Managing the Motor Complications of Parkinson’s Disease

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Objectives

• Risk factors for the development of motor fluctuations

• Review the management of the motor complications of PD
  • Fluctuations
  • Dyskinesias

• The Non-Motor fluctuations of PD
Disclosures

I have received educational grants from Allergan
The Spectrum of Motor Complications in PD

• The motor complications of PD can be broken into two categories
  • Fluctuations
  • Dyskinesias
Incidence of Motor Complications

Bjornestd *et. al.* (2015) monitored 189 newly-diagnosed, drug naïve patients (participants in the Norwegian ParkWest project) for emergence of motor complications

- Cumulative 5 year incidence of any fluctuation = 52.4%
  - For fluctuations = 42.9%
  - For dyskinesias = 24.3%
  - 28.3% of those experiencing complications (14.8% of the total) experienced both fluctuations and dyskinesias

Scott *et. al.* (2015) followed 183 patients in Scotland for 4 years:

- 39 (21.3%) developed motor complications
- 42 (28.3%) developed dyskinesias
- 23 (12.6%) developed both
Risk Factors for Motor Complications

• Lower age at diagnosis (HR 0.97 per year)
  • Age > 80  →  11%
  • Age < 60 → 64%

• Female gender (HR 1.84) – independent of body weight

• Higher baseline UPDRS motor score (HR per unit 1.04)

• In this cohort, time from motor onset did not predict onset of complications (p = 0.593)
Anders Bjornestad, Elin B. Forsaa, Kenn Freddy Pedersen, Ole-Bjorn Tysnes, Jan Petter Larsen, Guido Alves
Risk and course of motor complications in a population-based incident Parkinson’s disease cohort

Parkinsonism & Related Disorders, Volume 22, 2016, 48–53
Risk Factors for Motor Complications

• In this cohort, 84% of patients were on levodopa at the end of 5 years of f/u (41% at 1 year f/u)

• Among 36 patients not receiving levodopa, 5 experienced fluctuations and 4 experienced dyskinesias (for levodopa-treated patients 49.7 and 27.5%)

• Initial treatment with levodopa in this cohort was associated with an increased risk of fluctuations (HR 1.84) but not dyskinesias
The Role of Levodopa

• When dose at onset of motor fluctuations was included in multivariate analysis, the association between initial levodopa therapy and motor fluctuations was lost.

• The dose of levodopa is associated with fluctuations; per 100 mg of levodopa
  • Increased risk of fluctuations (HR 1.13 (1.01-1.26), p = 0.037)
  • Increased risk of dyskinesias (HR 1.28 (1.16-1.42), p < 0.001)
The Role of Levodopa

• Cilia et al. (2014) compared the rates of motor complications in a cohort of Ghanaian patients with an Italian cohort matched for age, gender and disease duration at the first assessment. Additional analysis was also carried out after matching for therapeutic regimen.

Table 1 Cross-sectional analysis of demographic and general clinical features of Ghanaian patients with Parkinson’s disease at the baseline visit compared to all consecutive Italian patients with Parkinson’s disease examined for the first time during the same 4-year study period

<table>
<thead>
<tr>
<th>Features</th>
<th>Ghanaian Parkinson’s disease (n = 91)</th>
<th>Italian Parkinson’s disease (n = 2282)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males n (%)</td>
<td>58 (63.7)</td>
<td>1291 (56.6)</td>
<td>0.196</td>
</tr>
<tr>
<td>Age at onset, mean (SD) [range], y</td>
<td>60.6 (11.3) [27–91]</td>
<td>62.0 (10.7) [20–89]</td>
<td>0.217</td>
</tr>
<tr>
<td>Early onset n (%)</td>
<td>19 (20.9)</td>
<td>344 (15.1)</td>
<td>0.137</td>
</tr>
<tr>
<td>Positive family history for Parkinson’s disease n (%)</td>
<td>19 (20.9)</td>
<td>356 (15.6)</td>
<td>0.140</td>
</tr>
<tr>
<td>Right body side of Parkinson’s disease onset n (%)</td>
<td>47 (51.7)</td>
<td>1,355 (59.4)</td>
<td>0.176</td>
</tr>
<tr>
<td>Never treated n (%)</td>
<td>32 (35.2)</td>
<td>143 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>9.0 (6.3)</td>
<td>10.3 (4.5)</td>
<td>0.016</td>
</tr>
<tr>
<td>Cigarette smoking n (%)</td>
<td>6 (6.6)</td>
<td>361 (15.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Family history of Parkinson’s disease in Ghana could not be directly documented by a neurologist in the majority of cases.
The Role of Levodopa

