Late Stage PD: clinical problems & management issues

Miguel Coelho, MD
Neurological Department, Hospital Santa Maria
Clinical Pharmacology Unit, IMM, Lisbon
Portugal

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Outline

• Progression & Staging of Parkinson’s disease (PD).

• The concept of Late-Stage PD (LS-PD).

• Clinical problems in LS-PD.

• Management issues in LS-PD.
Progression & Staging

- **Progression of PD**

  - Classically regarded as:
    - Increase in the severity of motor symptoms—either levodopa-responsive or levodopa-resistant.
    - The emergence of levodopa-induced motor complications (MC).
    - Non motor symptoms (NMS) not included.
- Motor progression is non-linear.
- Motor decline is faster in earlier stages.

<table>
<thead>
<tr>
<th>TABLE 5. Standardised progression rates for motor scores per yr by disease severity at baseline (means and SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in UPDRS III / yr over 1 yr (clinic-based sample)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>% Change in HY / yr over 1 yr (clinic-based sample)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>% Change in HY score/yr over 1 yr (community-based sample)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>% Change in HY score/yr over 4 yr (community-based sample)</td>
</tr>
<tr>
<td>Median</td>
</tr>
</tbody>
</table>
- Frequency of levodopa-induced MC varies between studies and population recruited.

### Levodopa-induced dyskinesia reported in community-based observational studies

<table>
<thead>
<tr>
<th>OBSERVATIONAL STUDIES</th>
<th>Community-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td>Longitudinal</td>
</tr>
<tr>
<td>Schrag &amp; Quinn 00</td>
<td>Dotchin 11</td>
</tr>
<tr>
<td>Wickremaratchi 11</td>
<td>Evans 11</td>
</tr>
<tr>
<td></td>
<td>Ahlskog &amp; Muenter 01</td>
</tr>
<tr>
<td></td>
<td>Van Gerpen 06 (retrospective)</td>
</tr>
<tr>
<td>19%</td>
<td>25% by 8.5 yrs of LD therapy</td>
</tr>
<tr>
<td></td>
<td>35% by 8 yrs of FU</td>
</tr>
<tr>
<td></td>
<td>40% by 5 yrs of LD therapy</td>
</tr>
<tr>
<td></td>
<td>30% by 5 yrs of LD therapy &amp; 59% by 10 yrs of LD therapy</td>
</tr>
</tbody>
</table>

Coelho & Ferreira, in press
• Last decade, non-motor symptoms (NMS) as important source of disability:

• Frequency & severity increase with disease duration.
• Determine disability in later stages of disease.
• Dementia, psychosis, falls → institutionalization
• Dementia, psychosis, falls, institutionalization.

Death

Coelho 10 & 14; Chaudhuri 06; Aarsland 99,03,07 Hely 05, 08; Forsaa 10; Buter 08; Papapetropoulos 05; Goetz 93,95
**Staging of PD**

- Several attempts to stage disease progression.

- **Pre-levodopa era:**
  - Hoehn & Yahr (H&Y) staging system
    - Impairment (objective signs)
    - Disability (functional deficits)

- **Advanced stage** according to HY staging:
  - Stages 4 or 5 (loss of physical independence).

Hoehn & Yahr 67
• **Levodopa era:**
  – Development of **MC** were noted.
  – They increase in frequency & severity with disease duration.
  – Impact on disability and QoL.

• **Advanced stage** in levodopa era:
  – presence of MC (or disabling MC).

• **Advanced stage** Tolosa & Katzenschlager:
  – cardinal symptoms plus disease-related or drug-induced motor and non-motor complications.

Tolosa & Katzenschlager 07; Hoehn & Yahr 67; Marras 04; Schrag 00; Goetz 04; Obeso 00; Slawek 05
• Overall, *Advanced stage* defined based upon:

  – disease-related motor symptoms (e.g. HY)

  – drug-induced motor symptoms (e.g. MC)
Concept of Late-Stage PD

- **Considerable heterogeneity in advanced-stage PD**

- The phenotype of PD patients in many studies of advanced PD do not fulfill the usual definition of advanced-stage.

