Update in the Management of Parkinson’s Disease
What’s standard? What’s new? What’s coming?

Bruno V. Gallo, M.D.
Assistant Professor of Neurology, FIU Wertheim College of Medicine
Director, Parkinson & Neuromodulation Center
Baptist Health, Miami Florida

Disclosures:
I am actively a consultant for the following:
Cyberonics, Inc.
Teva Pharmaceuticals
St. Jude Medical, Inc. (dba Abbott Labs)
Surgimon, LLC
ONS, Inc.

I am a member of the following speakers bureau:
TEVA Pharmaceuticals
Sunovion Pharmaceuticals

I have received Fellowship and/or Research Grants:
Medtronic International
Pfizer Pharmaceuticals
Glaxo-SmithKline
St. Jude Medical, Inc.

The gold standard since 1969
Levodopa 1969
Carbidopa / levodopa 1972
Carbidopa / levodopa controlled release 1992
Carbidopa / levodopa/entacapone 1996
Carbidopa and levodopa extended release capsules 2015
Levodopa intestinal gel 2016
Motor Fluctuations

Typical Clinical Pattern of Wearing Off

Adapted from Hauser RA. Geriatrics. 2006;61:14-20.

Symptoms not adequately controlled (“off time”)

Symptoms adequately controlled (“on time”)

PD Medication

“Wearing off” period

Time

Development of Motor Complications with Time on Levodopa – double edged sword

% Patients with Motor Complications

0 25 50 75 100

Time from Initiation of Therapy (years)

40% by 5 yrs

92% by 10 yrs


Management of Parkinson’s Disease?

Considerations Age Cognitive function Comorbidity

Nonpharmacologic

Dopamine agonist

Parkinson’s disease

Pharmacologic

Dopamine agonist

Levodopa (+/- COMT inhibitor)

Add COMT inhibitor

Motor complications

Unacceptable control with medical therapies

Continue to monitor

See section on control of motor complications

Consider surgery
Sites of Action of Parkinson’s Disease Drugs

Dopamine agonists
Levodopa
3-OMD
DDCI
Selegiline/Rasagiline
MAO-B (breaks down dopamine)
Dopamine agonists

Therapy for Advanced Parkinson’s Disease

Dyskinesias
- Decrease levodopa dose
- Add dopamine agonist
- Add amantadine

Wearing off
- Smaller, more frequent doses of levodopa or CR
- Add COMT inhibitor
- Add MAO-B inhibitor
- Add dopamine agonist
- Add amantadine

Non-motor symptoms
- Decrease doses of or discontinue offending medications
- Address specific problems with appropriate therapy

Intestinal Infusion of Levodopa Continuous Therapy

Intestinal Infusion of Levodopa Continuous Therapy

Response to Chronic Levodopa Therapy

Motor Fluctuation: Wearing Off

Chronic levodopa response is a narrowing of the therapeutic window. (A) Beginning of treatment. (B) Patient starts to experience motor complications. (C) Patient experiences severe motor complications.

Wearing off
- End-of-dose effect
- Most common motor fluctuation

Possible treatment options
- Switch to sustained release carbidopa/levodopa
- Increase frequency of levodopa/carbidopa dosing
- Add rasagiline
- Add entacapone
- Consider pramipexole, ropinirole, tolcapone
- May consider selegiline or zydis selegiline


Waters C. Diagnosis and Management of Parkinson’s Disease. 2006.
**AAN Recommendations for Therapy for “Off” Time**

- Entacapone and rasagiline **should be offered** to reduce “off” time (Level A).
- Pramipexole, ropinirole, and tolcapone **should be considered** to reduce “off” time (Level B).
  - Use tolcapone with caution (requires monitoring).
- Apomorphine and selegiline **may be considered** to reduce “off” time (Level C).
- Insufficient evidence to recommend one agent over another


**MAO-B Inhibitors—Role in Advanced PD**

<table>
<thead>
<tr>
<th>Selegiline</th>
<th>Selegiline disintegrating</th>
<th>Rasagline</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insufficient evidence that monotherapy prevents clinical progression or that adjunctive therapy prevents fluctuations</td>
<td>• Orally disintegrating tablet</td>
<td>• 2nd-generation</td>
</tr>
<tr>
<td>• Indicated as adjunctive therapy</td>
<td>• Reduced amphetamine-like metabolites</td>
<td>• Some neuroprotective properties seen in animal studies</td>
</tr>
<tr>
<td></td>
<td>• Indicated as adjunctive therapy</td>
<td>• Indicated as adjunctive therapy</td>
</tr>
</tbody>
</table>

Azulett P; Zelapar PI.