Ghanaian patients had:

- Longer delay from symptom onset to diagnosis (3.9 vs 1.1 years)
- Longer disease duration at initiation of levodopa (4.2 vs 2.4 years)
- A higher proportion of tremor-predominant disease (74.7 vs 52.2%)
- Higher UPDRS III scores in the OFF state (34.9 vs 24.9)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No Levodopa n (%)</th>
<th>Levodopa n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On chronic levodopa n (%)</td>
<td>160 (87.9)</td>
<td>59 (64.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Levodopa duration at assessment, median [IQR], y</td>
<td>2.5 [1–5]</td>
<td>1.0 [0–2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Levodopa dose, mg/day$^b$</td>
<td>426 (182)</td>
<td>365 (154)</td>
<td>0.012</td>
</tr>
<tr>
<td>Levodopa dose, mg/kg/day$^b$</td>
<td>6.0 (2.2)</td>
<td>6.5 (3.2)</td>
<td>0.589</td>
</tr>
<tr>
<td>On dopamine agonists n (%)</td>
<td>131 (72)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On anticholinergics n (%)</td>
<td>20 (11)</td>
<td>28 (30.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On amantadine n (%)</td>
<td>2 (1.1)</td>
<td>7 (7.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>On COMT inhibitors n (%)</td>
<td>35 (19.2)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On MAO-B inhibitor n (%)</td>
<td>52 (28.6)</td>
<td>4 (4.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cilia et. al. Brain 2014: 137; 2731–2742
Figure 2  (A) Relationship between initiation of levodopa therapy and onset of motor fluctuations, and between initiation of levodopa therapy and onset of dyskinesias in Ghanaian patients with Parkinson’s disease and Italian Parkinson’s disease control subjects with motor fluctuations (Supplementary Table 1).  (B) The Parkinson’s disease control group has been additionally matched for therapy regimen (Table 3).
The Role of Levodopa

• Disease duration and dose of levodopa seem to be the main factors driving the emergence of fluctuations

• Patients with severe disability should not be deprived of levodopa for fear of causing fluctuations

• Keep the dose as low as possible and supplement with other medications to optimize symptom control
Motor Fluctuations

- Wearing off
- Sudden offs
- Random offs
- “Super” offs

- Delayed kicking in
- Dose failure
- Freezing of gait (FOG)
- Off dystonia
Wearing Off

• Generally begins as end-of-dose failure

• Practical definition → <4 hour duration of an adequate dose of levodopa

• Early in disease, there is a long-duration response to levodopa; the clinical response persists despite a drop in the plasma concentration of levodopa

• As the disease progresses, this long-duration response is lost and clinical response parallels plasma levodopa concentration

• The offs become deeper and more severe with disease progression
Wearing Off

• Some patients develop sudden offs over minutes, instead of tens of minutes

• Random offs occur unpredictably without relation to the timing of doses

• Super offs are worse than the untreated state, and typically occur before or immediately after a dose
Wearing Off – Management Options

- Increase the dose of levodopa

- Shorten the interval between doses

- Inhibit the metabolism of dopamine
  - MAO-B inhibitors: selegiline, rasagiline
  - COMT inhibitor: entacapone
  - Each class of drug will reduce off time by about 1 hour/day

- Add a dopamine agonist
  - Pramipexole, ropinirole, rotigotine, (bromocriptine)
  - DA will reduce the depth of the off and reduce total off time
Wearing Off – Management Options

• Use a long-acting formulation of levodopa, alone or in combination with IR
  • NB levodopa/carbidopa CR has approximately 70% bioavailability compared to the IR formulation and takes longer to kick in

• Continuous administration of levodopa
  • Levodopa/carbidopa intestinal gel (Duopa)

• Deep brain stimulation
  • STN
  • Gpi
Levodopa/Carbidopa Intestinal Gel

• Levodopa/carbidopa intestinal gel (LCIG) has been available in the EU since 2004 and in North America since 2015.