Hely 05, 08; Coelho 10 & 14; Papapetropoulos 05, 07; Martin 73; Kempster 07, 10; Apaydin 02
Heterogeneity in advanced stages of PD

More nuanced definitions of the later stages of PD are needed
### Table 3 | Frequency of drug-induced motor complications and nonmotor symptoms in selected studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor fluctuations</td>
<td>39 (78)</td>
<td>50 (96)</td>
<td>30 (100)</td>
<td>NA</td>
<td>62 (64.0)</td>
<td>32 (47.8)</td>
<td>53 (22.1) at 9.1 years of disease duration</td>
<td>56 (53.3)</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>31 (62)</td>
<td>49 (94)</td>
<td>30 (100)</td>
<td>NA</td>
<td>60 (61.8)</td>
<td>28 (41.8)</td>
<td>NA</td>
<td>59 (56.2)</td>
</tr>
<tr>
<td>Troublesome or moderate–severe dyskinesias</td>
<td>13 (26)</td>
<td>6 (12)</td>
<td>3 (10)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>38 (36.2)</td>
</tr>
<tr>
<td>Dementia</td>
<td>25 (50)</td>
<td>25 (48)</td>
<td>25 (83)</td>
<td>70 (54) with cognitive disability</td>
<td>54 (55.6) with cognitive disability</td>
<td>34 (50.7)</td>
<td>21 (46.6) of those evaluated at 12 years</td>
<td>27 (24.7)</td>
</tr>
<tr>
<td>Falls</td>
<td>25 (50)</td>
<td>41 (81)</td>
<td>27 (87)</td>
<td>45 (35)</td>
<td>32 (33.0)</td>
<td>39 (58.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>22 (44)</td>
<td>26 (50)</td>
<td>23 (74)</td>
<td>77 (61)</td>
<td>57 (58.7)</td>
<td>35 (52.2)</td>
<td>12 (48.0) of those evaluated at 12 years</td>
<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td>31 (62)</td>
<td>22 (54%) of those tested</td>
<td>15 (50) on antidepressants</td>
<td>NA</td>
<td>NA</td>
<td>29 (43.3)</td>
<td>19 (24.0) at 17.0 years of disease duration</td>
<td>NA</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>32 (64)</td>
<td>22 (41)</td>
<td>22 (71)</td>
<td>NA</td>
<td>NA</td>
<td>19 (28.4) had autonomic dysfunction</td>
<td>n/a</td>
<td>NA</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>18 (36)</td>
<td>41 (79)</td>
<td>21 (70)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>40 (45.0) at 16.8 years of disease duration</td>
<td>NA</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>34 (68)</td>
<td>“Common”</td>
<td>15 (50) had choking</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>n/a</td>
<td>NA</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>49.2 (13)</td>
<td>41.2 (SD NA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>47.1 (20.7) at 16.8 years of disease duration</td>
<td>NA</td>
</tr>
</tbody>
</table>

Apart from UPDRS motor scores, values shown in the table refer to numbers of patients, and values in brackets express the number of patients as a percentage of the total number of patients in the cohort. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. Abbreviations: NA, not available or not applicable; UPDRS, Unified Parkinson Disease Rating Scale.
- **Disability:**
  - L-dopa resistant motor symptoms
  - NMS

**Table 6** Symptoms causing an extreme or severe impact on patients’ perceived health status in late-stage PD patients

<table>
<thead>
<tr>
<th>Impact of symptoms on patients’ perceived health status</th>
<th>Falls</th>
<th>Urinary dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms with extreme impact (score 4)</td>
<td>Unsteadiness</td>
<td>Sweats</td>
</tr>
<tr>
<td></td>
<td>Bradykinesia</td>
<td>Apathy</td>
</tr>
<tr>
<td></td>
<td>Freezing</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Speech problems</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
</tr>
</tbody>
</table>