**Offer Rasagiline to Reduce “Off” Time**

**Percentage Decreases in “Off” Time with Rasagiline**

- **29%**
  - 1.8 h
  - 1.0 mg
  - P<.001 vs PL

- **23%**
  - 1.41 h
  - 0.5 mg
  - P=.02

- **21%**
  - 1.18 h
  - 1.0 mg
  - P<.0001

Carbidopa/Levodopa + COMT Inhibitor—Role in PD

- Always given with levodopa
- Prolongs levodopa half-life; increases its transport to the brain; raises dopamine levels
- Reduces levodopa dosage
- Reduces “off” time
- May delay dyskinesias
- For idiopathic PD with signs and symptoms of end-of-dose wearing off
- May produce motor complications earlier

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Offer Entacapone to Reduce “Off” Time

![Graph showing the effects of entacapone on ON and OFF times with levodopa dose changes](image)

- Rinne et al.: ON time increased by 13%, OFF time decreased by 22%, p < .001
- Rascol et al.: ON time increased by 9%, OFF time decreased by 21%, p < .0001

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Consider Pramipexole to Reduce “Off” Time

![Graph showing the effects of pramipexole on OFF time decrease with levodopa dose changes](image)

- Lieberman et al.: OFF time decreased by 7%, p = .0006
- Guttman et al.: OFF time decreased by 15%

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Consider Ropinirole to Reduce “Off” Time

- Rascol et al.
  - OFF time decrease 4% \( P = .08 \)
  - Placebo 23%
  - Ropinirole 31%

- Lieberman et al.
  - OFF time decrease 13% \( P = .003 \)
  - Placebo 35%


Consider Tolcapone to Reduce “Off” Time

<table>
<thead>
<tr>
<th>Study</th>
<th>Decrease “Off” time</th>
<th>Mean ↓ levodopa dose</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajput</td>
<td>32% 48% 20%</td>
<td>≤200 mg</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baas</td>
<td>31.5% 26.2% 10.5%</td>
<td>109 mg ( P &lt; .05 )</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>


Potential Use of Apomorphine or Selegiline to Reduce “Off” Time

Apomorphine vs Placebo¹
- 34% ↓ (2 h) “off” time vs 0% placebo \( (p = 0.02) \)
- Mean inpatient UPDRS motor scores ↓ 62% and 1%, respectively \( (p < .001) \)

Selegiline vs Placebo²
- Mean hourly self-assessment of gait improved in 58% vs 30.4% placebo
- Mean hourly overall symptom control improved in 58% vs 26.7% placebo \( (p < .01) \)
- Mean daily levodopa dosage ↓ 17% vs 7% placebo

Oral disintegrating selegiline vs Placebo³
- 32% ↓ (2.2 h) “off” time vs 9% (0.6 h) placebo \( (p = 0.001) \)
- 20% (1.8 h) “on” vs 5% (0.4 h) placebo \( (p = 0.006) \)

**Motor Fluctuation: “On/Off”**

<table>
<thead>
<tr>
<th>On/Off phenomenon</th>
<th>Possible treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sudden and unpredictable</td>
<td></td>
</tr>
<tr>
<td>• Results from shifts between undertreated &amp; overtreated states</td>
<td></td>
</tr>
<tr>
<td>• Difficult to treat</td>
<td></td>
</tr>
<tr>
<td>• Change to liquefied carbidopa/levodopa (small doses throughout the day)</td>
<td></td>
</tr>
<tr>
<td>• requires highly motivated patient</td>
<td></td>
</tr>
<tr>
<td>• solution made daily</td>
<td></td>
</tr>
<tr>
<td>• Add dopamine agonist</td>
<td></td>
</tr>
<tr>
<td>• Increase the levodopa dose?</td>
<td></td>
</tr>
<tr>
<td>• Risks increased dyskinesias</td>
<td></td>
</tr>
</tbody>
</table>

Waters C. Diagnosis and Management of Parkinson’s Disease. 2006.