• Indicated in patients with advanced Parkinson’s disease with severe motor fluctuations and dyskinesias refractory to other medication therapies.

• Continuous infusion of concentrated levodopa via PEG-J tube results in a constant plasma level through the day.
Levodopa/Carbidopa Intestinal Gel

- Olanow *et. al.* (2014) reported an RCT of LCIG vs levodopa/carbidopa IR
  - Primary endpoint was reduction in off time
  - Secondary endpoint was increase in on-time without troublesome dyskinesias

<table>
<thead>
<tr>
<th>Primary efficacy outcome</th>
<th>Levodopa-carbidopa intestinal gel (n=35)</th>
<th>Immediate-release levodopa-carbidopa (n=31)</th>
<th>Treatment difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-time, h per day</td>
<td>-4.04 (0.65)</td>
<td>-2.34 (0.66)</td>
<td>-1.91 (-3.05 to -0.76)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary efficacy outcomes</th>
<th>Levodopa-carbidopa intestinal gel (n=35)</th>
<th>Immediate-release levodopa-carbidopa (n=31)</th>
<th>Treatment difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-time without troublesome dyskinesia, h per day</td>
<td>4.11 (0.75)</td>
<td>2.24 (0.76)</td>
<td>1.86 (0.56 to 3.17)</td>
<td>0.059</td>
</tr>
<tr>
<td>On-time without dyskinesia, h per day</td>
<td>3.37 (1.04)</td>
<td>1.09 (1.05)</td>
<td>2.28 (0.47 to 4.09)</td>
<td>0.042</td>
</tr>
<tr>
<td>On-time with non-troublesome dyskinesia, h per day</td>
<td>0.81 (0.86)</td>
<td>1.54 (0.86)</td>
<td>-0.73 (-2.22 to 0.76)</td>
<td>0.329</td>
</tr>
<tr>
<td>On-time with troublesome dyskinesia, h per day</td>
<td>-0.11 (0.52)</td>
<td>-0.03 (0.52)</td>
<td>0.08 (-0.98 to 0.82)</td>
<td>0.874</td>
</tr>
<tr>
<td>PDQ-39 summary index</td>
<td>-10.9 (3.3)</td>
<td>-3.9 (3.2)</td>
<td>-7.0 (-12.6 to -1.4)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mean CGI-I score at final assessment</td>
<td>2.3 (0.4)</td>
<td>3.0 (0.4)</td>
<td>-0.7 (-1.4 to 0.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>UPDRS part III</td>
<td>1.8 (1.3)</td>
<td>5.3 (1.3)</td>
<td>-3.5 (-5.3 to -0.8)</td>
<td>0.0086</td>
</tr>
<tr>
<td>UPDRS part III</td>
<td>1.5 (2.4)</td>
<td>2.9 (2.4)</td>
<td>1.4 (-2.8 to 5.6)</td>
<td>0.502</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>0.05 (0.04)</td>
<td>-0.02 (0.04)</td>
<td>0.07 (-0.01 to 0.15)</td>
<td>0.067</td>
</tr>
<tr>
<td>Zarit Burden Interview</td>
<td>2.8 (3.7)</td>
<td>5.7 (3.3)</td>
<td>4.5 (-0.7 to 1.7)</td>
<td>0.150</td>
</tr>
<tr>
<td>Levodopa total daily dose, mg</td>
<td>49.7 (96.6)</td>
<td>24.7 (94.9)</td>
<td>-15.0 (-32.4 to 2.5)</td>
<td>0.0625</td>
</tr>
<tr>
<td>Overall mean (SD) levodopa rescue dose, mg</td>
<td>139.8 (20.3)</td>
<td>180.6 (21.9)</td>
<td>-40.8 (-100.4 to 18.8)</td>
<td>0.1762</td>
</tr>
</tbody>
</table>

Data are the least squares mean change from baseline to week 12 (SE) unless otherwise stated. PDQ- Parkinson Disease Questionnaire. CGI-I - Clinical Global Impressions-Improvement. UPDRS- Unified Parkinson’s Disease Rating Scale. EQ-SD - EuroQol quality of life-Self Dimensions. *On-time without troublesome dyskinesia equals on-time without dyskinesia plus on-time with non-troublesome dyskinesia. Measure not part of hierarchical analysis. IfCGI-I is very much improved, 2 is much improved, 3 is minimally improved, 4 is no change, 5 is minimally worse, 6 is much worse, and 7 is very much worse. SUPDRS was completed in the on-state.