Coelho *et al* 2010

Hely *et al* 2008
• This progression of disability also applies to DBS patients

Deuschl 06

Castrioto 11
Progression of PD in the post-levodopa & DBS era
The concept of late-stage PD (LS-PD)

- At least a small subset of advanced-stage PD progress to a later, distinct phase of disease.
A proposed definition for late-stage PD

- Patients who progress beyond advanced-stage.
- Highly dependent on caregivers for ADL.
- Dependency due to:
  - treatment-resistant motor symptoms.
  - NMS.

- Operational definition: Schwab & England Scale.
LS-PD < 50% Schwab & England Scale, during *on period*

**VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE**

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort.
   Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

50% – More dependent. Help with half, slower, etc. Difficulty with everything.
40% – Very dependent. Can assist with all chores, but few alone.
# Clinical Features of LS-PD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD patients (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female (n (%))</strong></td>
<td>27 (54)</td>
</tr>
<tr>
<td>Patient from Barcelona (n (%))</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Patient from Lisbon (n (%))</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Age (years) (mean (SD))</td>
<td>74.1 (7.0)</td>
</tr>
<tr>
<td>Duration of disease (years) (mean (SD))</td>
<td>17.94 (6.3)</td>
</tr>
<tr>
<td>Moehn &amp; Yahr stage* (n* (%))</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30 (60)</td>
</tr>
<tr>
<td>5</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Levodopa (n (%))</td>
<td></td>
</tr>
<tr>
<td>mono-therapy</td>
<td>49 (98)</td>
</tr>
<tr>
<td>in combination</td>
<td>18 (36)</td>
</tr>
<tr>
<td>31 (62)</td>
<td></td>
</tr>
<tr>
<td>Daily dose of levodopa (mg) (mean (SD))</td>
<td>785 (315)</td>
</tr>
<tr>
<td>Range of daily dose of levodopa (mg)</td>
<td>250-1900</td>
</tr>
<tr>
<td>Agonists (n (%))</td>
<td></td>
</tr>
<tr>
<td>25 (50)</td>
<td></td>
</tr>
<tr>
<td>Amantadine (n (%))</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Entacapone (n (%))</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Selegiline (n (%))</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Anticholinergics (n (%))</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Brain surgery for PD (n (%))</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Neuroleptics (n (%))</td>
<td></td>
</tr>
<tr>
<td>25 (50)</td>
<td></td>
</tr>
<tr>
<td>clozapine (n (%)); daily dose (mg) (mean (SD))</td>
<td>17 (25); 58.2 (74.9)</td>
</tr>
<tr>
<td>olanzapine (n (%); daily dose (mg) (mean (SD))</td>
<td>5 (10); 125 (90.1)</td>
</tr>
<tr>
<td>other (n (%))</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benzodiazepines (n (%))</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Antidepressants (n (%))</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Rivastigmine (n (%))</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Non neurological medication (n (%))</td>
<td>32 (64)</td>
</tr>
</tbody>
</table>

