Parkinson’s Disease Foundation

PD ExpertBriefing:
PD Medications: Managing Side Effects

Led By: Hubert H. Fernandez, M.D.
Cleveland Clinic Lerner College of Medicine

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PD Medications: Managing Side Effects

Hubert H. Fernandez, M.D., F.A.A.N., F.A.N.A.
Professor of Medicine (Neurology)
Cleveland Clinic Lerner College of Medicine
Head of Movement Disorders
Cleveland Clinic, OH, USA
Disclosures

I have, over the past 12 months, been a paid consultant, paid speaker or performed clinical research under contract with:

AbbVie, Acadia, Avid, Biotie, Britannia, Chelsea Therapeutics, Civitas, EMD Serono, Eli Lilly, Forest Laboratories, Huntington Study Group, Ipsen, Merck, Merz, Michael J. Fox Foundation, National Parkinson Foundation, NIH/NINDS, Novartis, Parkinson Study Group, Prostrakan/Kyowa Hakko, Pfizer, Rhythm, Synosia, Teva, US WorldMeds, Zambon Pharmaceuticals

However, I have no owner interest in any pharmaceutical company.
What Are Our Current Symptomatic Treatment Options for Early PD?
Sites of Action of Current PD Drugs

**Substantia Nigra**
- Levodopa
- Amantadine

**BBB**
- Dopamine
- Levodopa
- 3-OMD

**DDC**
- Carbidopa

**COMT**
- COMT inhibitors: tolcapone, entacapone

**MAO-B inhibitors:**
- selegiline
- rasagiline

**Dopamine agonists:**
- bromocriptine
- pramipexole
- ropinirole
- rotigotine

**Anticholinergics:**
- trihexyphenidyl
- benztropine

Adapted from www.wemove.org
Symptomatic Treatment of Early PD

- **Carbidopa/levodopa** (Sinemet IR, Sinemet CR, Parcopa, Stalevo [with entacapone])
- **Dopamine agonist** (ropinirole, pramipexole, rotigotine patch)
- **MAO inhibitors** (selegiline, rasagiline)
- **Amantadine**
- **Trihexyphenidyl** (artane)
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 people with PD taking it have motor complications after 5-10 years (major source of disability)
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Levodopa Superiority vs Dopamine Agonists
Levodopa Superiority vs Dopamine Agonists

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

- Dyskinesias
- Dyskinesias Requiring Medication Adjustments
- Dyskinesias Resistant to Medication Adjustments

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

Hely et al, 2005
### Perception of Dyskinesias in People with PD

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

- **Group I** – Early Untreated PD patients who are not on dopaminergic medications
- **Group II** – PD patients who are on dopaminergic medications but do not have dyskinesias
- **Group III** – PD patients who are on dopaminergic medications and have dyskinesias

**UPDRS** – Unified Parkinson’s Disease Rating Scale

**Dyskinesia Scale**

**Hung et al, 2009**
Level of Concern about Dyskinesia

Bar chart showing the percentage of concern for dyskinesia among different groups:

- **Group I**: Early Untreated
- **Group II**: Treated No Dyskinesias
- **Group III**: Treated with Dyskinesias

Legend:
- Blue: not concerned
- Pink: mildly concerned
- Yellow: very concerned
- Light Green: extremely concerned

Hung et al, 2009
Individual Preference: Dyskinesia or Parkinsonism

Hung et al, 2009
Dopamine Agonists

- Mirapex® (pramipexole)
- Requip® (ropinirole)
- Neupro® (rotigotine)
- Now with once daily tablet or generic
- Dopamine agonists have been shown to delay motor complications
The Dopamine Agonist Advantage

Initial Dopamine Agonist Therapy Delays the Onset of Dyskinesia


Dopamine Agonists: *Problems*

- Does not control symptoms as well as levodopa
- Long titration period
- Associated with more side effects in older people
- Associated with “sleep attacks” and leg swelling/edema
- Associated with compulsive and impulsive behavior
Sleep Attacks
Weight Gain and Leg Swelling
Ropinirole vs L-dopa as Initial Therapy: Adverse Events*†

- **Hallucinations:**
  - REQUIP (n=179): 17.3%
  - Other: 5.6%

- **Somnolence:**
  - REQUIP (n=179): 27.4%
  - Other: 19.1%

- **Insomnia:**
  - REQUIP (n=179): 25.1%
  - Other: 23.6%

* 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

Pramipexole

Levodopa

P = .003

32.4%

17.3%

9.3%

3.3%

17.9%

8.0%

14.6%

4.0%

% of Patients

Somnolence

Hallucinations

Generalized Edema

Peripheral Edema

PARKINSON'S DISEASE FOUNDATION

Rotigotine Patch
Compulsive and Impulsive Disorders in PD

- Compulsive behavior
  - Compulsive dopaminergic medication use
  - Punding

- Impulse Control Disorder (ICD)
  - Pathological gambling
  - Hypersexuality
  - Compulsive shopping
  - Excessive spending
  - Binge eating