Table 2: Treatment efficacy
Almost all of the patients had an adverse event, mostly related to the procedure or device. These occurred mainly in the first week and resolved in all cases.

89% had device-related complications, including:
- Tube dislocation or obstruction
- PEG-J insertion complications
- Pump malfunctions
- Stoma problems

Medication-related side effects were no different between groups.
Off-Period Dystonia

• Commonly occurs in the early morning when plasma levodopa concentration is low

• Can be treated with any of the above classes of medications
  • Long-acting formulations of levodopa or DA at bedtime
  • MAO-B inhibitors can result in less deep off periods and may attenuate painful dystonia

• If dystonia is focal and refractory to medication therapy, injections with botulinum toxin can be effective
Delayed Kicking In

• Defined as taking >30 minutes for a dose of levodopa to start working

• Especially common for the first AM dose

• Due to any or all of:
  • Delayed gastric emptying
  • Constipation
  • Poor absorption due to competition with large neutral amino acids
    • In the gut
    • At the blood-brain barrier
Delayed Kicking In - Management

- Aggressively manage constipation → Aim for a daily bowel movement
- Space levodopa at least 30 minutes from protein
- Crush/chew levodopa
- Take medication with a carbonated beverage
- Switch to a short-acting formulation of levodopa
Delayed Kicking In - Management

• Add an MAO-B inhibitor
  • Offs are less deep

• Add a long-acting dopamine agonist (rotigotine)

• Some patients require a higher dose first thing in the morning
“The Drugs Don’t Work”

• Some symptoms require higher doses of levodopa to treat, especially tremor and freezing

• Increasing the dose to treat these symptoms can worsen dyskinesias and drug side effects

• Use alternate medications when possible to treat these

• Tremor can respond well to:
  • Amantadine
  • Propranolol
  • Trihexyphenidyl (in the young and cognitively intact)
Freezing of Gait

• Pathophysiology complex and poorly understood
  • Interplay of dopaminergic, cholinergic and other neurotransmitter systems

• Occurs more commonly when off → treat as per wearing off

• Distinguish between “pseudo-on” and true “on” freezing
  • Pseudo-on freezing will respond to higher doses of levodopa → increased side effects
  • In rare cases, levodopa itself can cause freezing (true “on” freezing)
    • May improve with lower doses of levodopa more frequently to reduce peak concentration, though other symptoms may worsen
Freezing of Gait

- A recent open-label study found rotigotine (4-12 mg/day) could improve freezing of gait compared to extended-release pramipexole (1.5-4.5 mg/day) and ropinirole (8-16 mg/day)

![Graph showing changes in FOG scores](image)
Freezing of Gait

- Droxidopa has shown modest improvement in freezing in a double-blind, placebo-controlled trial

- Open-label studies of LCIG have shown improvements in FOG

- A meta-analysis (Schlenstedt et al. 2016) failed to show benefit of STN DBS for FOG in the Med on/stim on state, but did show benefit in the med off/stim on state

- Other therapies have shown mixed results in trials → MAO-B inhibitors, amantadine

- Physiotherapy and sensory tricks can be helpful
Falls

• ~70% of patients with PD will fall every year; 39% fall recurrently

• Median survival in patients with recurrent falls is 6 years

• In patients who have not fallen, 21% will fall in the next 3 months
Falls

• Often multifactorial
  • Postural instability
  • Freezing
  • Dyskinesias
  • Orthostatic hypotension
    • Possibly even if asymptomatic
  • Polypharmacy
  • Sensory loss
  • Cognitive impairment

• Evidence points to cholinergic denervation of the PPN and nucleus basalis of Meynert as a contributor to falls
Preventing Falls

• Optimize dopaminergic therapy

• Address modifiable factors (e.g. treat OH)