N = 50

Coelho 10; Coelho 14, *in press*
### Table 2: Motor symptoms in late-stage PD patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>PD patients ($n = 50$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric disease ($n (%)$)</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Slowness of movement ($n (%)$)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>UPDRS limb bradykinesia items, median$^a$</td>
<td>3</td>
</tr>
<tr>
<td>Postural instability ($n (%)$)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Dysarthria ($n (%)$)</td>
<td>48 (96)</td>
</tr>
<tr>
<td>UPDRS speech, median$^a$</td>
<td>3</td>
</tr>
<tr>
<td>Neck rigidity ($n (%)$)</td>
<td>39 (78)</td>
</tr>
<tr>
<td>UPDRS neck rigidity, median$^a$</td>
<td>2</td>
</tr>
<tr>
<td>Dysphagia ($n (%)$)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>UPDRS swallowing, median$^a$</td>
<td>2</td>
</tr>
<tr>
<td>Limb rigidity ($n (%)$)</td>
<td>32 (64)</td>
</tr>
<tr>
<td>UPDRS limb rigidity items, median$^a$</td>
<td>1</td>
</tr>
<tr>
<td>Freezing ($n (%)$)</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Falls ($n (%)$)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Tremor ($n (%)$)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Rest tremor ($n (%)$)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Asymmetric rest tremor ($n (%)$)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Postural tremor ($n (%)$)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Head tremor ($n (%)$)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>UPDRS tremor items, median$^a$</td>
<td>0</td>
</tr>
<tr>
<td>Fixed dystonia ($n (%)$)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Bone fractures in the previous 5 years ($n (%)$)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Need for a wheelchair ($n (%)$)</td>
<td>39 (78)</td>
</tr>
<tr>
<td>Gastrostomy ($n (%)$)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>UPDRS motor on (mean (SD))$^b$</td>
<td>49.18 (13.0)</td>
</tr>
</tbody>
</table>

### Table 3: Levodopa-induced complications in late-stage PD patients at the time of study assessment

<table>
<thead>
<tr>
<th>Complication</th>
<th>PD patients ($n = 59$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa-induced motor complications ($n (%)$)</td>
<td>30 (78)</td>
</tr>
<tr>
<td>Wearing-off ($n (%)$)</td>
<td>30 (78)</td>
</tr>
<tr>
<td>Off duration &gt;75% of the day ($n (%)$)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>No on response ($n (%)$)</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Morning dystonia ($n (%)$)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Off dystonia ($n (%)$)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Delayed on response ($n (%)$)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Morning akinesia ($n (%)$)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>On/off phenomena ($n (%)$)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Dyskinesia ($n (%)$)</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Peak-dose ($n (%)$)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Diphasic ($n (%)$)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Square-wave ($n (%)$)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Troublesome dyskinesias ($n (%)$)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Dyskinesia duration &gt;75% of the day ($n (%)$)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Severe or complete disabling dyskinesia ($n (%)$)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Levodopa-induced non-motor fluctuations ($n (%)$)</td>
<td>33 (66)</td>
</tr>
<tr>
<td>Neuropsychiatric ($n (%)$)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Dysautonomic ($n (%)$)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Sensory ($n (%)$)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>UPDRS part IV (mean (SD))$^b$</td>
<td>5.3 (3.5)</td>
</tr>
</tbody>
</table>

### Table 4: Performance in the activities of daily living of late-stage PD patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>On (mean (SD))</th>
<th>Off (mean (SD))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS ADL$^a$</td>
<td>28.2 (6.3)</td>
<td>29.6 (5.8)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>S&amp;E$^b$</td>
<td>31.0 (15.7)</td>
<td>23.2 (14.2)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>
Handicap

Table 4. Multiple linear regression model for London Handicap Scale

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardized Beta</th>
<th>Standardized Beta</th>
<th>SE</th>
<th>95% CI</th>
<th>P</th>
<th>Dependent variable</th>
<th>R</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of dementia (DSM-IV)</td>
<td>-0.123</td>
<td>-0.406</td>
<td>0.037</td>
<td>-0.200; -0.031</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score in UPDRS Part I</td>
<td>-0.015</td>
<td>-0.348</td>
<td>0.035</td>
<td>-0.04; -0.001</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn &amp; Yahr staging in off</td>
<td>-0.117</td>
<td>-0.341</td>
<td>0.034</td>
<td>-0.183; -0.046</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Non-motor complications in late-stage PD patients