Levodopa

Dopamine agonists
DOMINION Study: Dopamine Agonists and ICD

• Cross-sectional study of over 3,000 people with PD
• People with PD on dopamine agonists (DAs) were two to three times more likely to develop ICD (class finding)
• Associated factors:
  – Young age
  – Single
  – Family History of ICD
  – Levodopa treatment
• Modifications to DA and/or levodopa is important for treatment

### Punding, Gambling, Hypersexuality, Binge Eating

<table>
<thead>
<tr>
<th>Feature</th>
<th>Punding</th>
<th>Gambling</th>
<th>Hypersexuality</th>
<th>Binge eating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>8.25%</td>
<td>7.8%</td>
<td>4.3%</td>
<td>1% (BED) 8% (subthreshold)</td>
</tr>
<tr>
<td>Young age</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male dominance</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious and angry</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep deprived</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STN DBS</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Impulsive nature</td>
<td></td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Compulsive nature</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

What is Punding?
Emerging Theme...!

Punding

Gambling

Hyper-sexuality
Anticholinergics

- **Examples:** trihexyphenidyl (Artane®) benztpine (Cogentin®)

- **Indications:** tremor, drooling

- **Benefits:** Cost effective, thought to be most effective for tremor control

- **Side effects:** confusion, dry mouth, constipation, blurry vision, urinary retention, cognitive impairment
MAO-B Inhibitors

- Irreversibly bind to brain MAO-B
- Loss of effect is dependent on MAO-B turnover in the brain – half-life ~30 days
- Formulations
  - Oral (and orally-disintegrating tablets)
    - Selegiline (Deprenyl®): approved as adjunct therapy (moderate to advanced PD)
    - Rasagiline (Azilect®): approved as monotherapy (early PD) and adjunct therapy (moderate to advanced PD)

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
Rasagiline for Early Monotherapy

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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

Sensitivity to Levodopa: Early vs Advanced PD

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

Therapeutic window

Early disease

Moderate disease

Advanced disease

Dyskinesia threshold

Efficacy threshold

Plasma levodopa concentrations

* Parkinson’s Disease Foundation
Managing Dyskinesias

- Lower frequent doses of levodopa
- Add dopamine agonist (DA) or MAO-B inhibitor while lowering levodopa dose
- Clozapine
- Amantadine
- Deep brain stimulation
Amantadine

- **Mechanism:** NMDA antagonist, dopamine releasing agent
- **Indications:** Early PD, dyskinesias, fatigue
- **Benefits:** Mild symptomatic benefit, effective for dyskinesias
- **Side effects:** Leg swelling, livedo reticularis, neuropsychiatric, anticholinergic

### Amantadine vs placebo for levodopa-induced dyskinesias

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<th>Amantadine*</th>
<th>Placebo*</th>
<th>P value†</th>
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<tr>
<td>Total dyskinesia</td>
<td>22.0 (13.2)</td>
<td>29.0 (12.6)</td>
<td>0.004</td>
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<td>Maximal dyskinesia</td>
<td>5.2 (2.6)</td>
<td>6.3 (2.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS IVa dyskinesia</td>
<td>3.2 (1.6)</td>
<td>4.3 (1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS III motor off</td>
<td>38.4 (14.8)</td>
<td>41.7 (13.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>UPDRS III motor on</td>
<td>22.3 (12.1)</td>
<td>23.4 (9.0)</td>
<td>0.44 NS</td>
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*Mean score (SD)
†Wilcoxon signed-rank test
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†Wilcoxon signed-rank test
Levido Reticularis
COMT Inhibitors

- Tolcapone (Tasmar®) and Entacapone (Comtan®)

- Effects:
  - Increase t1/2 levodopa
  - Decrease plasma levodopa peak-trough variations, resulting in reduction of OFF periods

- Adjunctive therapy to levodopa

- Adverse effects:
  - Diarrhea
  - Urine discoloration
  - Fulminant liver failure in several cases treated with tolcapone

- Combination levodopa/carbidopa/entacapone now available
  - Bioequivalence demonstrated vs levodopa/carbidopa + entacapone