• Gait aids → Walker >> cane

• Physiotherapy
  • Fall prevention
  • How to fall safely
Preventing Falls

• Several studies have shown a reduction in falls with acetylcholinesterase inhibitors
  • ReSPonD trial (Henderson et. al. 2016) enrolled 130 patients with moderate PD (H&Y 2-3) with at least one fall in the previous year.
    • Randomized to rivastigmine (up to 12 mg /day) vs placebo for 32 weeks
    • The treatment group had a 45% reduction in falls (1.4 vs 2.4/month, p = 0.002)
Deep Brain Stimulation for Fluctuations

• DBS of the Gpi and STN has been FDA-approved since 2002 for patients with medically-refractory motor complications

• Multiple trials have shown 24-69% improvement in UPDRS motor scores from both procedures; most fail to show a significant difference between the two targets but some do favour STN

• In general, STN DBS allows greater reduction in levodopa dose, while Gpi DBS has greater anti-dyskinesia effect
Non-Motor Fluctuations

• A detailed description of the non-motor symptoms of PD is beyond the scope of this talk

• Any of the non-motor symptoms can fluctuate, and non-motor offs may or may not correlate to motor offs

• Bothersome, fluctuating non-motor symptoms may respond to similar treatment strategies as motor fluctuations
Dyskinesias

• Abnormal, involuntary movements related to dopaminergic therapy

• May be ballistic, choreiform or dystonic

• Two main patterns:
  • Peak dose – onset generally corresponds to the peak of the anti-parkinsonian effect of medications (1-2 hours post dose)
  • Diphasic (D-I-D) – can occur several minutes after taking a dose as the plasma level rises, or several hours later as the level drops
Impact of Dyskinesias

• Dyskinesias may:
  • Cause embarrassment and avoidance of social activities
  • Be painful
  • Contribute to falls
  • Complicate ability to titrate medications
  • Contribute to fatigue
  • Increase risk of cervical disc herniations
Dyskinesias

• The pathophysiology of dyskinesias is incompletely understood

• Risk correlates to disease duration as well as dose of levodopa
  • In their Ghanaian cohort, Cilia et al. (2011) described a 61-year old woman who developed dyskinesias after her first-ever dose of levodopa (150 mg) after having PD for about 6 years (UPDRS III 19/108)

• Risk factors also include:
  • Female sex
  • Young-onset PD
  • Low body weight
  • PIGD subtype
Management of Dyskinesias

• As with motor fluctuations, use the lowest effective dose of levodopa to delay the onset of dyskinesias

• It is important to distinguish peak-dose from diphasic dyskinesias
  • Diphasic dyskinesias are managed as per wearing off

• Peak dose dyskinesias may improve with smaller, more frequent doses of dopaminergic medications
Management of Dyskinesias

• Amantadine has documented long-term efficacy in the treatment of dyskinesias
  • Wolf et. al. (2010) randomized 32 patients (mean disease duration 16.8 years) on stable amantadine therapy for at least one year (mean = 4.8 years) to continuation of amantadine or change to placebo.
  • After 3 weeks of follow-up, there was a significant increase in score on UPDRS IV questions regarding dyskinesia duration and severity (increase from 3.06 to 4.28, p = 0.02)
  • Diary data also showed an increase in time on with troublesome dyskinesia (from 1.7 to 3.5 hours per day)
Management of Dyskinesias

• Clozapine has also been shown to be effective in reducing on time with dyskinesia by about 1 hour in an RCT with 50 patients

• Mixed results have been found in small studies with:
  • Cannabinoids
    • One small study (N=7) found a reduction in dyskinesias with nabilone
    • No effect of oral cannabis
  • Memantine
  • Levetiracram

• Perampanel was found to be ineffective
Management of Dyskinesias

- Deep brain stimulation is effective at reducing dyskinesias
  - STN DBS allows reduction in levodopa dosage
  - GPi DBS has direct anti-dyskinetic effect
Take Home Points

• Patients with advanced PD are complex and it can be overwhelming to manage the symptoms

• Focus on the symptom that bothers the patient most

• Make one change at a time

• Keep levodopa doses small and use alternative medications to help manage symptoms when possible
  • Avoid the 250/25 tablets!