dose, diphasic or wearing-off


Net Effect of PD Medications in Improving “Off” State in Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Drug/Trial</th>
<th>Dose</th>
<th>Net reduction in off time (hours)</th>
<th>% Net Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole (Rascol, 1996)</td>
<td>6.6 mg/d</td>
<td>-0.6 hrs</td>
<td>19%</td>
</tr>
<tr>
<td>Ropinirole (Pahwa, 2007)</td>
<td>18.8 mg/d</td>
<td>-1.6 hrs</td>
<td></td>
</tr>
<tr>
<td>Ropinirole (Lieberman, 1998)</td>
<td>&lt;24 mg/d</td>
<td>-0.31</td>
<td>7%</td>
</tr>
<tr>
<td>Pramipexole (Guttman, 1997)</td>
<td>3.36 mg/d</td>
<td>-2.3 hrs</td>
<td>12%</td>
</tr>
<tr>
<td>Pramipexole (Lieberman, 1997)</td>
<td>4.5 mg/d</td>
<td>-1.7 hrs</td>
<td>24%</td>
</tr>
<tr>
<td>Selegilene (Waters, 2004)</td>
<td>2.5 mg/d</td>
<td>-1.6 hrs</td>
<td>23%</td>
</tr>
<tr>
<td>Selegilene (Ondo, 2006)</td>
<td>2.5 mg/d</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td>Rasagiline (PRESTO, 2005)</td>
<td>1.0 mg/d</td>
<td>-0.94 hrs</td>
<td>14%</td>
</tr>
<tr>
<td>Rasagiline (LARGO, 2005)</td>
<td>1.0 mg/d</td>
<td>-0.8 hrs</td>
<td>14%</td>
</tr>
<tr>
<td>Entacapone (LARGO, 2005)</td>
<td>200 mg/d</td>
<td>-0.8 hrs</td>
<td>14%</td>
</tr>
<tr>
<td>Entacapone (Poewe, 2002)</td>
<td>200 mg/d</td>
<td>-0.7 hrs</td>
<td>12%</td>
</tr>
<tr>
<td>Entacapone (Rinne, 1998)</td>
<td>200 mg/d</td>
<td>-1.2 hrs</td>
<td>22%</td>
</tr>
<tr>
<td>Tolcapone (Rajput, 1997)</td>
<td>200 TID</td>
<td>-1.8 hrs</td>
<td>28%</td>
</tr>
<tr>
<td>Tolcapone (Adler, 1998)</td>
<td>200 TID</td>
<td>-2.2 hrs</td>
<td></td>
</tr>
<tr>
<td>Tolcapone (Kurth, 1997)</td>
<td>200 TID</td>
<td>-1.77 hrs</td>
<td></td>
</tr>
<tr>
<td>Apomorphine (Dewey, 2001)</td>
<td>5.4 mg/d</td>
<td></td>
<td>34%</td>
</tr>
</tbody>
</table>
Newly Approved Rx for Motor Complications

- Carbidopa-Levodopa Extended Release (Rytary)
- Safinamide (Xadago)
- Amantadine Extended Release (Gocovri)

Hauser et al. Mov Disord. 2011;26:2246-52.

Classical Progression of Parkinson Disease

> 10 years: therapeutic window diminished

Figure adapted from Nyholm D, et al. (2007) Parkinsonism Relat Disord, S13-S17.
Moderate Dyskinesias


EDS, excessive daytime sleepiness; MCI, mild cognitive impairment; RBD, REM sleep behavior disorder.

Advanced Therapies for PD Patients

Subcutaneous apomorphine injections

Deep brain stimulation

Subcutaneous apomorphine infusion

Duodenal carbidopa/levodopa gel infusion

STN DBS: The Start of a Revolution

The New England Journal of Medicine

ELECTRICAL STIMULATION OF THE SUBTHALAMIC NUCLEUS IN ADVANCED PARKINSON’S DISEASE

UPDRS II

UPDRS III
DBS Surgery for PD

DBS Screening and Evaluation

Comprehensive, Multidisciplinary Deep Brain Stimulation Screening for Parkinson Patients: No Room for “Short Cuts”

Abstract: Careful, often cumbersome, screening is a fundamental part of DBS evaluation in Parkinson disease (PD). It often involves a brain MRI, neuropsychological testing, neurological, surgical, and psychiatric evaluations, and "ON/OFF" motor testing. Given that DBS has now been a standard treatment for advanced PD, with clinicians’ improved comfort and confidence in screening and referring patients for DBS, we wondered whether we can now streamline our lengthy evaluation process. We reviewed 36 PD patients evaluated for DBS at our center between 2008 and 2009 and analyzed the reasons for candidacy and the shortcomings despite passing the screening process. A total of 32 PD patients who underwent DBS evaluation had complex ratings. Only 19 (59.4%) patients were also considered candidates. Patients (73.3%) were excluded after screening because of significant cognitive decline (50%), early disease with rapid medication requirements (50%), bilateral dysfunction (50%), uncorrected secondary parkinsonism or atypical parkinsonism syndromes (51.6%), or lack of compliance (51.6%). In addition, 31 (93.3%) patients were deemed not suitable for surgery but rather chosen over them (93%). Patients were then followed-up 70 patients, or were denied by medical insurance (11%). Through careful screening, a significant percentage of surgical candidates continue to be identified on a consistent basis because of a variety of reasons. This underscores the continued need for a comprehensive, multidisciplinary screening process.
**Best Candidates for Parkinson DBS Surgery**

- Patient’s symptoms are markedly improved in the *on medication* state relative to the *off medication* state
- Problematic motor fluctuations despite the best medical therapy
- A significant portion of the day is spent functionally impaired (outside of therapeutic window)
- Cognitively intact and emotionally stable
- Realistic expectations
- Adequate social support

**Not Candidates for PD DBS Surgery**

- Poor response to levodopa
- Progressive Cognitive Dysfunction/Dementia
- Hallucinosis that is not medication related
- Diagnoses other than PD
- Medically infirm (extremely aged)
Our Intraoperative MRI Suite (IMRIS)

Using IMRIS, the neurosurgeon can plan and precisely place leads while the patient is under general anesthesia. Previously, almost all DBS required awake
The LCIG Intestinal Infusion System

**LCIG (CLES) Components**

- Levodopa/carbidopa (4:1) in gel suspension
- Ambulatory pump provides controllable, continuous infusion via percutaneous access port
- Duodenal tube inserted into the intestine through the stomach using percutaneous endoscopic gastrostomy (PEG)

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Levodopa Pump Open-Label study: *mean PD symptom diary*

- 'On' time without troublesome dyskinesia
- 'Off' time
- 'On' time with troublesome dyskinesia

*P < 0.05

Fernandez HH et al. Parkinsonism and Related Disorders 2013; 19(3):339-345 (Preliminary Paper);
Fernandez et al. Movement Disorders, In Press (Final Paper)
PD Pipeline: A Message of Hope

Acknowledgement

Movement Disorders Team
Center for Neurological Restoration
Cleveland Clinic