<table>
<thead>
<tr>
<th></th>
<th>PD patients (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition, mood and behavior (n (%))</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Depression (n (%))</td>
<td>31 (62)</td>
</tr>
<tr>
<td>BDI in 15 testable depressed patients (mean (SD))</td>
<td>16.8 (5.29)</td>
</tr>
<tr>
<td>Symptoms suggestive of apathy (n (%))</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Slowness of thinking (n (%))</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Anxiety (n (%))</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Dementia (n (%))</td>
<td>25 (50)</td>
</tr>
<tr>
<td>MMSE in 44 testable patients (demented and non-demented) (mean (SD))</td>
<td>17.7 (8.1)</td>
</tr>
<tr>
<td>MMSE in 22 demented patients (mean (SD))</td>
<td>11.6 (6.5)</td>
</tr>
<tr>
<td>MMSE in 22 non-demented patients (mean (SD))</td>
<td>23.5 (4.5)</td>
</tr>
<tr>
<td>Visual hallucinations (n (%))</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Irritability (n (%))</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Delusions (n (%))</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Aggressive behavior (n (%))</td>
<td>8 (16)</td>
</tr>
<tr>
<td>UPDRS part I (mean (SD))</td>
<td>6.4 (3.9)</td>
</tr>
<tr>
<td>Dysautonomic complications (n (%))</td>
<td>48 (96)</td>
</tr>
<tr>
<td>Constipation (n (%))</td>
<td>41 (82)</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>32 (64)</td>
</tr>
<tr>
<td>(Incontinence, urgency or retention) (n (%))</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Hyperhidrosis (n (%))</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Sweats (n (%))</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Orthostatism (item 42 of UPDRS) (n (%))</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Dyspnea (n (%))</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Syncope (n (%))</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pain, Sleep and other symptoms</td>
<td>-</td>
</tr>
<tr>
<td>Night sleep problems (n (%))</td>
<td>30 (60)</td>
</tr>
<tr>
<td>Diurnal somnolence (n (%))</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Pain (n (%))</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Anorexia (n (%))</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Paresthesias (n (%))</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Sleep attacks (n (%))</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Weight loss (n (%))</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Fatigue (n (%))</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Drooling (n (%))</td>
<td>35 (70)</td>
</tr>
<tr>
<td>Kyphoscoliosis (n (%))</td>
<td>8 (16)</td>
</tr>
</tbody>
</table>
Health Care use, Residence & Caregivers

Table 6. Use of health resources in late-stage PD patients

<table>
<thead>
<tr>
<th>Health Resource</th>
<th>PD patients (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients living in their home (n (%))</td>
<td>35 (70)</td>
</tr>
<tr>
<td>Patients living in their relatives’ home (n (%))</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Patients living in a nursing home (n (%))</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Patients with an informal caregiver (n (%))</td>
<td>43 (90)</td>
</tr>
<tr>
<td>Patients with a paid caregiver (n (%))</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Patients with both informal and paid caregiver (n (%))</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Patients visited at State-owned hospitals (n (%))</td>
<td>43 (86)</td>
</tr>
<tr>
<td>Patients visited at private clinics (n (%))</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Patients visited at State-owned hospitals &amp; private clinics</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Visits to family physician in the preceding 6 months (includes visits to get prescription only) (mean (SD))</td>
<td>2.2 (3.0)</td>
</tr>
<tr>
<td>Visits to neurologist in the preceding 6 months (includes visits to get prescription only) (mean (SD))</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>Hospital admissions in the preceding 12 months (mean (SD))</td>
<td>0.78 (1.0)</td>
</tr>
<tr>
<td>Patients using a physiotherapist (n (%))</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Patients using a speech therapist (n (%))</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Patients using a homecare nurse (n (%))</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
Caregivers’ Burden

**Time spent caregiving**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time spent on informal caregiving (measured as y days x 24 hours/week)</td>
<td>5 days/week</td>
<td>2.57</td>
<td>7 days/week</td>
</tr>
<tr>
<td>(meaning 5 x 24 hours/week)</td>
<td>(meaning 7 x 24 hours/week)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Caregivers’ burden**