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[Graph showing levodopa time-concentration curve with and without entacapone]
COMT Inhibitors for Wearing Off
Using Entacapone as an Adjunct to DDCI/Levodopa

Change in proportion of 'on' time

Change in daily 'on' time (h)

Change in daily 'on' time (h) (mean of months 4 and 6)

Total 'on' time (h)

Levodopa/DDCI plus entacapone  Levodopa/DDCI plus placebo
Reduction in mean total daily “Off”

Increase in mean total daily “On”

-1.85
-1.41
-0.91
1.19
1.82
0.79

Rasagiline 0.5 mg
Rasagiline 1 mg
Placebo

*Parkinson's Rasagiline: Efficacy & Safety in the Treatment of “Off”

Rasagiline versus Entacapone

Reduction in mean total daily “Off”

Increase in mean total daily “On”

All Patients on LD/DDI

*Lasting effect in Adjunct therapy with Rasagiline Given Once daily


As described in the text:

1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5

-1.18
-1.2
0.0
0.4
1.13
1.01
0.27

Rasagiline 1 mg
Entacapone 200 mg
Placebo

Change from baseline (hours)
Rasagiline versus Entacapone

Rasagiline 1 mg
Entacapone 200 mg
Placebo

Reduction in mean total daily “Off”

Increase in mean total daily “On”

All Patients on LD/DDI

*Lasting effect in Adjunct therapy with Rasagiline Given Once daily

Apomorphine (Apokyn®)

- Short-acting dopamine agonist
  - Subcutaneous injection
- Main indication—“rescue” therapy for:
  - Unpredictable “offs”
  - “Off” periods in people who cannot swallow
  - “Off” periods not controlled with oral medications
  - Painful “off” periods
- Trimethobenzamide pretreatment necessary
  - Can be halted after 6 weeks of apomorphine therapy
- First dose requires BP monitoring
- Side effects: injection site reaction, nausea, falls, dyskinesias, dizziness, somnolence (sleepiness)
Apomorphine Injections
## 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>&lt;4.5 mg/d</td>
<td>-1.7 hrs</td>
<td>24%</td>
</tr>
<tr>
<td>Selegiline (Waters, 2004)</td>
<td>2.5 mg/d</td>
<td>-1.6 hrs</td>
<td>23%</td>
</tr>
<tr>
<td>Selegiline (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/levo</td>
<td>-0.8 hrs</td>
<td>14%</td>
</tr>
<tr>
<td>Entacapone (Poewe, 2002)</td>
<td>200 mg/levo</td>
<td>-0.7 hrs</td>
<td>12%</td>
</tr>
<tr>
<td>Entacapone (Rinne, 1998)</td>
<td>200 mg/levo</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>
Treatment Options for Wearing Off and Advanced PD

Oral agents
- 1-1.5 hours more “on” time

Apomorphine
- 2-3 hours more “on” time

Duodopa (LCIG)
- 4 hours more “on” time

DBS
- 4 hours more “on” time
A Multidisciplinary Team Approach Is Often Necessary
A Multidisciplinary Team Approach is often necessary
A Multidisciplinary Team Approach is often necessary
Non-Motor Signs and Symptoms

- **Craniofacial** - masked faces, sialorrhea (drooling), anosmia (loss of sense of smell), hypophonia (soft speech), dysarthria (motor speech disorder), dysphagia (difficulty swallowing)

- **Sensory** – pain

- **Autonomic** - urinary disturbance, constipation, sexual dysfunction

- **Neuropsychiatric** - depression, anxiety, apathy, cognitive impairment, psychosis

- **Other** – fatigue, sleep disturbance, seborrheic dermatitis, eye abnormalities
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PD Pipeline: A Message of Hope
Acknowledgement

Movement Disorders Team
Center for Neurological Restoration
Cleveland Clinic
THANK YOU!
Questions and Discussion
Upcoming *PD Expert Briefings*

When PD Interferes with Gastrointestinal Function
Tuesday, **June 24**, 1:00 PM - 2:00 PM ET

*Peter A. LeWitt, M.D., Professor of Neurology, Wayne State University School of Medicine and Director, Parkinson’s Disease and Movement Disorder Program, Henry Ford Hospital*
Resources from PDF

**Fact Sheets**
- Understanding Medications
- Medication Log

**PD Resource List**
- 750 Resources

**Online Seminars**
- Impulsive and Compulsive Behaviors in Parkinson’s
- Sexuality and Intimacy in Parkinson’s
- Demystifying Hallucinations, Night Terrors and Dementia

*Parkinson’s Disease Foundation*
Please complete our SURVEY.

Your responses help us to improve the work that we do.

Thank you.