**Motor Fluctuation: Freezing**

<table>
<thead>
<tr>
<th>Freezing episode</th>
<th>Possible treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Occurs during “off” state and “on” state</td>
<td></td>
</tr>
<tr>
<td>• “Off”-state freezing</td>
<td></td>
</tr>
<tr>
<td>• control levodopa off-time</td>
<td></td>
</tr>
<tr>
<td>• “On”-state freezing</td>
<td></td>
</tr>
<tr>
<td>• does not respond to dopaminergic therapy</td>
<td></td>
</tr>
<tr>
<td>• Increase levodopa/carbidopa dose</td>
<td></td>
</tr>
<tr>
<td>• Add dopamine agonist</td>
<td></td>
</tr>
<tr>
<td>• Add selegiline</td>
<td></td>
</tr>
<tr>
<td>• Reduce medication dose (risks wearing off)</td>
<td></td>
</tr>
<tr>
<td>• Nonpharmacologic techniques (auditory, visual, proprioceptive cues)</td>
<td></td>
</tr>
</tbody>
</table>

Waters C. Diagnosis and Management of Parkinson’s Disease. 2006.
Motor Complications: Levodopa-Related Dyskinesias

- Peak-dose dyskinesia
- Diphasic dyskinesia
- Off dystonia (wearing off/early morning)
- Myoclonus (awake, during sleep)
- Akathisia (wearing off, peak-dose)
- Respiratory dyskinesia/dysregulation
- Punding

Adapted from Waters C. Diagnosis and Management of Parkinson's Disease. 2006.

Potential of Amantadine to Reduce Dyskinesia

- Antiviral with antiparkinson effects
- Rapid, short-acting
- 45% ↓ total UPDRS dyskinesia score
  - Antidyskinetic effects last <8 months
- May be considered to reduce dyskinesia


Peak-Dose Dyskinesia

<table>
<thead>
<tr>
<th>Peak-dose dyskinesia</th>
<th>Possible therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common type</td>
<td>Reduce individual levodopa dose (risks more severe ‘off’ state)</td>
</tr>
<tr>
<td>Occurs at the time of peak plasma levels and maximal levodopa benefit</td>
<td>More frequent, lower dosages</td>
</tr>
<tr>
<td></td>
<td>Substitute IR for CR levodopa</td>
</tr>
<tr>
<td></td>
<td>Early morning akinesias—add IR to CR first thing upon awakening</td>
</tr>
<tr>
<td></td>
<td>Add COMT inhibitor, dopamine agonist, amantadine</td>
</tr>
</tbody>
</table>

**Diphasic Dyskinesia**

<table>
<thead>
<tr>
<th>Diphasic dyskinesia</th>
<th>Possible therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less common</td>
<td>• Substitute IR for CR levodopa</td>
</tr>
<tr>
<td></td>
<td>• Increase dopamine agonist dose</td>
</tr>
<tr>
<td></td>
<td>• Restrict levodopa to several early and/or midday doses</td>
</tr>
</tbody>
</table>

• Occurs with rising or falling plasma levels
  – beginning or end of levodopa response cycle


**Dystonia**

<table>
<thead>
<tr>
<th>Dystonia</th>
<th>Possible therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Occurs as levodopa levels are rising or falling</td>
<td></td>
</tr>
<tr>
<td>• Most common as a wearing-off effect in the “off” state</td>
<td></td>
</tr>
<tr>
<td>• Painful, fixed postures predominantly affecting distal extremities</td>
<td></td>
</tr>
</tbody>
</table>
  – includes morning or nocturnal painful foot cramps |
| • Bedtime dose of CR levodopa |
| • Early morning levodopa |
| • Nocturnal dopamine agonist |


**Continuous Therapy Approach for Motor Complications**

• More physiologic stimulation of brain dopaminergic receptors
• Reduced risk of motor complications
• Therapeutic strategies:
  – Subcutaneous apomorphine
  – Continuous infusion of levodopa (intestinal gel)
  – Long-acting dopamine agonists (CR & ER forms)
  – Transdermal rotigotine patch

Apomorphine Continuous Therapy

Levodopa dose decrease

OFF time decrease (based on patient diary)

55%

38%


Rotigotine Patch Continuous Therapy

OFF time

-2.7 h

2.1 h

2.7 h

P<.001

P<.003

P<.001

40 cm²

60 cm²

40 cm²

60 cm²

Responder rate*

34%

34%

57%

55%


Rotigotine Patch Continuous Therapy vs Pramipexole

OFF time

-2.44 h

-2.52 h

-0.88 h

ON time without dyskinesia

2.8 h

2.7 h

1.4 h

*P<.001 rotigotine vs placebo

ropinirole CR / pramipexole ER

- New formulations of dopamine agonists
- Double-blind, placebo-controlled, 24-week studies
  - Primary outcome measure: reduction in daily "off" time
    - Mean reduction in daily levodopa of 278 mg
    - Mean reduction in daily "off" time of 2.1 hours vs 0.3 hours with placebo
  - Secondary outcome measures significantly improved
    - 42% responders vs 14% placebo on CGI-I scale (p <.001)
    - 52% responders vs 20% placebo based on change in "off" time and levodopa dose (20% reduction, p <.001)