- Mean: 3.5 (SD 0.8) (No impact: 0; major impact: 4)
- Correlated with patients’ handicap ($r = -0.5; p<0.01$)
- Domains: “Mobility” and “Orientation” ($p<0.05$)

Coelho 14, *in press*
Sydney’s cohort

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor fluctuations</td>
<td>50 (96)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>49 (94)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Troublesome or moderate–severe dyskinesias</td>
<td>6 (12)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Dementia</td>
<td>25 (48)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Falls</td>
<td>41 (81)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>26 (50)</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Depression</td>
<td>22 (54% of those tested)</td>
<td>15 (50) on antidepressants</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>22 (41)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>41 (79)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>“Common”</td>
<td>15 (50) had choking</td>
</tr>
</tbody>
</table>

Increase from 15 to 20 yrs of PD:

- Dementia
- Visual hallucinations
- Falls
- Urinary dysfunction

Hely et al 05 & 08
Some symptoms cluster before death

Fig. 1 Milestones of disease advancement and total disease course. Error bars for standard error of the mean. The grey rectangles represent disease duration.

Figure 1: Disease course and disability milestones for the five age-at-death groupings, aligned for time of death. Regular

Figure 2: Disease course and disability milestones for five age-at-onset groups. Disease courses aligned for time of death. Same milestone legend as Fig. 1. Error bars show the standard error of the mean disease duration.
## Disability milestones

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Parkinson disease disability milestones in selected longitudinal cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Sydney cohort, 15 years (2005)</strong></td>
</tr>
<tr>
<td>Number of patients</td>
<td>52</td>
</tr>
<tr>
<td>Age</td>
<td>71</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>Visual hallucinations</strong></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>66.7</td>
</tr>
<tr>
<td>Time to onset</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>67.5</td>
</tr>
<tr>
<td>Time to onset</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Residential home admission</strong></td>
<td></td>
</tr>
<tr>
<td>Age at admission</td>
<td>NA</td>
</tr>
<tr>
<td>Time to admission</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dementia</strong></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>75.2</td>
</tr>
<tr>
<td>Time to onset</td>
<td>15.1</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
</tr>
<tr>
<td>Age at death</td>
<td>75.5</td>
</tr>
<tr>
<td>Time to onset</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Apart from numbers of patients, all data, unless otherwise stated, represent mean values in years. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. †We calculated these values on the basis of the data provided in the original studies. ‡Estimated value for initial sample. Abbreviation: NA, not available.
Management Issues in LS-PD

• Patients tend to withdraw from specialized medical care.
• Patients & caregivers: special needs.
• Heavy burden for health-care systems and families.
• Orphan-like disease:
  – patients left out from clinical trials.
  – disability milestones not usual outcomes in RCTs.
Unmet needs in LS-PD

• Focus on:
  – NMS: dementia, apathy, depression, psychosis, EDS, urinary dysf
  – axial symptoms: dysphagia, dysarthria, falls, fractures, freezing, gait

• Motor complications: less a priority.

• Management strategies: simplify; avoid adverse effects.

• Multidisciplinary team: PT, OT, SP, nurses, social workers, psychiatrists, psychologists, neurologists
This study will evaluate the needs and provision of care for patients in the late stages of Parkinsonism and their carers in several European countries. This will be done through an in-depth assessment of patients and carers, interrogation of national and regional databases, and assessment and outcome of management strategies in six European countries. We will compare the effectiveness and cost of different health and social care systems, and carry out a trial comparing assessment by a specialist with management suggestions, guidance and access to telephone advice to that of usual care.
Conclusions

- Prevalence of LS-PD is likely to increase.
- LS-PD: patients progressing beyond advanced-stage.
- Highly handicapped. Dependent on caregivers.
- Handicap: predicted by severity of parkinsonism, dementia and neuropsychiatry complaints.
- Severe impact on caregivers’ life. Much time allocated to caregiving.
- Unmet needs and low use of medical resources.