Surgical Therapy: Goals and Criteria for Patient Selection

Goals:
- Reduce abnormal neuronal activity
- Restore dopaminergic tone
- Not simple, widespread effects distant from stimulation

Consider surgical treatment in a patient:
- with uncontrolled, disabling dyskinesias
- with significant motor fluctuations and/or disabling tremor despite optimal medical management
- long-lasting benefit from antiparkinson medications
- Good medical condition without contraindications to surgery
- without cognitive deficits, includes untreated existing depression

Surgical Therapy: Ablative Procedures/Stimulation

- Ablative
  - Thalamotomy
  - Pallidotomy
- Deep-brain stimulation
  - reduces "off" time; increases "on" time without dyskinesias; reduces levodopa dose; improves tremor
  - Can never make you better than your best medicated "on" time, but can give you more "on" time. I feel it’s better to best medical therapy, and it has been shown in clinical trials
Deep Brain Stimulation:

**Advantages**
- No destruction of brain tissue
- Can adjust stimulus parameters
- Can perform bilateral operations

**Disadvantages**
- Implanted foreign body, risk of infection
- Battery replacement / Cost of equipment
- Time & effort needed for programming

DBS of the STN for PD

<table>
<thead>
<tr>
<th>Investigator (Year)</th>
<th>No. of Patients</th>
<th>Follow-Up (Months)</th>
<th>Main Outcome (%)</th>
<th>Reduction Daily Levodopa Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al (1998)</td>
<td>10</td>
<td>6-18</td>
<td>54</td>
<td>NA</td>
</tr>
<tr>
<td>Limousin et al (1998)</td>
<td>24</td>
<td>12</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>(99)</td>
<td>12†</td>
<td>24</td>
<td>5†</td>
<td></td>
</tr>
<tr>
<td>Burchiel et al (1999)</td>
<td>5‡</td>
<td>12</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>Moro et al (1999)</td>
<td>7</td>
<td>16</td>
<td>42</td>
<td>65</td>
</tr>
<tr>
<td>Houeto et al (2000)</td>
<td>23</td>
<td>6</td>
<td>67</td>
<td>61†</td>
</tr>
<tr>
<td>(11)</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molinuevo et al (2000)</td>
<td>15</td>
<td>6</td>
<td>66</td>
<td>80.4†</td>
</tr>
<tr>
<td>(2009)</td>
<td>9</td>
<td>36</td>
<td>61</td>
<td>38</td>
</tr>
</tbody>
</table>

The near future of medications: Coming soon....

**Accordion Pill (levodopa)**

The new accordion pill is under investigation. There was success in the Phase II clinical trials. Briefly this consists of a unique "gastric retentive" formulation that is made of biodegradable films. It is folded up to look like an accordion and upon reaching the stomach the capsule dissolves and the accordion pill unfolds and is retained in the stomach for up to 12 hours. It slowly releases the drug in a controlled manner towards the upper part of the gastrointestinal tract.
The near future of medications: Coming soon….

Inhaled Levodopa for the treatment of PD “off” episodes called: CVT-301

CVT-301 is currently in development in Phase 2 and 3 clinical trials as an inhaled form of levodopa. The trials just completed in the EU. It is indicated as a “rescue” medicine for patients experiencing a lot of “off” times. It is a self-administered inhaled therapy. The early trials were funded by a grant from the MJF Foundation. It will be a nice addition to our arsenal of therapies for patients who can use it properly.

Gallo BV

The near future of medications: Coming soon….

APL-130277

Apomorphine is not new to PD and some patients may have used the subcutaneous injection. What is unique here is that APL-130277 is in development as a sublingual (under the tongue) rescue medication.

The good news is that in the clinical trials it seemed to work as fast as the injections. After completing the current study, APL-130277 will complete the other necessary clinical studies to support its approval by the FDA. These studies, performed in the United States, include people who have Parkinson’s disease who suffer from “off” episodes.

These studies are completed for APL-130277 and the FDA approval should appear in mid to late 2019.

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Surgical Therapy - Neurorestorative: coming soon…

- Fetal & stem cell, fibroblast pleuripotential transplantation?
- Neurotrophic factor infusions?
- Gene therapy?